









*Ο Πρότανης  
του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών  
καθηγητής Μελέτιος-Αθανάσιος Κ. Δημόπουλος  
έχει την τιμή να σας προσκαλέσει  
στην τελετή επίδοσης του τιμητικού τόμου με τίτλο*

***«50 χρόνια Καρδιοχειρουργικής  
Κωνσταντίνος Ε. Αναγνωστόπουλος, Ομότιμος Καθηγητής Καρδιοχειρουργικής  
Ιατρικής Σχολής  
Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών»***

*στον Ομότιμο Καθηγητή Καρδιοχειρουργικής  
Κωνσταντίνο Ε. Αναγνωστόπουλο,*

*Η τελετή θα πραγματοποιηθεί  
την Παρασκευή, 11 Μαΐου 2018 και ώρα 19:00  
στην Μεγάλη Αίθουσα του Πανεπιστημίου Αθηνών  
(κεντρικό κτήριο, Πανεπιστημίου 30).*

***Μετά το πέρας της τελετής  
θα ακολουθήσει δεξίωση στην Αθηναϊκή Λέσχη  
Πανεπιστημίου 11***



*The Rector*

*Of the the National and Kapodistrian University of Athens*

*professor Meletios.-Athanasios K. Dimopoulos*

*has the honour of inviting you to*

‡ the presentation of the honorary volume Liber Amicorum (Festschrift) entitled:

***"50 years of Cardiac Surgery***

***Constantine E. Anagnostopoulos, Professor of Cardiac Surgery Emeritus***

***School of Medicine,***

***National and Kapodistrian University of Athens"***

*To Constantine E. Anagnostopoulos  
Professor of Cardiac Surgery Emeritus*

*The formal ceremony will take place  
on Friday, May 11, 2018, at 19.00  
in the University Hall (Aula)  
(central building ,30 Panepistimiou Street)*

.

*A reception will follow at Athens Club (Athinaiki Leschi),  
11 Panepistimiou Street*



Τιμητικός Τόμος

«50 Χρόνια Καρδιοχειρουργικής»

ΚΩΝΣΤΑΝΤΙΝΟΣ Ε. ΑΝΑΓΝΩΣΤΟΠΟΥΛΟΣ

Ομότιμος Καθηγητής Καρδιοχειρουργικής  
Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

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\* This volume includes original Greek *Laudations with English translations* as well as 59 selected texts **mainly** in English.

\*\* In the contents list, the order is alphabetic under the senior author name.

\*\*\**The senior author name appears on the left upper corner of the first page of each publication.*

\*Στον παρόντα τόμο περιλαμβάνονται πρωτότυποι *Επαινοι στα Ελληνικά με μετάφραση στα αγγλικά* καθώς και 59 *επιλεγμένα κείμενα κυρίως στα Αγγλικά.*

\*\* Στον κατάλογο περιεχομένων η σειρά είναι αλφαβητική για το όνομα του senior Author.

\*\*\*Στην πρώτη σελίδα κάθε εργασίας, αριστερά επάνω, τυπώνεται ο senior Author.

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Τιμητικός Τόμος

«50 Χρόνια Καρδιοχειρουργικής»

Κωνσταντίνος Ε. Αναγνωστόπουλος

*Ομότιμος Καθηγητής Καρδιοχειρουργικής  
Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών*

Liber Amicorum (Festschrift)

«50 Years of Cardiac Surgery»

Constantine E. Anagnostopoulos

*Professor of Cardiac Surgery Emeritus  
School of Medicine, National and Kapodistrian University of Athens*

*National and Kapodistrian University of Athens 2018*

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Εθνικό και Καποδιστριακό Πανεπιστήμιον Αθηνών

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Τυπογραφείο: Τ. Ποδαράς και Σία Ο.Ε.

Βιβλιοδεσία: Χρυσός Τύπος

PARISIANOS

ISSN ??????????????????

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*Καρδιοχειρουργική      Αναισθησιολογία*  
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Χρήστος Κίττας, *π. Υπουργός Υγείας και Κοινωνικής Αλληλεγγύης, Πρύτανης*

## Δομή του έργου

Στον Τιμητικό Τόμο του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών για τον Ομότιμο Καθηγητή Καρδιοχειρουργικής Κωνσταντίνο Ε. Αναγνωστόπουλο που έπεται, υπάρχει μια σειρά κειμένων στα Ελληνικά και Αγγλικά.

1. Στην αρχή υπάρχουν **πρόλογοι / Έπαινοι στα ελληνικά** με αγγλική μετάφραση (με λατινική αρίθμηση) από μέλη της Καθηγητικής Εκδοτικής Επιτροπής:

Καθηγητές:

**Δημήτριος Αγγουράς** και **Γεωργία Κωστοπαναγιώτου** – πρόεδροι και συνεργάτες του τιμωμένου

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**Χρήστος Κίττας** – πρώην Πρύτανης, Πρόεδρος Ιατρικής ΕΚΠΑ και Υπουργός Υγείας

**Πέτρος Σφηκάκης** – Πρόεδρος Ιατρικής ΕΚΠΑ

**Παναγιώτης Σουκάκος** – Καθηγητής Ορθοπαιδικής

**Θεόδωρος Λιακάκος** – Διευθυντής Χειρουργικού Τομέα, Αντιπρόεδρος Ιατρικής ΕΚΠΑ

**Δημήτριος Δουγένης** – Καθηγητής Καρδιοχειρουργικής «ΑΤΤΙΚΟΝ» ΕΚΠΑ

2. Άλλοι **πρόλογοι / Έπαινοι στα αγγλικά / ελληνικά** ακολουθούν (στην κύρια αλφαβητική σειρά κειμένου) από τους συναδέλφους του Καθηγητές:

**J.M. Levett, MD**

**A.Little, MD**

**S.Rammos, MD, PhD**

και η οικογένεια του τιμωμένου:

**M.L.L.R. Anagnostopoulos, MBA**

**A-M Αναγνωστοπούλου, MD**

**S.R. Natan, MD**

**P.P.Reese, MD**

**A.H. Reese, MD**

3. Μετά τον κατάλογο όλων των συγγραφέων και τίτλων δημοσιεύσεων, ολοκληρώνεται ο Τιμητικός Τόμος με το πλήρες κείμενο – σε αλφαβητική σειρά του υποβάλλοντος συγγραφέα (κυρίως στα **αγγλικά** με μερικά **πρωτότυπα άρθρα στα ελληνικά**) 59 επιλεγμένων δημοσιεύσεων.

Από τα μέλη της Καθηγητικής Εκδοτικής Επιτροπής  
Εθνικών και Καποδιστριακών Πανεπιστημίων Αθηνών  
Φεβρουάριος 2018

# Structure of the volume

In the following University of Athens Festschrift volume in honour of Emeritus Cardiac Surgery Professor Constantine E. Anagnostopoulos there is a sequence of texts in Greek and English.

1. There are **opening introductory laudations in Greek** translated to English (numbered in Latin) by members of the Professorial Editorial Committee Professors: **Dimitrios Angouras** and **Georgia Kostopanagiotou** –co-chairs and co-workers of the honoree

**Meletios-Athanasios Dimopoulos** – Rector

**Christos Kittas** – former Rector, Medical School President and Minister of Health

**Petros Sfikakis** – Medical School President

**Panayotis Soucacos** – Professor of Orthopedics

**Theodoros Liakakos** – Chair University Surgery

**Dimitrios Dougenis** – Professor of Cardiac Surgery

2. Other **Laudations in English and Greek** follow (in the main alphabetical text sequence) by professors colleagues.

**J.M. Levett, MD**

**A. Little, MD**

**S. Rammos, MD PhD**

and family of the honoree:

**M.L.L.R Anagnostopoulos, MBA**

**A-M Anagnostopoulos, MD**

**S.R. Natan, MD**

**P.P. Reese, MD**

**A.H. Reese, MD**

3. After the list of individual authors and publication titles the full text – in alphabetical sequence of the submitting author (mostly in **English** with some **original articles in Greek**) of 59 selected publications concludes the Honorary Volume.

From the members of the Professorial Editorial Committee  
University of Athens  
February 2018



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# Χαιρετισμός

## Πρύτανη ΕΚΠΑ Καθηγητού Μελέτιου-Αθανασίου Δημόπουλου

Με ιδιαίτερη τιμή χαιρετίζω εκ μέρους των Πρυτανικών Αρχών του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών την έκδοση του παρόντος τόμου από την Καρδιοχειρουργική Κλινική του Πανεπιστημίου μας προς τιμή του Ομότιμου Καθηγητή Καρδιοχειρουργικής κ. Κ. Αναγνωστόπουλου.

Ο κ. Αναγνωστόπουλος, κατόπιν πολυετούς και αξιοζήλευτης ακαδημαϊκής σταδιοδρομίας στις ΗΠΑ, επέστρεψε στη χώρα μας και μετά από την εξαετή του θητεία ως Καθηγητής Καρδιοχειρουργικής στο Πανεπιστήμιο Ιωαννίνων, που οδήγησε στην οργάνωση και επιτυχή λειτουργία της ομώνυμης κλινικής, εξελέγη Καθηγητής Καρδιοχειρουργικής της Ιατρικής Σχολής του Πανεπιστημίου μας, το 2003. Η πληθωρική του προσωπικότητα, η μεθοδικότητά του, η οργανωτική του ικανότητα, η εργατικότητα και η διορατικότητα, σε συνδυασμό με τις γνώσεις και τη μεγάλη του εμπειρία, αποτέλεσαν τους παράγοντες που του επέτρεψαν να προσφέρει, γενικότερα, σημαντικό έργο, να ξεπεράσει ποικίλα εμπόδια και δυσκολίες, συχνά συμφυή με το μέγεθος του εγχειρήματος και, ειδικότερα, να οργανώσει και λειτουργήσει εκ του μηδενός στο νεοσύστατο Πανεπιστημιακό Νοσοκομείο «Αττικών» την Καρδιοχειρουργική Κλινική του ΕΚΠΑ, το 2006.

Η Κλινική αυτή έχει προσφέρει υψηλού επιπέδου κλινικό έργο στην ευαίσθητη περιοχή της Δυτικής Αθήνας όλα αυτά τα χρόνια. Παραλλήλως, όμως, προς αυτό, καθώς η διδασκαλία, η έρευνα και η δημοσίευση μελετών και νέων προτάσεων αποτελούν την πεμπτουσία της ακαδημαϊκής οντότητας, οφείλουμε να προβάλλουμε το γεγονός ότι υπό την καθοδήγησή του, τα μέλη της καρδιοχειρουργικής ομάδας του Πανεπιστημίου μας παρήγαγαν σημαντικό κλινικό και πειραματικό ερευνητικό έργο, που οδήγησε σε διεθνείς δημοσιεύσεις και την παρουσίαση σε εθνικά και διεθνή φόρα μεγάλου αριθμού άρθρων και περιλήψεων, το σύνολο των οποίων υπερβαίνει τα 100 σε βραχύ χρονικό διάστημα. Σημαντική υπήρξε, επίσης, η παρουσία της νεοσύστατης κλινικής σε διδακτικά συγγράμματα για τους φοιτητές μας και σε διεθνείς εκδόσεις. Είναι δε άξιο σχολιασμού ότι οι αναφορές του Ομότιμου Καθηγητή κ. Αναγνωστόπουλου, ενός μάχιμου καρδιοχειρουργού με περισσότερες από 11.500 επεμβάσεις στο ενεργητικό του, ξεπερνούν τις 3.000, γεγονός που τον καθιστά πρότυπο ακαδημαϊκού χειρουργού.

Από τη θέση αυτή, εκφράζω τις θερμές ευχαριστίες του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών στον Ομότιμο Καθηγητή κ. Αναγνωστόπουλο για την προσφορά του, η οποία παρά τη σχετική σύντομη χρονική της διάρκεια (2003-2007), υπήρξε εξαιρετικά σημαντική. Ελπίζω το έργο του να αποτελέσει πηγή έμπνευσης για τους νεότερους. Είμαι σίγουρος ότι με την πολύτιμη πείρα του θα συνεχίσει να συνδράμει το έργο της Καρδιοχειρουργικής Κλινικής του Πανεπιστημίου μας από τη θέση του Ομότιμου Καθηγητή.

Professor Meletios-Athanasios Dimopoulos  
Rector  
National and Kapodistrian University of Athens  
Salutations

With great pleasure, I welcome on behalf of the Governing Bodies of the National and Kapodistrian University of Athens the publication of this volume from the Cardiac Surgical Clinic of our University in honour of the Emeritus Professor of Cardiac Surgery Constantine E. Anagnostopoulos.

Dr Anagnostopoulos, after a long and enviable academic career in the USA, returned to Greece and after his six-year term as Professor of Cardiac Surgery at the University of Ioannina leading to the founding and successful operation of the homonymous clinic there, was elected Professor of Cardiac Surgery in the Medical School of our University in 2003. His exuberant personality, orderly thinking, organizational ability, diligence and insight, combined with his knowledge and great experience, were the factors that enabled him to provide a significant endeavor on a wide scale, to overcome a variety of challenges, often inherent to the size of such venture and more specifically to organize and operate from scratch his Cardiac Surgery Clinic at the newly founded National and Kapodistrian University of Athens “Attikon” Hospital in 2006.

This clinic has been providing high-quality clinical work in the sensitive area of West Athens over me years. However, apart from teaching, research and the publication of studies and new proposals which are the quintessence of the academic entity, we must also point out that, under his guidance, the members of the University’s Cardiac Surgery team produced significant clinical and experimental research projects that led to international publications and presentations of articles and abstracts to a large number of national and international fora, exceeding 100, in a short amount of time. The presence of the newly established clinic was also an important influence to textbooks and international publications. It is worthwhile commenting that the reports of the Emeritus Professor Dr. Anagnostopoulos, an active surgeon in the field of cardiac surgery, with more than 11,500 operations on his track record, exceed 4,000, making him an exemplary academic surgeon.

From this position, I extend the warm thanks of the National and Kapodistrian University of Athens to Professor Emeritus Anagnostopoulos for his contribution, which despite its relatively short duration (2003-2007) was extremely important. I hope his work will be a source of inspiration for younger people. I am sure that, with his valuable experience, he will continue to assist the work of the Cardiac Surgery Clinic of the University as Professor Emeritus.

# Χαιρετισμός

## Καθηγητού Πέτρου Π. Σφηκάκη

Είναι ιδιαίτερη τιμή για εκπροσωπώντας τις καθηγήτριες και τους καθηγητές της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών να προλογίσω τον τιμητικό τόμο του Ομότιμου Καθηγητή Καρδιοχειρουργικής της Σχολής μας, κ. Κωνσταντίνου Αναγνωστόπουλου.

Ο Καθηγητής Αναγνωστόπουλος υπήρξε ο πρώτος Διευθυντής της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής από ιδρύσεως του ΕΚΠΑ και της Ιατρικής Σχολής.

Ο Κωνσταντίνος Αναγνωστόπουλος, καταξιωμένος καθηγητής και διαπρεπής επιστήμονας στις ΗΠΑ και διεθνώς γνωστός καρδιοχειρουργός, οραματιζόταν πάντα την επιστροφή του στην Ελλάδα. Πολλά χρόνια πριν, οι δρόμοι της αναζήτησης της επιστήμης οδήγησαν τον Έλληνα μαθητή με ρίζες από την ορεινή Φωκίδα, μετά το τέλος των γυμνασιακών του σπουδών, στις ΗΠΑ όπου και σπούδασε την Ιατρική στο Πανεπιστήμιο Georgetown, στην Washington, D.C., αποφοιτώντας με άριστα (M.D. with Honors, 1963). Φιλομαθής και ακαταπόνητος, ειδικεύτηκε στην Καρδιοχειρουργική στα φημισμένα Πανεπιστήμια Columbia και Yale των ΗΠΑ, όπου και ανήλθε όλη την ακαδημαϊκή ιεραρχία μέχρι τη βαθμίδα του πρωτοβάθμιου Καθηγητή Καρδιοχειρουργικής. Θήτευσε ως Καθηγητής και Διευθυντής Πανεπιστημιακών Καρδιοχειρουργικών Κλινικών για πολλά έτη στις ΗΠΑ.

Μετά από μια λαμπρή σταδιοδρομία και παρά το γεγονός ότι η αγαπημένη του οικογένεια ήταν εγκατεστημένη στις ΗΠΑ, εκείνος αποφάσισε να επιστρέψει στην πατρίδα του προσφέροντας ως καθηγητής Καρδιοχειρουργικής, πρώτα στην Ιατρική Σχολή του Πανεπιστημίου Ιωαννίνων και στη συνέχεια, στην Ιατρική Σχολή Αθηνών, γενόμενος και ο πρώτος Διευθυντής στο νεοϊδρυθέν Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων και στη συνέχεια στο ΠΓΝ «ΑΤΤΙΚΟΝ», ενώ συνέβαλλε και στην ανάπτυξη της Καρδιοχειρουργικής Κλινικής Ενηλίκων και Παιδών του «Ωνασείου» Καρδιοχειρουργικού Κέντρου. Εκτός από το ακαδημαϊκό και κλινικό του έργο στην Ελλάδα, ο Καθηγητής Αναγνωστόπουλος δεν παραμέλησε τη μεγάλη του αγάπη που ήταν η πειραματική έρευνα. Ακόμη από τότε που ήταν στο Πανεπιστήμιο των Ιωαννίνων, οργάνωσε εκεί ένα ιδιαίτερα δημιουργικό Πειραματικό Εργαστήριο, όπου εκπαίδευσε πολλούς νέους ερευνητές, συνεχίζοντας κατόπιν το ίδιο και στην Αθήνα, προτρέποντας διαρκώς και εκπαιδεύοντας τους νέους συνεργάτες του να δημιουργούν σε όλα τα επίπεδα: κλινική-εκπαίδευση-έρευνα-συγγραφή.

Από ενάρξεως λειτουργίας του ΠΓΝ «ΑΤΤΙΚΟΝ», το 2003, κατέβαλε επίμονες και επίμονες προσπάθειες για την οργάνωση και έναρξη λειτουργίας της υπό την διεύθυνσή του νεοϊδρυθείσας Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής. Το 2006, έγινε η 1<sup>η</sup> επέμβαση ανοικτής καρδιάς και ακολούθησαν πολλές, πολύπλοκες και σύμπλοκες τις περισσότερες φορές επεμβάσεις, μοναδικές για τα ελληνικά δεδομένα της καρδιοχειρουργικής. Τα ακαδημαϊκά χρόνια στο «ΑΤΤΙΚΟΝ» κύλησαν γρήγορα, αλλά δημιουργικά. Το 2007 αφηγήρησε αφήνοντας την ευθύνη της Καρδιοχειρουργικής Κλινικής στα στιβαρά χέρια των ικανών συνεργατών του, οι οποίοι και συνεχίζουν το δημιουργικό του έργο, παρακαταθήκη που ο ίδιος άφησε.

Σπανίως καταξιωμένοι Καθηγητές και Διευθυντές Κλινικών από τις ΗΠΑ επιστρέφουν στην Ελλάδα, με τόση αποφασιστικότητα και δύναμη ψυχής, προκειμένου να ξεκινήσουν από μηδενική βάση την οργάνωση και έναρξη λειτουργίας μιας ιδιαίτερα απαιτητικής ειδικότητας, όπως η καρδιοχειρουργική, σε ακαδημαϊκό και κλινικό επίπεδο, και μάλιστα σε δύο νεοϊδρυθέντα πανεπιστημιακά νοσοκομεία. Ήταν το ελληνικό πείσμα του, ο «νόστος», η αγάπη του για την Ελλάδα, η υπόσχεση στον εαυτό του ότι ο κύκλος της λαμπρής σταδιοδρομίας του θα έκλεινε εκεί από όπου ξεκίνησε; Τελικά, ο Καθηγητής Αναγνωστόπουλος ευτύχησε να κάνει το όνειρό του πραγματικότητα!

Ο Καθηγητής Αναγνωστόπουλος τίμησε την Ιατρική Σχολή του ΕΚΠΑ με το έργο του, ένα πολύπλευρο ακαδημαϊκό έργο που κατάφερε μέσα σε τόσο σύντομο χρονικό διάστημα και μέσα από πάμπολλες δυσκολίες, οργανωτικές, υλικοτεχνικές και ότι άλλο η έναρξη λειτουργίας μιας Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής απαιτεί.

Η Ιατρική Σχολή του ΕΚΠΑ του αποδίδει τα εύσημα και τις ευχαριστίες της!

Καθηγητής Πέτρος Π. Σφηκάκης

Professor Petros P. Sfrikakis  
President, School of Medicine  
National and Kapodistrian University of Athens

## Salutations

On behalf of the professors of the Medical School of the National and Kapodistrian University of Athens, it is a great honour to present a salutation to the honorary volume of the Professor Emeritus of Cardiac Surgery of our School, Dr. Constantine Anagnostopoulos.

Professor Anagnostopoulos was the first Director of the University Cardiac Surgery Clinic since the founding of the University of Athens and the Medical School.

Constantine Anagnostopoulos, a well-known professor and prominent scientist in the USA and an internationally known cardiac surgeon, has always envisioned his return to Greece. Many years ago, the path in search of science led the Greek student (with paternal roots originating in mountainous Potidaneaia –Dorida area of Fokida– and maternal roots from Kozani and Salonica in Macedonia), after his Greek Gymnasium graduation, to the United States at Georgetown University, Washington, DC, where he studied Medicine and graduated with M.D. with Honors in 1963. Being studious and tireless, he did his specialization on Cardiac Surgery at the renowned Columbia and Yale Universities in the US, where he rose through the entire academic hierarchy up to the level of full tenured Professor of Cardiac Surgery at The University of Chicago. He served as Professor and Director of University Cardiac Surgery Clinics for many years in New York.

After a brilliant career and despite the fact that his beloved family lived in the USA, he decided to return to his homeland as Professor of Cardiac Surgery, first at the Medical School of the University of Ioannina and then at the Athens Medical School, and as the first Director at the newly founded General Hospital of Ioannina and then at “ATTIKON”, while also contributing to the development of the Cardiac Surgery Adult and Pediatric Clinic of the “Onassis” Cardiac Surgical Center. In addition to his academic and clinical work in Greece, Professor Anagnostopoulos did not neglect his great love, for experimental research. Ever since he was at the University of Ioannina, he organized a highly creative Experimental Laboratory, where he trained many young researchers, and then in Athens, he continuously prompted and trained his new collaborators to create in all levels: clinical-education-research-writing.

Since the start of operation of the University General hospital “ATTIKON”, in 2003, he has made strenuous and persistent efforts for the organization and startup of the newly established University Cardiac Surgery Clinic. In 2006, the first open-heart

surgery was performed, followed by many, complex procedures which were most of the time, unique for the Greek scene of cardiac surgery. Academic years at “ATTIKON” went fast, but creatively. In 2007 he retired, leaving the responsibility of the Cardiac Surgery Clinic to the robust hands of his capable collaborators, who continue his creative work. Rarely do established US Clinically active Professors and Clinic Directors return to Greece with so much resolve and psyche in order to start from zero the organization and operation of a highly demanding speciality, such as cardiac surgery, at both an academic and a clinical level, in two newly established university hospitals. Was his Greek stubbornness, his “home-sickness”, his love for Greece, the promise to himself his brilliant career would end where it started? Finally, Professor Anagnostopoulos has made his dream come true!

Professor Anagnostopoulos honoured the Medical School of the University of Athens with a multi-faceted academic project which, within such a short time and through many challenges, organizational, logistical and whatever else the operation of a University Cardiac Surgery Clinic requires, he accomplished.

The Medical School of the University of Athens presents to him its honourable “festschrift” volume and thanks!

# Εσαγωγικό σημείωμα

Θεοδώρου Λιακάκου, Καθηγητή Χειρουργικής  
Αναπληρωτή Προέδρου της Ιατρικής Σχολής  
Διευθυντή του Χειρουργικού Τομέα ΕΚΠΑ

Με ιδιαίτερη χαρά προλογίζω τον ανά χείρας τόμο προς τιμή του κ. Κωνσταντίνου Αναγνωστόπουλου, Ομότιμου Καθηγητή Καρδιοχειρουργικής της Ιατρικής Σχολής του ΕΚΠΑ.

Ο κ. Αναγνωστόπουλος υπήρξε ένας εκ των πλέον διαπρεπών και διεθνώς αναγνωρισμένων Ελλήνων καρδιοχειρουργών. Εκπαιδεύτηκε και εργάστηκε επί σειρά ετών στα μεγαλύτερα πανεπιστημιακά κέντρα των ΗΠΑ, συμπεριλαμβανομένων των Georgetown University, Washington, D.C, Columbia Presbyterian Medical Center, New York, NY και Yale University School of Medicine, U.S.P.H.S., New Haven, CT. Επίσης, υπήρξε καθηγητής στο State University of New York at Stony Brook (1983 – 1991) και στο Columbia University - St. Luke's/Roosevelt Hospital Center, New York, NY, ολοκλήρωσε δε την ακαδημαϊκή του καριέρα στο Icahn School of Medicine at Mount Sinai, New York, NY.

Θεωρώ όμως ως σημαντικότερο έργο του κ. Αναγνωστόπουλου την παράλληλη εργασία και προσφορά του στην Ελληνική Καρδιοχειρουργική Κοινότητα και την μεγάλη του συμβολή τόσο στην αρχική ανάπτυξη και λειτουργία του Ωνασείου Καρδιοχειρουργικού κέντρου, αλλά και στην ίδρυση και λειτουργία της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής στην Ιατρική Σχολή του Πανεπιστημίου Ιωαννίνων, όπου εξελέγη καθηγητής το 1997. Ίδρυσε Πειραματικό Εργαστήριο, εκπαίδευσε δε και ανέδειξε συνεργάτες που σε συνεργασία μαζί του έθεσαν τις βάσεις για την σταθερή και έκτοτε επιτυχημένη κλινική πορεία της περιφερειακής αυτής πανεπιστημιακής κλινικής, συμβάλλοντας έτσι σημαντικότερα στην νοσηλευτική φροντίδα των Καρδιοθωρακοχειρουργικών ασθενών της περιφέρειας.

Τον ομότιμο καθηγητή κ. Αναγνωστόπουλο γνώρισα το 2004, όταν έχοντας εκλεγεί Καθηγητής Καρδιοχειρουργικής στο ΕΚΠΑ, ξεκίνησε στο ΠΓΝ «Αττικών» τις προσπάθειες για εγκατάσταση και λειτουργία της ομώνυμης Κλινικής. Φρόντισε για την στελέχωση της κλινικής, για την προμήθεια υλικοτεχνικού εξοπλισμού και πέτυχε την έναρξη των επεμβάσεων ανοικτής καρδιάς τον Ιούνιο του 2006.

Ο Ομότιμος Καθηγητής κ. Αναγνωστόπουλος αποτέλεσε ένα πρότυπο καρδιοχειρουργού και ακαδημαϊκού δασκάλου, με μια λαμπρή ακαδημαϊκή σταδιοδρομία στις ΗΠΑ, αλλά παράλληλα, και αυτό είναι το σημαντικότερο, με μια εξαιρετικά σημαντική συνεισφορά στη διαμόρφωση του τοπίου της σύγχρονης καρδιοχειρουργικής στη χώρα μας. Χάρη στη βαθύτατη γνώση του γνωστικού του αντικειμένου, στην διοικητική ικανότητα και στην μακρά του εμπειρία, έθεσε σε λειτουργία δυο Πανεπιστημιακές

Κλινικές στη Χώρα μας, πράγμα σχεδόν μοναδικό για τα Ελληνικά Ακαδημαϊκά δεδομένα.

Στο σύντομο διάστημα της γνωριμίας μας, η συνεργασία μαζί του ήταν άριστη. Εντυπωσιάστηκα από τον προσηνή χαρακτήρα του, την έμφυτη καλοσύνη του, την άριστη συνεργασία του με όλους. Όντας πολυγραφότατος και παραδειγματικός ερευνητής, δεν θα ήταν υπερβολή να τον χαρακτηρίσω ως έναν εκ των πλέον διαπρεπών και διεθνώς αναγνωρισμένων Ελλήνων καρδιοχειρουργών, με λαμπρή ακαδημαϊκή σταδιοδρομία στις ΗΠΑ αλλά παράλληλα με σημαντικότερη συνεισφορά στην καρδιοχειρουργική στη Χώρα μας. Η ακαδημαϊκή ιατρική κοινότητα και ο Χειρουργικός Τομέας της Ιατρικής Σχολής του οφείλουμε τιμή και βαθύτατα τον ευχαριστούμε για την συνολική του προσφορά.

Θεόδωρος Λιακάκος  
Διευθυντής Χειρουργικού Τομέα  
Αναπληρωτής Πρόεδρος της Ιατρικής Σχολής ΕΚΠΑ

Νοέμβριος 2017

Theodoros Liakakos, Professor of Surgery  
Deputy President of the Medical School  
Director of the Surgery Division  
National and Kapodistrian University of Athens

## An introductory note

It is a great pleasure to write a foreword honouring Dr Konstantinos Anagnostopoulos, Professor Emeritus of Cardiac Surgery at the Medical School of Athens.

Dr Anagnostopoulos was one of the most prominent and internationally recognized Greek cardiac surgeons. He has trained and worked for many years in some of the largest US universities, including Georgetown University, Washington, DC, Columbia Presbyterian Medical Center, New York, NY and Yale University School of Medicine, U.S.P.H.S., New Haven, CT. He was also a professor at the State University of New York at Stony Brook (1983-1991) and Columbia University / Luke's / Roosevelt Hospital Center, New York, NY, completing his academic career at the Icahn School of Medicine at Mount Sinai, New York, NY.

However, I also consider important the parallel work of Dr. Anagnostopoulos with the Hellenic Cardiosurgical Community and his great contribution to the initial development and operation of Onassis Cardiac Surgery Center and to the establishment and operation of the University Clinical Cardiac Surgery at the Medical School of the University of Ioannina, where he was elected professor in 1997. He founded an Experimental Laboratory where he trained collaborators and worked with them, and who together with him, laid the foundations for a stable and successful clinical course of this regional university clinic, thus contributing greatly to the nursing care of the cardiothoracic patients in the region.

Professor Anagnostopoulos, Professor of Emeritus, whom I met in 2004 when he was elected Professor of Cardiac Surgery at the University of Athens, was the one who started the efforts to establish and operate the homonymous Clinic at «Attikon» General Hospital. He took care of staffing of the clinic and supplying it with logistical equipment and succeeded in commencing operations for open heart surgeries in June 2006.

Professor Emeritus Anagnostopoulos was a model of a cardiac surgeon and academic teacher with a brilliant academic career in the USA, and most importantly, with an extremely important contribution to the shaping of the modern cardiac surgery landscape in our country. Thanks to his profound knowledge on the field, his administrative capacity and his expertise, he has set up two University Clinics in our country, which is almost unique to Greek Academic scene.

In the short term of our acquaintance, my cooperation with him was excellent. I was impressed with his prominent character, his clemency, and his excellent cooperation with everyone. Being a prolific and exemplary researcher, it would not be an exaggeration to call him one of the most prominent and internationally recognized Greek cardiac surgeons, with a brilliant academic career in the US but also a major contribution to cardiac surgery in our country. The academic medical community and the Surgery Division of our Medical School owe him a great debt and we thank him for his contribution in total.

Theodoros Liakakos  
Professor, Director of Surgery  
Deputy President of the Medical School  
National and Kapodistrian University of Athens

November 2017

# Τιμητική Καταγραφή

## Καθηγητού Παναγιώτη Ν. Σουκάκου

Με τον Καθηγητή Κωνσταντίνο Αναγνωστόπουλο –Ντίνο– υπήρξαμε συμμαθητές από την ΣΤ΄ τάξη του Δημοτικού Σχολείου, «Σύντροφοι εν Σχολείοις», κατά παράφραση γνωστής γραφής. Από τότε που τον γνώρισα, από τότε που βρεθήκαμε μαζί στα ίδια θρανία, ήταν ο 1<sup>ος</sup> μαθητής στην τάξη και ακόμα περισσότερο, υπήρξε και αναγνωρίζονταν από όλους μας, σαν ο διαχρονικά καθολικός μαθητής. Οι υπόλοιποι 14 (συνολικός αριθμός μαθητών στην τάξη 15) ακολουθήσαμε ο καθένας με την αξία του και την αξιωσύνη του.

Οι δρόμοι των συμμαθητών μετά την αποφοίτηση από το σχολείο, ακολούθησαν όπως ήταν φυσικό και αναμενόμενο, μια γραμμική απόκλιση ανάλογα με τις επιλογές του καθενός και τους μελλοντικούς του προσανατολισμούς. Τέσσερις από τους 15 μοιραστήκαμε το ίδιο δρομολόγιο, επιβαίνοντας όμως σε διαφορετικό όχημα. Ο Ντίνος Αναγνωστόπουλος έγινε Καρδιοχειρουργός, ο Δημήτρης Εμμανουήλ Παθολόγος-Νεφρολόγος, ο Στέφανος Γερουλάνος Χειρουργός και ο υποφαινόμενος Χειρουργός Ορθοπαιδικός. Η επιστημονική μας περιπλάνηση οδήγησε τελικά όλους μας, σε κοινό ακαδημαϊκό βηματισμό – στους πανεπιστημιακούς δηλαδή γεωγραφικούς χώρους και τόπους της χώρας μας, με στόχευση την υπηρετήση και προαγωγή της Εκπαίδευσης, της Έρευνας και της Ιατρικής φροντίδας.

Από το σχολικό-μαθητικό του μικρό-κοσμο, ο Ντίνος προσανατολίστηκε και σημάδεψε τον επιστημονικό του μεγά-κοσμο. Αυτή η στράτευση, του πρόσφερε επιστημονική ολοκλήρωση και πληρότητα και παράλληλα ακαδημαϊκή αναγνώριση και καταξίωση.

Ο βηματισμός αριστείας υπήρξε η «κατά συνέχεια και η κατ' εξακολούθηση» επιλογή του Καθηγητού Κωνσταντίνου Αναγνωστόπουλου, σε μεγάλης εμβέλειας Πανεπιστημιακά Κέντρα και Ιατρικές Σχολές των Η.Π.Α., Georgetown University, Washington, D.C., Columbia Presbyterian Medical Center, New York, NY και Yale University School of Medicine, New Haven, Connecticut, όπου σε ορισμένες εξ αυτών διετέλεσε Καθηγητής, όπως παραδείγματος χάριν στο State University of New York at Stony Brook (1983-1991) και στο Columbia University, St. Luke's, Roosevelt Hospital Center, New York, NY, ολοκλήρωσε δε την ακαδημαϊκή του σταδιοδρομία στην Αμερική, στο Icahn School of Medicine at Mount Sinai, New York, NY.

Η πληθωρικότητα του έργου του, χαρακτηρίζεται από δείγματα υψηλής επιστημονικής καταξίωσης και αναγνώρισης σε παγκόσμιο πλέον διαμέτρημα. Ένα πλήθος τιμητικών διακρίσεων, τίτλων, επαίνων, προσκλήσεων και αναφορών, συνοδεύει την επιστημονική του παρουσία στο διεθνή στίβο, ενώ το συγγραφικό του έργο υψηλής εμβέλειας και προσφοράς (μεγάλος αριθμός επιστημονικών εργασιών, κεφάλαια βιβλίων και επιστημονικών εγχειριδίων) λειτουργεί ως λαμπρό παράδειγμα «μύησης και μίμησης» για τους ειδικευόμενους, τους ειδικευμένους και τα στελέχη των Πανεπι-

στημιακών και Καρδιοχειρουργικών Κλινικών των μεγάλων Νοσοκομείων του Εθνικού Συστήματος Υγείας της χώρας μας.

Πέρα όμως αυτής της αξιοζήλευτης σταδιοδρομίας και ενεργού παρουσίας στα μεγάλα διαμετρήματα ακαδημαϊκά κέντρα των Η.Π.Α., η επιστροφή του στη Ελλάδα σηματοδοτεί και υπογραμμίζει ένα εξίσου γιγαντιαίο έργο, στο Ωνάσειο Καρδιοχειρουργικό Κέντρο και στις Καρδιοχειρουργικές Κλινικές των Ιατρικών Σχολών των Πανεπιστημίων Ιωαννίνων και Αθηνών όπου και εθήτευσε ως Καθηγητής και Διευθυντής των αντιστοίχων Καρδιοχειρουργικών Κλινικών.

Το έργο του, «η εκ του μηδενός ίδρυση και λειτουργία Καρδιοχειρουργικών μονάδων στο Πανεπιστημιακό Νοσοκομείο Ιωαννίνων και στο Αττικό Πανεπιστημιακό Νοσοκομείο», όχι μόνον δεν είναι δυνατόν να περάσει απαρατήρητο, αλλά υπογράφει και υπογραμμίζει τον σπινθήρα και τη φλόγα από την οποία ξεπήδησε αξιοσημείωτη υποδομή για συνέχιση του έργου Εκπαίδευσης, Έρευνας και Ιατρικής φροντίδας στα αναφερόμενα κέντρα. Σπορέας της διδαχής, “εξ’ αδιαιρέτου και αθροιστικά” μαζί με τους μαθητές και συνεργάτες του, εγκυβώτισε και αξιοποίησε τα διαθέσιμα αποθέματα της ιατρικής του συνείδησης και επάρκειας για την προαγωγή της μάθησης και της γνώσης.

Η τεχνογνωσία και η πρόοδος της Επιστήμης και της Ιατρικής, καλπάζουν στο χωρόχρονο που βιώνουμε, με απίστευτα γοργούς ρυθμούς. Η γνώση διπλασιάζεται κάθε 2-2.5 χρόνια και ότι πρόκειται να συμβεί στα επόμενα 5-10 χρόνια, υπολογίζεται ότι δεν έχει επιτελεστεί τα προγούμενα 2.000 χρόνια. Όμως, η ανώνυμη φωνή του χρόνου και τα μηνύματα της ιστορίας και της επιστημοσύνης, θα παραμένουν όρθια, αναλλείωτα και ηχηρά, για να διδάσκουν και να δείχνουν υπενθυμητικά, αυτούς που άνοιξαν δρόμους και θεμελίωσαν αρχές και ιδέες.

Κοντολογής αυτοί, όπως ο Καθηγητής Κωνσταντίνος Αναγνωστόπουλος – ο Ντίνοσ-, που κατάφεραν το “μέγα από το ελάχιστο”, έχουν καρδίσει τον έπαινο της συλλογικής συνείδησης και της ιστορίας.

Παναγιώτης Ν. Σουκάκος  
Καθηγητής Ορθοπαιδικής  
Ορθοπαιδικό Κέντρο Έρευνας & Εκπαίδευσης  
Αττικό Πανεπιστημιακό Νοσοκομείο, Ιατρική Σχολή  
Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών

# Professor Panayotis N. Soucacos

## An accolade

Professor Konstantinos Anagnostopoulos (Dinos) and I have a long history, as we were classmates from the 6th Grade of Elementary School, that is “Comrades in School”, paraphrasing a well-known quote. Ever since I’ve known him, which is from the time we studied at the same school, he was always the best in the class. Moreover, everyone recognized him as an interminable, all-embracing student. The remaining 14 students in the class, of a total of 15, each followed a path based on their own talents and merits.

Following graduation, the paths of each of us in our class naturally followed a linear deviation dependent upon each classmate’s preference and inclination for the future. Four out of 15 shared the same road, but on a different vehicle. Dinos Anagnostopoulos became Cardiac Surgeon; Dimitris Emmanouil; a Internal Medicine-Nephrologist; Stefanos Geroulanos, a Surgeon and myself, an Orthopaedic Surgeon. Eventually, our scientific journey led us all to a common academic path, leading us all to a University in our homeland, with the common aim to serve and promote Education, Research and Medical Care.

From the “micro-cosmos” of his school days, Dinos aimed and made his mark in the “macro-cosmos” of science. His exploits offered him scientific integrity and fulfilment, while at the same time academic recognition and appreciation.

Professor Konstantinos Anagnostopoulos path of excellence has been “constant and consistent” with choices for high caliber Universities and Medical Centers in the USA, such as the Georgetown University, Washington, D.C., Columbia Presbyterian Medical Center, New York, NY and Yale University School of Medicine, New Haven, Connecticut. At many of these universities he served as Professor, including the State University of New York at Stony Brook (1983-1991) and at Columbia University, St. Luke’s Roosevelt Hospital Center, New York, NY, and at the Icahn School of Medicine at Mount Sinai, New York, NY where he concluded his academic career in the US.

The vast magnitude of his work is characterized by scientific acceptance and recognition in the international arena. Professor Anagnostopoulos has received innumerable distinctions, titles, awards, invitations and references, all of which underscore his scientific presence worldwide. His academic profile, including a myriad of scientific articles, book chapters and textbooks, serves as benchmark for residents, specialists and staff of the University and Cardiac Surgery Units of the major Hospitals of the National Health System of our country to imitate.

Despite Professor Anagnsotopoulos’ enviable career and note-worthy presence in the high-caliber academic centers in the USA, his return to Greece marks an equally colossal effort. In Greece, he made his academic presence felt at the Onassis

Cardiothoracic Surgery Center and the Cardiothoracic Surgery Units of the Medical Schools of the Universities of Ioannina and Athens. At the latter, he also served as Professor and Chairman of each respective Department.

His efforts in founding and operating new Cardiothoracic Surgery Units *de novo* at the University Hospital of Ioannina and the Attikon University Hospital, in Athens, cannot go unnoticed. These mammoth efforts mark the spark, which fired the remarkable growth in infrastructure for continuing the Education, Research and Medical Care projects in these centers. As a believer of the axiom “indiscriminate and cumulative”, Professor Anagnostopoulos along with his students and colleagues, encapsulated and exploited all of the available resources to promote learning and knowledge.

Science and Medicine have been expanding exponentially throughout our time. By some estimates, the body of medical knowledge is believed to double every 2 to 2.5 years. As a result, it is estimated that technological and scientific knowledge we obtain over the next 5-10 years, will be far greater than that accumulated over the course of the last 2000 years. With the anonymous voice of time and the messages of history, science will remain upright and resonant, to remind us of those who opened the way and founded our principles and ideas.

In short, it is those individuals, like Professor Konstantinos Anagnostopoulos, who by managing to make “the most out of the least”, have earned and deserve our accolades.

Panayotis N. Soucacos, MD, FACS  
Professor of Orthopaedic Surgery  
Orthopaedic Research & Education Center  
Attikon University Hospital, School of Medicine  
National & Kapodistrian University of Athens

# Πρόλογος

## Καθηγητού Χρήστου Κίττα

Το να προλογίζει κανείς έναν τιμητικό τόμο αφιερωμένο σε μία Ακαδημαϊκή προσωπικότητα με παγκόσμια εμβέλεια, όπως ο Ομότιμος Καθηγητής Καρδιοχειρουργικής της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών κος Κωνσταντίνος Ε. Αναγνωστόπουλος, αποτελεί ξεχωριστή τιμή για τον ίδιο τον γράφοντα.

Ο Καθηγητής Αναγνωστόπουλος, Έλληνας της διασποράς της περιόδου μετά τον Β΄ Παγκόσμιο Πόλεμο, αλλά και τον εμφύλιο, έζησε από το 1953 στις Ηνωμένες Πολιτείες της Αμερικής, όπου σπούδασε, έκανε οικογένεια και μεγαλούργησε ως Καρδιοχειρουργός τιμώντας την πατρίδα μας και τη γενέτειρα του Θεσσαλονίκη. Οι επιτυχίες του τον κατέστησαν παγκοσμίως γνωστό, αλλά εκείνος αποφάσισε τελικώς, να υπακούσει στα κελεύσματα της νοσταλγίας για την πατρίδα και να επιστρέψει στην Ελλάδα, αφιερώνοντας όλες του τις δυνάμεις στην περαιτέρω εξέλιξη της Καρδιοχειρουργικής στον τόπο που γεννήθηκε.

Συnergάτης αρχικά του «Ωνασείου Καρδιοχειρουργικού Κέντρου» από το 1993, με 400 περίπου επεμβάσεις σε μικρούς ασθενείς, πρώτος Καθηγητής και δημιουργός της Καρδιοχειρουργικής Κλινικής του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων το 1998 και τελικά Καθηγητής – Διευθυντής της Καρδιοχειρουργικής Κλινικής της Ιατρικής Σχολής του Πανεπιστημίου Αθηνών το έτος 2003, όταν και οι δρόμοι μας συναντήθηκαν ουσιαστικά για πρώτη φορά. Τη χρονιά εκείνη ως Πρόεδρος της Ιατρικής Σχολής έδινα τη δική μου μάχη για την «Πανεπιστημιοποίηση» του ΓΝ «ΑΤΤΙΚΟΝ», μια μάχη που κερδήθηκε αρχικά ως προς την ένταξή του και συνεχίσθηκε τα μετέπειτα χρόνια από τη θέση του Αντιπρύτανη Ακαδημαϊκών Υποθέσεων και υπεύθυνου εκ μέρους του Πανεπιστημίου για τα Πανεπιστημιακά Νοσοκομεία και κυρίως από τη θέση του Πρύτανη του ΕΚΠΑ, μέχρι την επίτευξη της πλήρους λειτουργίας του, με τη βοήθεια τόσων και τόσων άξιων μελών της Ιατρικής Πανεπιστημιακής Κοινότητας.

Στο πρόσωπο του Ντίνου (ζητώ συγνώμη για την οικειότητα, αλλά έτσι αισθάνομαι) αμέσως μετά την εκλογή του, κατάλαβα ότι βρήκαμε πλέον ως Διοίκηση του Πανεπιστημίου, εκείνον που θα έλυσε ένα μεγάλο πρόβλημα που είχε δημιουργηθεί από τις αρχές της δεκαετίας του 1990 και δεν ήταν άλλο από την εγκατάσταση και τη λειτουργία της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής.

Είναι γνωστό στην Πανεπιστημιακή Κοινότητα, ότι το πρόβλημα αυτό είχε πάρει τις διαστάσεις ενός σύγχρονου γαφυριού της Άρτας και γύρευε τον αρχιμάστορά του για να το λύσει. Ο αρχιμάστορας αυτός δεν ήταν άλλος από τον νεοεκλεγέντα το 2003 Καθηγητή κύριο Κωνσταντίνο Αναγνωστόπουλο. Με επιμονή και πάθος, ακούραστος εργάτης, πληθωρικός, αλλά πάντοτε προσηνής, αγαπητός και σεβαστός από όλους, Καθηγητές ή/και υφιστάμενους, Καθηγητής – Διευθυντής πλέον της Κλινικής κατάφερε

όχι μόνο να εμπνεύσει και να πείσει νέους και ικανούς καρδιοχειρουργούς να πλαισιώσουν την ομάδα του, αλλά και να υπερνικήσει όλα τα γραφειοκρατικά και άλλα εμπόδια, τα τόσο δυστυχώς γνωστά σε όλους, όσους προσπαθούν να δημιουργήσουν κάτι στη χώρας μας. Ο γεννημένος πάντοτε νικητής – Καθηγητής Αναγνωστόπουλος πέτυχε σε ελάχιστο χρόνο και πρόλαβε πριν την αφυπηρέτησή του το 2007 να δει την Πανεπιστημιακή Καρδιοχειρουργική Κλινική της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου να λειτουργεί άριστα και τελικά την παρέδωσε στους άξιους συνεργάτες του, που συνεχίζουν το έργο του με μεγάλη επιτυχία καθιστώντας την Κέντρο Αριστείας όχι μόνο στον Ελλαδικό, αλλά και στον Διεθνή Καρδιοχειρουργικό χώρο. Ο **Δάσκαλος** άλλωστε είναι πάντοτε εκεί, δίπλα στους μαθητές του που ανέλαβαν το δύσκολο έργο της επιτυχημένης συνέχειας, πρόθυμος να τους συμβουλέψει και να τους συμπαρασταθεί.

Ως Ακαδημαϊκός προϊστάμενος του Ομότιμου Καθηγητή Καρδιοχειρουργικής και Κωνσταντίνου Ε. Αναγνωστόπουλου, τα χρόνια που αυτός λειτούργησε στο Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, αισθάνομαι υπερήφανος που ένας παγκόσμιας ακτινοβολίας επιστήμονας, ερευνητής και ανθρωπιστής ιατρός υπηρέτησε στο παλαιότερο Ανώτατο Εκπαιδευτικό Ίδρυμα της χώρας μας, ο συνάδελφος του Καθηγητή αισθάνομαι τυχερός που τον γνώρισα και συνεργάστηκα μαζί του και τέλος, ως απλός άνθρωπος ενώνω και τις δικές μου ευχές με τις ευχές των χιλιάδων ασθενών που ευεργέτησε για μακροήμερεύσή του, αλλά και διαρκή επιστημονική εγρήγορση γιατί είμαι βέβαιος ότι, αγαπητέ Ντίνο μου, μπορείς να προσφέρεις ακόμη πάρα πολλά.

Κίττας Χρήστος

Ομότιμος Καθηγητής Ιατρικής Σχολής

Πρώην Πρύτανης του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

# Professor Christos Kittas

## Foreword

To preface an honourable dedication to an academic member with global reach, (the Emeritus Professor of Cardiac Surgery of our Medical School of the National and Kapodistrian University of Athens, Dr. Constantine E. Anagnostopoulos), is a special honour for the writer himself.

Professor Anagnostopoulos, a Greek post-World War II and civil war member of diaspora, lived in the United States of America since 1958, where he studied, made a family and became a Cardiac Surgeon honouring our homeland and birthplace of Thessaloniki. His successes have made him world-famous, but he finally decided to give in to the nostalgia for his homeland and return to Greece, dedicating all his might to the further development of Cardiac Surgery in the country where he was born.

He returned as principal member and honorary Chief of the Onassis Cardiac Surgery Center in 1993, with approximately 400 operations in young and adult patients, then as Professor and the creator of the Cardiac Surgery Clinic of the University Hospital of Ioannina in 1998 and in the end as a Professor and Director of the Cardiac Surgery Clinic of the University of Athens Medical School in 2003 when our roads crossed for the first time. That year as President of the Medical School I gave my own battle to make “ATTIKON” hospital centre a part of the University, (a battle that was initially won, leading to its clinical opening and which continued from my position as Vice-Rector of Academic Affairs and responsible for University Hospitals and eventually as Rector of the University of Athens), until its full operation, with the help of so many of the honourable members of the Medical University Community.

In the person of Dinos (I apologize for the intimacy, but that’s how I feel) immediately after his election, I realized that we had found (as Administrators of the University), the one who would solve a big problem that had appeared since the early 1990s which was none other than the establishment and operation of the University Cardiac Surgery Clinic.

It is well known to the University Community that this problem had taken the form of a modern unfinished “bridge of Arta” and was looking for its own mastermind to solve it. This mastermind was none other than the newly elected Professor Dr. Constantine Anagnostopoulos in 2003. A passionate, persistent and tireless worker, exuberant but always approachable, beloved and respected by all, Professors /Associates, Clinic Managers managed to not only inspire and persuade young and competent cardiac surgeons to become part of his group but also to overcome all the bureaucratic and other obstacles, which are unfortunately well known to all those

who are trying to create something in our country. A born winner –Professor Anagnostopoulos– succeeded in a very short time, and before his retirement in 2007 he was able to see the University Cardiac Surgery Unit of the Medical School of the National and Kapodistrian University work perfectly, eventually handing it over to his worthy associates who continue his work with great success, making the Center of Excellence not only in Greece but also in the International Cardiac Surgical Area. Besides **the Teacher** is always there, next to his students who have undertaken the difficult task of a successful continuity, willing to counsel and support them.

As an Academic Chief of the Emeritus Professor of Cardiac Surgery, Dr. Constantine E. Anagnostopoulos during the years he worked at the National and Kapodistrian University of Athens, I feel proud that a world reknown scientist, researcher and humanitarian physician has served at the oldest Higher Education Institution of our country. As a colleague to the Professor, I feel fortunate to have met him and work with him, and finally, as a simple man, I also add my best wishes to the thousands of patients he benefited, for his longevity and continuous scientific vigilance because I am sure, my dear Dino, you have still too much to offer.

Christos Kittas  
Emeritus Professor of Medical School  
Former Rector of the National and Kapodistrian University of Athens

# Αντί Προλόγου

## Δημήτριος Αγγουράς

### Αναπληρωτής Καθηγητής Καρδιοχειρουργικής

#### τ. Διευθυντής Καρδιοχειρουργικής Κλινικής ΠΓΝ «Αττικόν»

Η Καρδιοχειρουργική Κλινική της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών στεγάστηκε και ξεκίνησε το κλινικό και ακαδημαϊκό της έργο στο Αττικό Νοσοκομείο πριν από 11 έτη περίπου, υπό τη διεύθυνση του Καθηγητή κ. Κωνσταντίνου Ε. Αναγνωστόπουλου. Η έναρξη λειτουργίας μιας Πανεπιστημιακής Κλινικής σ' ένα υπό ανάπτυξη νοσοκομείο, ιδιαιτέρως όταν το κλινικό της έργο περιλαμβάνει εξειδικευμένες, πολύπλοκες και μεγάλης βαρύτητας χειρουργικές επεμβάσεις, απαιτεί βαθιά γνώση του γνωστικού αντικειμένου, μακρά εμπειρία, μοναδικές διοικητικές ικανότητες και απόλυτη προσήλωση στον στόχο. Ο Καθηγητής κ. Αναγνωστόπουλος, συνδυάζοντας τα ανωτέρω χαρακτηριστικά στον υπέρτατο βαθμό και υπερνικώντας αμέτρητες αντιξοότητες πάσης φύσεως, όχι μόνο κατέστησε δυνατή τη λειτουργία της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής αλλά παραλλήλως έθεσε τις βάσεις για την επιτυχή συνέχιση του έργου της μετά την αφυπηρέτησή του. Ο παρών τόμος αποτελεί έναν φόρο τιμής της Ιατρικής Σχολής και ιδιαιτέρως της Καρδιοχειρουργικής Κλινικής του ΕΚΠΑ στον θεμελιωτή και πρώτο διευθυντή της. Αποτελεί δε για μένα, ευγνώμονα μαθητή του και έναν εκ των συνοδοιπόρων του στην πρώιμη εκείνη προσπάθεια, μεγάλη χαρά και εξαιρετική τιμή η συμβολή μου στη δημιουργία αυτού του τόμου, όπως και η συγγραφή του παρόντος σύντομου προλογικού σημειώματος.

Κανείς εξ όσων γνωρίζουν τον ίδιο και το έργο του, δεν θα θεωρήσει υπερβολή αν πω ότι ο Ομότιμος Καθηγητής κ. Κ. Ε. Αναγνωστόπουλος είναι ένας εκ των πλέον διαπρεπών και διεθνώς αναγνωρισμένων Ελλήνων καρδιοχειρουργών, με μια λαμπρή ακαδημαϊκή σταδιοδρομία στις ΗΠΑ και μια εξαιρετικά σημαντική συνεισφορά στη διαμόρφωση του τοπίου της σύγχρονης καρδιοχειρουργικής στη χώρα μας.

Γεννήθηκε στη Θεσσαλονίκη το 1940 και πέρατσε τις γυμνασιακές του σπουδές στο «Εθνικόν Εκπαιδευτήριον Αναβρύτων». Σπούδασε ιατρική στο Georgetown University, Washington, D.C., απ' όπου αποφοίτησε με διάκριση (M.D. with honors, 1963). Εκπαιδεύτηκε στη γενική και καρδιοθωρακική χειρουργική στα Πανεπιστήμια Columbia (Columbia Presbyterian Medical Center, New York, NY) και Yale (Yale University School of Medicine, U.S.P.H.S., New Haven, CT). Υπηρέτησε στο Yale University School of Medicine ως Instructor in Surgery (1967-1969), στο University of Chicago ως Επίκουρος, Αναπληρωτής και Πρωτοβάθμιος Καθηγητής (1969-1983) και ακολούθως ως Καθηγητής και Διευθυντής των Κλινικών Καρδιοθωρακικής Χειρουργικής στο State University of New York at Stony Brook (1983-1991) και στο Columbia University - St. Luke's/Roosevelt Hospital Center, New York, NY (1991-1998). Διατήρησε τη θέση του Καθηγητή και εν συνεχεία του Κλινικού Καθηγητή στο εν λόγω Πανεπιστήμιο κατά τα έτη 1998-2007 και 2007-2016, ενώ από το

έτος 2016 έως σήμερα έχει θέση Κλινικού Καθηγητή Καρδιοαγγειακής Χειρουργικής στο Icahn School of Medicine at Mount Sinai, New York, NY.

Παράλληλα και από το 1991, δραστηριοποιήθηκε ενεργά στην Ελλάδα με τη συνεργασία του και την καθοριστική συμβολή του στην ανάπτυξη της Καρδιοχειρουργικής Κλινικής Παίδων και Ενηλίκων του Ωνασείου Καρδιοχειρουργικού Κέντρου (1991-1998). Το 1997 εκλέχθηκε Καθηγητής στο Πανεπιστήμιο Ιωαννίνων και οργάνωσε την Καρδιοχειρουργική Κλινική και ένα παραγωγικό Πειραματικό Εργαστήριο στο εν λόγω Πανεπιστήμιο (1997-2003), εκπαίδευσε και ανέδειξε πολλούς συνεργάτες και έθεσε τις βάσεις για την επιτυχή πορεία της περιφερειακής αυτής πανεπιστημιακής κλινικής. Τέλος, το 2003 εκλέχθηκε Καθηγητής Καρδιοχειρουργικής στο ΕΚΠΑ και ξεκίνησε μια επίπονη προσπάθεια στέγασης, στελέχωσης και οργάνωσης της ομώνυμης Κλινικής, που κατέληξε στην ουσιαστική έναρξη λειτουργίας της με την πρώτη επέμβαση ανοιχτής καρδιάς τον Ιούνιο του 2006. Η οξυδέρκεια και αποφασιστικότητά του στον διοικητικό τομέα, το εύρος της γνώσης και της εμπειρίας και η προσήλωσή του στη λεπτομέρεια στην κλινική διάσταση αλλά και η επιμονή του στην εκπαιδευτική και ερευνητική (πειραματική και κλινική) συνιστώσα του έργου της κλινικής χαρακτηρίζουν εκείνη την πρώιμη περίοδο και τα χαρακτηριστικά αυτά συναπαρτίζουν τον λόγο για τον οποίο ο Καθηγητής κ. Αναγνωστόπουλος αποτέλεσε και εξακολουθεί να αποτελεί για μένα πρότυπο καρδιοχειρουργού και ακαδημαϊκού δασκάλου. Παρά την αφυπηρέτησή του τον Αύγουστο του 2007, είχαν ήδη τεθεί οι βάσεις, που θα επέτρεπαν την μετέπειτα εξέλιξη της Κλινικής. Σ' αυτήν, έχουν μέχρι σήμερα πραγματοποιηθεί περισσότερες από 2.200 επεμβάσεις ανοιχτής καρδιάς όλου του φάσματος της σύγχρονης καρδιοαγγειακής χειρουργικής με αξιοζήλευτα αποτελέσματα και έχουν εφαρμοστεί με απόλυτη επιτυχία πρωτοποριακές για τα ελληνικά δεδομένα σύγχρονες τεχνικές, προβάλλοντας την Πανεπιστημιακή Καρδιοχειρουργική Κλινική του ΕΚΠΑ ως έναν θύλακα κλινικής αριστείας, παρά την εξαιρετικώς αντίξοχη τρέχουσα οικονομική συγκυρία και τις αυξημένες απαιτήσεις, τις συμφυείς με τη φύση της ειδικότητας.

Παράλληλα προς το κλινικό του έργο, εκατοντάδες παρουσιάσεις και δημοσιεύσεις, ελληνικές και διεθνείς, κατέδειξαν την ερευνητική παραγωγικότητα της σταδιοδρομίας του στις ΗΠΑ αλλά και της δεκαπενταετούς παρουσίας του στην Ελλάδα. Η ερευνητική του ενασχόληση με τα θέματα του αορτικού διαχωρισμού, της μετάθεσης των μεγάλων αγγείων, της υποθερμίας και γενικότερα των στρατηγικών προστασίας του νωτιαίου μυελού σε επεμβάσεις επί της θωρακικής και θωρακοκοιλιακής αορτής, της δημιουργίας και διαχείρισης βάσεων δεδομένων και πολλών άλλων, με περισσότερες των 2.500 βιβλιογραφικών αναφορών στη βάση δεδομένων Scopus, αποτελούν μια πράγματι αξιοθαύμαστη ακαδημαϊκή επίδοση για κλινικό καρδιοχειρουργό. Η δε σημαντική διάσταση του εκπαιδευτή και μέντορα καταδεικνύεται μεταξύ άλλων και από το γεγονός ότι πέντε από τους στενούς συνεργάτες του είναι ήδη Διευθυντές – Καθηγητές.

Όλο το επιστημονικό προσωπικό της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής τον ευχαριστεί βαθύτατα για το έργο του. Ιδιαίτερος δε οι παλαιοί στενοί του συνεργάτες νοιώθουμε εξαιρετική χαρά, τιμή και ευγνωμοσύνη για την παρουσία του στον επαγγελματικό μας βίο.

Τέλος, επιτρέψτε μου από τη θέση αυτή να αναφερθώ και στους εκλεκτούς συναδέλφους / Καθηγητές, που ανταποκρινόμενοι αμέσως και με συγκινητικό τρόπο στην πρόσκλησή μου, τίμησαν τον Ομότιμο Καθηγητή κ. Αναγνωστόπουλο και την Πανεπιστημιακή Καρδιοχειρουργική Κλινική με το επιστημονικό τους πόνημα και συνέβαλαν στη δημιουργία αυτού του τόμου, που κατά τη γνώμη μου αποτελεί ένα εξαιρετικό δείγμα της παραγόμενης γνώσης στην Ιατρική Σχολή του ΕΚΠΑ και όχι μόνο. Τους ευχαριστώ όλους εκ βάθους καρδιάς.

Δημήτριος Αγγουράς  
Αναπληρωτής Καθηγητής Καρδιοχειρουργικής  
Ιατρική Σχολή Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

Dimitrios Angouras  
Associate Professor Cardiac Surgery  
from Cardiac Surgery Clinic «Attikon» Hospital

## In place of a Prologue

The Cardiac Surgery Clinic of the National and Kapodistrian University of Athens Medical School was housed and began its clinical and academic work at the “Attikon” Hospital about 11 years ago under the direction of Professor Constantine E. Anagnostopoulos. The initiation of a University Clinic in a developing hospital, especially when its clinical work involves specialized, complex and highly important surgical procedures, requires a profound knowledge of the subject, long experience, unique administrative abilities and absolute commitment to the goal. Professor Anagnostopoulos, combining the above attributes to the highest degree and while overcoming countless adversities of all kinds, not only made the operation of the University Cardiac Surgery Clinic possible but at the same time laid the foundations for the successful continuation of his work after his retirement. This volume is a tribute of the Medical School and especially of the Cardiac Surgery Clinic of the University of Athens for its founding and first manager. It is to me, a student thankful to his teacher and one of his companions during those early efforts, a great joy and a great honour, to contribute to the creation of this volume, as well as the writing of this short foreword/note.

Not one person that knows him and his work will consider it to be an exaggeration saying that Emeritus Professor C. E. Anagnostopoulos is one of the most prominent and internationally recognized Greek cardiac surgeons, with a brilliant academic career in the USA, and an extremely important contribution to shaping the landscape of modern cardiac surgery in our country.

He was born in Thessaloniki in 1940 and completed his high school studies at the Anavryta National School. He studied medicine at Georgetown University, Washington, D.C., where he graduated with honours (M.D. with Honours, 1963). He trained in general and cardiothoracic surgery at Columbia Universities (Columbia Presbyterian Medical Center, New York, NY) and Yale (Yale University School of Medicine, New Haven, CT) where he served as an Instructor in Surgery (1967-1969). He served at the University of Chicago as Assistant, Associate and Tenured Full Professor (1969-1983) and subsequently as Professor and Director of Clinical Cardiothoracic Surgery at the State University of New York at Stony Brook (1983-1991) and Columbia University - St. Luke's / Roosevelt Hospital Center, New York, NY (1991-1998). He held the post of Professor and then Clinical Professor at the University in the years 1998-2016, and since 2016 until today he has been appointed the title of Clinical Professor of

Cardiovascular Surgery at the Icahn School of Medicine at Mount Sinai, New York, NY.

At the same time, and since 1991, he has been actively involved in Greece and his collaboration and contribution to the development of the Cardiac Surgery Clinic of Children and Adults of the Onassis Cardiac Surgery Center was crucial (1991-1998). In 1997 he was elected Professor at the University of Ioannina and organized the Cardiac Surgery Clinic and a productive Experimental Laboratory at that University (1997-2003). He has trained and helped many collaborators distinguish themselves and laid the foundations for the successful course of this regional university clinic. Finally, in 2003 he was elected Professor of Cardiac Surgery at the University of Athens and started the hard work of housing, staffing and organizing the homonymous Clinic, which led to its opening with the first open-heart operation in June 2006. His determination and decisiveness in administration, the wealth of knowledge and experience and his attachment to detail in the clinical dimension, his persistence on the elucidative and research (experimental and clinical) component of clinical trials define that early period, and these features make up the reason why Professor Anagnostopoulos has always been the model of a cardiac surgeon and academic teacher to me. In spite of his retirement in August 2007, the foundations are already in place to allow the clinic to evolve further. More than 2,200 open-heart operations have been carried out to date in most of the spectrum of modern cardiovascular surgery with remarkable results and innovative techniques, never seen before in Greece. These have been applied with great success and have defined the Cardiac Surgery Clinic of the University of Athens as an enclave of clinical excellence, despite the exceptionally adverse current economic situation and the increased demands inherent to the nature of the specialty.

Parallel to his clinical work, there are hundreds of presentations and publications, both Greek and international, that demonstrate the research productivity of his career in the USA and his twenty seven year presence in Greece. His research on acute aortic dissections, on transposition of great vessels, hypothermia, and spinal cord protection strategies during thoracic aortic operations, the creation and management of relevant databases, and more than 3,500 bibliographic citations in the Scopus database are a truly admirable academic performance for a clinical cardiac surgeon. Furthermore, the important dimension of the instructor and mentor is highlighted, among other things, by the fact that five of his close associates are already Department Directors/Professors.

All the scientific staff of the University Cardiac Surgery Clinic thanks him sincerely for his work. His old associates, in particular, feel great joy, honour and gratitude for his presence in our professional life.

Last but not least, let me also thank the honourable colleagues / professors, who responded immediately and in a touching way to my invitation, and honoured Professor Emeritus Anagnostopoulos and the University Cardiac Surgical Clinic with their scientific work and contributions to this volume, which in my opinion, is an excellent example of the knowledge produced in the Medical School of the University of Athens and beyond. I thank them all sincerely from the heart.

Dimitrios Angouras  
Associate Professor of Cardiac Surgery  
Medical School of National and Kapodistrian University of Athens

Γεωργία Γερολουκά-Κωστοπαναγιώτου  
Καθηγήτρια Αναισθησιολογίας Ιατρικής Σχολής ΕΚΠΑ  
Διευθύντρια Β΄ Πανεπιστημιακής Κλινικής

## Πρόλογος

Είναι ιδιαίτερη τιμή και χαρά για εμένα να προλογίζω τον τόμο προς τιμή του Ομότιμου Καθηγητή Καρδιοχειρουργικής της Ιατρικής Σχολής του ΕΚΠΑ κ. Κωνσταντίνο Αναγνωστόπουλο.

Είχα ακούσει από αρκετά χρόνια πριν για έναν Καθηγητή Καρδιοχειρουργικής που άφησε την επιτυχημένη ακαδημαϊκή του καριέρα στις ΗΠΑ και ήλθε στην Ελλάδα, στο Πανεπιστήμιο των Ιωαννίνων, προσπαθώντας εκεί να οργανώσει την Πανεπιστημιακή Καρδιοχειρουργική Κλινική –δύσκολα χρόνια για ένα τέτοιο εγχείρημα σε μια ιδιαίτερα απαιτητική ειδικότητα. Θαύμασα το κουράγιο του!

Γνώρισα τον Καθηγητή Αναγνωστόπουλο το 2004 στο ΠΓΝ «Αττικόν», όντας Επίκουρη Καθηγήτρια Αναισθησιολογίας και Διευθύντρια της νεοσύστατης Β΄ Πανεπιστημιακής κλινικής Αναισθησιολογίας που εγκαταστάθηκε στο νοσοκομείο αυτό το 2003.

Ο κ. Αναγνωστόπουλος μου έκανε εντύπωση για την αγωνία και την επιμονή του να προλάβει να ξεκινήσει πριν αφυπηρητήσει την επίσης νεοσύστατη Πανεπιστημιακή Καρδιοχειρουργική Κλινική της Ιατρικής Σχολής του ΕΚΠΑ. «Άφησα τις ΗΠΑ γι' αυτό το σκοπό και θέλω να με βοηθήσετε εσείς οι Αναισθησιολόγοι να λειτουργήσει η Κλινική μου!» Επειδή δεν έπαιρνε αναβολή η πρόθεσή του και κανείς δεν μπορούσε να του αρνηθεί, παρόλο που και η Αναισθησιολογία τότε αντιμετώπιζε άπειρες δυσκολίες για την έναρξη και οργάνωσή της σε ακαδημαϊκή μονάδα, συνέβαλε στο τολμηρό εγχείρημά του.

Η μεγαλύτερη αγωνία μας αφορούσε την ασφάλεια και την καλή έκβαση των καρδιοχειρουργικών ασθενών. Σημαντικό πρόβλημα ήταν η εκπαίδευση των αναισθησιολόγων στην Καρδιοαναισθησιολογία και των νοσηλευτών μας επίσης, αλλά και στην άρτια λειτουργία της Καρδιοχειρουργικής Μονάδας Μετ-Αναισθητικής Φροντίδας (ή αλλιώς «ΚΡΧ ΜΕΘ») όπως συνηθίζουμε να την αποκαλούμε ακόμη και μέχρι σήμερα χάριν συντομίας!). Ακόμη και Εσωτερικό Κανονισμό λειτουργίας συντάξαμε μαζί και με τον κ. Αναγνωστόπουλο και τον τότε Καθηγητή Καρδιολογίας κ. Δ. Κρεμαστινό. Κάθε αρχή και δύσκολη! Ο Καθηγητής Αναγνωστόπουλος ξενυχτούσε συχνά μετά το πέρας του χειρουργείου δίπλα στον ασθενή και πολλές φορές κοιμόταν στο φορείο μέχρι να βεβαιωθεί ότι ο ασθενής του ήταν από χειρουργικής πλευράς ασφαλής. Συγκρότησε μια Ομάδα νέων και ικανών καρδιοχειρουργών οι οποίοι υλοποίησαν το όνειρό του. Σήμερα, η Πανεπιστημιακή Καρδιοχειρουργική Κλινική στο ΠΓΝ Αττικόν αντιμετωπίζει

ασθενείς όχι μόνον από όλη τη 2<sup>η</sup> ΥΠΕ, δηλ. τη Δ. Αττική συμπεριλαμβανομένων και των νησιών του Αιγαίου, αλλά σχεδόν και από όλη την Ελλάδα.

Η Β' Πανεπιστημιακή Κλινική Αναισθησιολογίας οφείλει ιδιαίτερη τιμή και ευγνωμοσύνη στον καθηγητή Αναγνωστόπουλο, γιατί εξ αρχής αναγνώρισε τη σημασία της συμβολής της στην ανάπτυξη της καρδιοχειρουργικής και κατ' επέκταση στην έκβαση των καρδιοχειρουργικών ασθενών. Ο Καθηγητής Αναγνωστόπουλος είχε άποψη συνεργασία μαζί μας και η επιστημονική άποψή του που πήγαζε μέσα από την πολυετή γνώση και εμπειρία του ήταν πάντα καλοδεχούμενη, εκπαιδευτική και ουσιαστική για τη συνεργασία μας. Έτσι επιτύχαμε. Σήμερα, 12 χρόνια μετά, η Πανεπιστημιακή Καρδιοχειρουργική Κλινική υπό την διεύθυνση του Καθηγητή Δ. Δουγένη, με τους άξιους συνεργάτες του, συνεχίζει το έργο που οραματίστηκε ο καθηγητής Αναγνωστόπουλος.

Σε μια εποχή που το οικονομικό δέλεαρ μαζί με τις οργανωτικές δυσκολίες οδηγούσαν τους καρδιοχειρουργούς στον ιδιωτικό τομέα, αλλά και το πιο πρόσφατο φαινόμενο του «brain drain» που οδήγησε πολλούς ικανούς νέους χειρουργούς να αναζητήσουν την τύχη τους εκτός Ελλάδας, ο καθηγητής Αναγνωστόπουλος όπως και άλλοι καταξιωμένοι επιστήμονες, επέστρεψαν στην πατρίδα και αγωνίστηκαν για να προσφέρουν ένα καλύτερο αύριο ακαδημαϊκής ιατρικής. Ο καθηγητής Αναγνωστόπουλος κατάφερε να δημιουργήσει την 1<sup>η</sup> Πανεπιστημιακή Καρδιοχειρουργική Κλινική της Ιατρικής Σχολής στο Αθήνησι Εθνικόν και Καποδιστριακόν Πανεπιστήμιον, το 2005, να την αναπτύξει και να την φέρει σε επίπεδο μιας σύγχρονης Πανεπιστημιακής Κλινικής. Πολυγραφότατος συγγραφέας, παραδειγματικός ερευνητής, γιατρός με ευρύ πεδίο γνώσεων και πνεύμα ακαδημαϊσμού. Χωρίς ίχνος αλαζονείας, με διακριτικό χιούμορ και έμφυτη καλοσύνη, ακούραστος και πάντα πρόθυμος στην επικοινωνία μαζί του. Προσηνής προς όλους, ασθενείς, νοσηλευτές, γιατρούς, φοιτητές...

Η ακαδημαϊκή ιατρική κοινότητα γενικότερα και ειδικότερα η του ΠΓΝ Αττικών οφείλουμε τιμή στον καθηγητή Κ. Αναγνωστόπουλο. Είμαστε υπερήφανοι που συνεργαστήκαμε μαζί του. Ως Διευθύντρια της ιατρικής Υπηρεσίας του ΠΓΝ Αττικών εκφράζω την εκτίμηση και την αγάπη όλου του κόσμου του «Αττικού» που γνώρισε και συνεργάστηκε μαζί του. Εύχομαι στον τιμώμενο καθηγητή και την οικογένειά του εκ μέρους της ιατρικής Υπηρεσίας του «Αττικόν» υγεία και μακροζωία.

**Κ**αι μιας και η αρχική του επιστημονική καριέρα ήταν στις ΗΠΑ, ας μου επιτραπεί να αναφέρω την φράση του Νίκου Καζαντζάκη αγγλιστί, όπως θα την έλεγε εκεί ο δάσκαλος Κ. Αναγνωστόπουλος: *“True teachers are those who use themselves as bridges over which they invite their students to cross; then, having facilitated their crossing, joyfully collapse, encouraging them to create on their own.”*

Καθηγήτρια Γεωργία Γερολουκά – Κωστοπαναγιώτου  
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## Foreword

It's a special honour and pleasure to write a foreword to a volume in honour of Emeritus Professor of Cardiac Surgery of the Medical School of the University of Athens, Mr Konstantinos Anagnostopoulos.

A few years ago I heard about a Professor of Cardiac Surgery that left his very successful academic career in the USA and came to Greece to the University of Ioannina, trying to organize the University Cardiac surgery clinic – a feat quite challenging during that era in a very demanding specialization. I admired his courage!

I met Professor Anagnostopoulos in 2004 at «Attikon» University General Hospital, while I was an Assistant Professor of Anesthesiology and a Director of the newly established 2nd University Clinic of Anesthesiology which was established in the hospital in 2003.

Dr Anagnostopoulos impressed me with his eagerness and persistence to start the newly established University Cardiology Surgery Clinic of the Medical School of the University of Athens before he retired. «I left the United States for this purpose and I want you the anesthesiologists to help my Clinic function!» Because his will could not be postponed and no one could deny him, even though Anesthesiology then faced countless difficulties in initiating and organizing itself as an academic unit, we contributed to his bold task.

Our greatest anxiety was for the outcome of “open” cardiac surgeries to be a success and for the patients to come out unharmed. An important problem was the training of anesthesiologists in cardiac anesthesia and of our nurses as well, and the well-functioning of the Cardiac Surgery Unit of Post-Anesthesia Care (or “CRT ICU” as we usually call it even today for the sake of brevity!). We even drafted together with Dr Anagnostopoulos and the then Professor of Cardiology Dr D. Kremastinos Internal Rules of Procedure. Every beginning is difficult! Professor Anagnostopoulos often stayed at the end of the open surgical procedure next to

the patient and often slept on the stretcher until he was sure that his patient was surgically safe. He formed a team of young and competent cardiac surgeons who realized his dream. Today, the University Cardiac Surgical Clinic at “Attikon” University General Hospital, treats patients not only from the entire 2nd Attica District (ie Western Attica, including the Aegean islands), but also from all over Greece.

The 2nd University Clinical Anesthesiology owes a special debt of gratitude to Professor Anagnostopoulos since he recognized from the beginning the importance of its contribution to the development of cardiac surgery and consequently to the outcome of cardiac surgical patients. Professor Anagnostopoulos had an excellent cooperation with us and his scientific view that he had gained through his many years of knowledge and experience was always welcome, educational and essential to our cooperation. That’s how we did it. Today, 12 years later, the University Cardiac Surgery Clinic under the direction of Professor D. Dougeni, and his worthy associates continues the work envisaged by Professor Anagnostopoulos.

At a time when the financial attraction along with the organizational difficulties led cardiac surgeons to the private sector, as well as the most recent phenomenon of «brain drain» that led many competent new surgeons to seek their fate outside Greece, Professor Anagnostopoulos and others renowned scientists, returned home and fought to offer a better tomorrow in academic medicine. Professor Anagnostopoulos managed to create the 1st University Cardiac Surgery Clinic of the Medical School in Athens, the National and Kapodistrian University in 2005 to develop and ascend it to the level of a modern University Clinic. He is a prolific writer, an exemplary researcher, a physician with a broad field of knowledge and a spirit of scholarship. He is without a trace of arrogance, but with distinctive humour and innate goodness, tireless and always willing when communicating and kind to everyone, patients, nurses, doctors, and students.

The academic medical community in general and, in particular, the “Attikon” University General Hospital, owe a great debt to Professor C.E. Anagnostopoulos. We are honoured to have worked with him. Also, as the Director of the Medical Service of “Attikon» University General Hospital I express the appreciation and the love of everyone in «Atticon» that met and collaborated with him. I wish the Honored Professor and his family on behalf of the “Attikon” Medical Service Center health and prosperity.

*And since his original scientific career was in the US, let me mention the phrase of Nikos Kazantzakis in English, as would the teacher Constantine Anagnostopoulos say it: «True teachers are those who use themselves as bridges over which they invite their students to cross; then, having facilitated their crossing, joyfully collapse, encouraging them to create on their own.»*

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Διευθυντής Καρδιοχειρουργικής Κλινικής «Αττικών»  
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## Τιμής Ένεκεν

Ήταν καλοκαίρι του 1980 όταν ως εφημερεύων νέος ειδικευόμενος χειρουργός ήλθα σε επαφή με την θανατηφόρα επιπλοκή του οξέος αορτικού διαχωρισμού, τη ρήξη και το αιμοπερικάρδιο. Οι εικόνες αυτές σημάδεύτηκαν στο μυαλό μου και με έκαναν να αναζητήσω με τα πενιχρά μέσα που είχαμε τότε σχετική βιβλιογραφία. Με επιμονή και κόπο βρήκα μία αναφορά στο Index Medicus, μια πρόσφατα δημοσιευμένη εργασία στο Am J Cardiology, συγγραφείς Anagnostopoulos CE et al.

Από τότε ένιωθα επιστημονικό δέος και βαθύτατη εκτίμηση για τον πρωτοπόρο αυτόν επιστήμονα της διασποράς που με ενθουσίασε με την εργασία του. Ήταν η πρώτη ακαδημαϊκή «διηπειρωτική γνωριμία» με τον τιμώμενο σήμερα Ομότιμο Καθηγητή Κωνσταντίνο Αναγνωστόπουλο. Μια γνωριμία που σημάδευσε τα πρώτα επιστημονικά μου βήματα και αναμφισβήτητα με επηρέασε στην απόφασή μου να ασχοληθώ με την Καρδιοθωρακική Χειρουργική. Έκτοτε, μου άρεσε να διατηρώ ως νεότερος αυτή τη μυστική σχέση και να παρακολουθώ την ανοδική του πορεία.

Αργότερα, δεν ήταν έκπληξη για μένα το γεγονός ότι έγινε ο μοναδικός επιστήμονας στη χώρα μας που «άνοιξε» δύο Καρδιοχειρουργικές Πανεπιστημιακές κλινικές, στο Πανεπιστήμιο Ιωαννίνων και στο Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών (ΕΚΠΑ). Δεν φανταζόμουν όμως ποτέ ότι θα είχα τη τιμή να συνυπάρξουμε παράλληλα καθηγητές σε δυο περιφερειακά πανεπιστήμια και Ιατρικές σχολές, εγώ στην Πάτρα και αυτός στα Ιωάννινα. Ούτε βέβαια φανταζόμουν ότι θα έλθει στιγμή που ένας συνεργάτης από την τότε κλινική μου στο Πανεπιστημιακό Νοσοκομείο Πατρών, ο νυν Καθηγητής Καρδιοχειρουργικής Ε. Αποστολάκης θα τον διαδεχθεί ως Καθηγητής στα Ιωάννινα. Και πόσο μάλλον, ότι θα έχω την τιμή να τον διαδεχθώ ως Καθηγητής στην Αθήνα στο Πανεπιστημιακό Γενικό Νοσοκομείο «Αττικών».

*Τύχη αγαθή έδοξε* για με να γράφω αυτό το σύντομο εισαγωγικό σημείωμα για τον τιμητικό τόμο του επιστήμονα που πριν 37 χρόνια είχα «γνωρίσει» και βαθύτατα έκτοτε εκτιμήσει. Θεωρώ ότι ο Ομότιμος Καθηγητής Κ. Αναγνωστόπουλος υπήρξε ίσως ο καλύτερος ανάμεσα στους καλύτερους Έλληνες Καρδιοχειρουργούς, διαθέτοντας σε υπερθετικό βαθμό την απόλυτη τριάδα: **άριστος χειρουργός, ερευνητής, δάσκαλος**.

Ο ανά χείρας τόμος είναι μόνο ένα ελάχιστο δείγμα αναγνώρισης, γιατί η μεγάλη αναγνώριση υπάρχει διάχυτα ριζωμένη στην Ελληνική Καρδιοθωρακοχειρουργική κοινότητα, η οποία του οφείλει πολλά. Ως πρώην πρόεδρος της δε αισθάνομαι περήφανος που ένα μέλος της είχε διεθνή εξέλιξη, αλλά και σημαντικότερη παρουσία στη χώρα μας, συνδυασμός δύσκολος μα εξαιρετικά σημαντικός. Οι νεότεροι οφείλουν να τον έχουν ως πρότυπο και παράδειγμα στην επιστημονική και ακαδημαϊκή τους πορεία.

Ευελπιστώ να συμβάλλω στην περαιτέρω ανάπτυξη και διεθνή επιστημονική αναγνώριση της ήδη διακεκριμένης Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής, ΕΚΠΑ, που δημιούργησε ο Κωνσταντίνος Αναγνωστόπουλος και οι εξαιρετικοί του συνεργάτες συνεχίζουν. Στον τιμώμενο και την οικογένεια του εύχομαι Υγεία, Χαρά και Ευτυχία. Πιστεύω ότι θα τον έχουμε κοντά μας να τον συμβουλευόμαστε, η δε πληθωρική και εκ φύσεως νεανική του προσωπικότητα θα βρει και άλλους δρόμους έκφρασης και παράλληλης με την Χειρουργική δημιουργίας. Η Ελληνική Καρδιοθωρακοχειρουργική κοινότητα είναι περήφανη για την τεράστια συμβολή του και εμείς πάντα ευγνώμονες για το έργο του.

Δημήτριος Δουγένης

Αθήνα 22/9/2017

Dimitrios Dougenis  
Professor of Cardiac Surgery  
Director Cardiac Clinic «Attikon» Hospital  
National and Kapodistrian University of Athens

## In Tribute

It was summer 1980 when, as an on-duty new surgeon, I came into contact with the lethal complications of acute aortic dissection, hemopericardium and rupture. These images were marked in my mind and made me search in the relevant bibliography with the meager means we had at that time. With perseverance and effort, I found a reference in Index Medicus, a recently published work in Am J Cardiology, authors Anagnostopoulos CE et al.

Since then I have felt a scientific awe and a deep appreciation for this pioneering scientist of the diaspora who fascinated me with his work. It was the first academic intercontinental acquaintances with the currently honoured Emeritus Professor Constantine Anagnostopoulos. An acquaintance that has marked my first scientific steps and has undoubtedly influenced my decision to get into Cardiothoracic Surgery. Since then, I liked to keep this secret relationship with him as a younger doctor and to follow his upward course.

Later, it came as no surprise to me that he was the only scientist in our country to open two Cardiac Surgery Clinics, at the University of Ioannina and at the National & Kapodistrian University of Athens. But I had never imagined that I would have the honour of being colleagues with him at two regional universities and medical schools, him in Ioannina and me in Patra. Nor did I imagine that a colleague from the clinic at the University Hospital of Patras where I used to work back then, now Professor of Cardiac Surgery E. Apostolakis would succeed him as a Professor in Ioannina. All the more, I would have the honour of succeeding him as a Professor in Athens at Attikon University Hospital.

“By fortune’s grace” (as the ancient Greeks would say when gathering in the Pnyka hill in front of the Acropolis to introduce some new law to a democratic vote) it was a pleasure for me to write this short introductory note on the honorary volume of the scientist that 37 years ago I had «met» and have deeply appreciated ever since. I consider that Emeritus Professor C. E. Anagnostopoulos was probably the best among the best Greek cardiac surgeons, possessing to the superlative degree the absolute

triad: excellent surgeon, researcher, and teacher. This volume is only a minimal example of recognition because great recognition already exists widely in the Greek Cardiothoracic Surgery community, which owes much to him. As a former chairman, I feel proud that one of its members has advanced internationally but also contributed a very important presence in our country, a combination that is difficult but extremely important. The younger ones should view him as a model and example in their scientific and academic careers.

I hope to contribute to the further development and international scientific recognition of the already distinguished University Cardiac Surgery Clinic, which was created by Constantine Anagnostopoulos and that his outstanding collaborators now continue. To the honoree and his family, I wish Health, Joy and Happiness. I believe we will have him with us to consult, and his exuberant and inherently youthful personality will find yet other ways of expression in parallel to creative Surgery. The Hellenic Cardiothoracic Surgery community is proud of his enormous contribution and we are always grateful for his work.

Dimitrios Dougenis

Athens 22/9/2017

# Constantine E. Anagnostopoulos M.D. (2017)

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Date of birth: November 9, 1940  
Place of birth: Salonica, Greece  
Came to the U.S. in 1958 after my father became Commercial Counselor of  
the Greek Embassy, Washington, DC  
Citizenship: United States and Hellenic  
Married, 1983: Madelaine Low Reese (after my first wife, Dr. Marilyn Hruby, died in 1980)  
Children: Dr. Anne-Marie Anagnostopoulos, Dr. Peter Reese, Dr. Annie Reese

## Grammar and High School (Gymnasium)

1946-1958 Athens, Greece - Psychiko and Anavryta National School (honors June 1958)

## Academic Training:

Georgetown University, Washington, D.C.  
A.B. with honors, September 1959  
M.D. with honors, May 1963  
University of Athens, Greece, School of Medicine, Equivalence Examinations,  
June 1963  
Doctor of Science, University of Athens, Athens Greece-with honors, 1967

## Medical Licensure –

1965 State of Washington  
1965 Athens, Greece  
1969 State of Illinois  
1982 State of New York #152539 -active 2001 State of New Jersey

Traineeship:

1963-1964	Columbia University, Columbia Presbyterian Medical Center, New York, New York; Surgery
1964-1969	Yale University, School of Medicine, General and Thoracic Surgery
1964-1965	Yale University School of Medicine, U.S.P.H.S. Fellow, Cardiovascular Surgery

Board Certification:

1964	National Board of Medical Examiners
1970	American Board of Surgery
1970	American Board of Thoracic Surgery
1970	General and Thoracic Surgery Certification in Greece

Military Service:

Registered for U.S. and Hellenic Selective Service 1-A to 1972

Professional Organizations and Societies:

1965	American Heart Association, Cardiovascular Surgery Member
1965	Sigma Xi Honor Scientific Society Athens Medical Society
1970	Association for Academic Surgery
1970	Fellow, American College of Cardiology
1972	Fellow, American College of Surgeons
1972	International Cardiovascular Society
1973	Chicago Surgical Society
1974	American Association for Thoracic Surgery
1975	European Society for Surgical Research
1976	Chicago Heart Association Committee on Cardiovascular Surgery
1980	Society for Vascular Surgery
1983	American Medical Association
1984	International Society for Heart Transplantation
1989	Suffolk County Medical Society
1992	New York County Medical Society
1991	New York Society for Thoracic Surgeons
1993	The New York State Society of Surgeons, Inc.
1995	Hellenic Society for Cardiothoracic Surgery
1996	The Yale Surgical Society
1996-99	Harvard Medical School Dean's Council
1996	The University of Chicago Surgical Society
2008	Athens Greece Academy of Medicine
2009	JOHN JONES Surgical Society, Columbia University

Academic and Hospital Appointments ( USA )

	<u>Yale University School of Medicine</u>
1967-1969	Instructor in Surgery
	<u>The University of Chicago</u>
1969-1973	Assistant Professor of Surgery Thoracic and Cardiovascular Surgery
1973-1979	Associate Professor of Surgery Thoracic and Cardiovascular Surgery
1979-1983	Professor of Surgery
	<u>State University of NY at Stony Brook</u>
1982 - 1991	Chief, Division of Cardiothoracic Surgery
1982 - 1991	Professor and Attending in Surgery
	<u>St. Luke's/Roosevelt Hospital Center, NY, NY</u> <u>A University Hospital of Columbia University</u> <u>College of Physicians &amp; Surgeons to Dec.2014</u>
1991 - 1998	Sr. Attending, Chair and Chief, Division of Cardiothoracic Surgery Professor of Surgery
1998-2007	Sr. Attending, Division of Cardiothoracic Surgery Professor of Surgery
2008- 2016	Clinical Professor of Surgery Columbia University Medical Center Senior Attending Cardiac Surgery St. Luke's Roosevelt Hospital at Columbia University NY
2016-	Clinical Professor of Cardiovascular Surgery Icahn/ Mount Sinai School of Medicine Senior Attending Cardiac Surgery /MtSinai/St. Luke's Hospital

Consulting and Other Appointments ( USA and Greece )

Jul - Aug 1973	<u>Massachusetts General Hospital, Harvard University, Boston, Mass.</u> Sabbatical Visit
1975	<u>Michael Reese &amp; St. Elizabeth's Hospital., Chicago</u> Visiting Consultant
1976	<u>Christ Hospital Oak Lawn, Chicago</u> Visiting Consultant
1985	<u>Veterans Administration Medical Center, Northport, NY</u> Visiting Consultant
1992-2002	<u>Harlem Hospital Center, New York, NY</u> <u>Affiliated with Columbia University</u> <u>College of Physicians &amp; Surgeons</u> Consultant, Cardiac Surgery and Cardiology Chief, Cardiothoracic Surgery - 1998
1993-1998	<u>Onassis Heart Surgery Center, Athens, Greece</u>

	Honorary Chair Surgery and Founder of Clinic of Pediatric Cardiac Surgery
1997-2003	<u>University of Ioannina</u> , Greece Professor of Cardiac Surgery Founder of Clinic of Cardiothoracic Surgery
1997-2001	<u>Euroclinic Medical Center</u> , Athens Greece Consulting Scientific Director Founder of Clinic of Cardiothoracic Surgery
2003-2007	National and Kapodistrian <u>University of Athens</u> , Greece Professor of Cardiac Surgery, Founder of Clinic of Cardiothoracic Surgery Attikon Hospital Center
2007-	Professor Emeritus of Cardiac Surgery

Honors and Awards:

A.B., M.D. and Sc.D. with honors  
 Alpha Omega Alpha Honor Medical Society, 1961  
 Established Investigator, American Heart Association, 1971-76  
 Teaching Award, Medical Class of 1978. The University of Chicago  
 Who's Who in America, 1978  
 "Paul Harris Fellow" - Rotary Club International, 1987  
 Graduating Chief Residents in Surgery – 1988  
 Appreciation Plaque, University Hospital at Stony Brook  
 St. Paul's Medal - Archdiocese of North and South America  
 of the Greek Orthodox Church, Glen Cove, NY, 1989  
 "KRIKOS" Scientific Organization - Honored guest and Lecturer,  
 New York, NY 1991  
 Hellenic Medical Society of New York - Honored Guest and Lecturer,  
 New York, NY 1993

Fellowship, Research, Fundraising, and Support for Clinical Projects (as principal investigator):

1971-1973	American Heart Association "Rectus Sheath Cardiovascular Grafts"
1971-1976	American Heart Association, \$75,000 Established Investigator award
1973-1975	U.S.P.H.S. (NIH), \$80,000, American Heart \$30,000 "Animal Model Transposition of Great Vessels I and II"
1973-1975	U.S.P.H. (NIH) \$45,000 "Rectus Sheath, Vascular Grafts"
1975-1977	U.S.P.H.S. (NIH) \$45,000 "S.C.O.R. - Retrograde Coronary Venous Perfusion"
1983-1984	GRS Support - S.U.N.Y. at Stony Brook "Rectus Sheath Aortic Valve"
1984-1986	CPMP Support - S.U.N.Y. at Stony Brook "Growing Vascular Grafts"
1986-1989	Stony Brook Foundation - S.U.N.Y. at Stony Brook - "International

	Children's Program"
1986-1989	University Hospital at Stony Brook "Teaching Case Support" International Children's Program
1987-1989	Greek Orthodox Church at Pt. Jefferson and Glen Cove, New York - \$35,000 for Transport Needs, International Children's Program
1987	Rotary Club International "Gift of Life"
1987	"Heal The Children Program"
1989	"Vascucare Company" Research use of \$40,000 Angioscopy equipment
1990	GRS Support-Autologous Grafts and Growth (Co-Investigator) \$12,000
1991	Variety Club International Program
1991	Sphinx Pharmaceuticals Grant in Aid \$32,000 Protein Kinase Inhibitor and Cardiac Cross Clamp Injury - canine model
1992-1994	Sphinx Pharmaceuticals Grant in Aid \$64,000 Protein Kinase Inhibitor and Cardiac Cross Clamp Injury - canine and isolated heart models
1993-1996	Onassis Cardiac Surgery Center, Athens, Greece. Clinical Affiliation \$250,000
2000-2003	St. Jude International Research Grant-University of Ioannina Greece \$130,000
2003-2007	"Pythagoras" and "Kapodistria" Research grants University of Athens, Greece Euro 65,000
2009-present	"Kapodistria" Research grants University of Athens, Greece Euro 85,000

Departmental and University Committees:

St. Luke's-Roosevelt Hospital Center:

Heart Center Advisory Committee - 1995

Invasive Procedures Quality Assurance Subcommittee - Chair, 1992

Executive Committee of the Department of Surgery, 1991

SUNY and University of Chicago

Credentials Committee

Operating Room Committee

Teaching:

- Weekly 3rd year medical student surgery course (U of Chicago and SUNY)
- Daily clinical operative teaching and rounds in intensive care unit with attending surgeons, residents, and students (3rd and 4th year elective) - St. Luke's/Roosevelt, (Columbia University) State University of New York at Stony Brook and the Univ. of Chicago
- Cardiac Anatomy and Embryology Course - The Univ. of Chicago
- Weekly Cardiac Surgery Conference, Journal Club (SLRHC), Weekly Cath Conference, (HHC)
- Cardiac Surgery Course, University of Ioannina.
- Cardiac Surgery Course, University of Athens Greece

Editorial Boards and National Committees:

1985 -2001	Cardiology Board Review
1992-present	Journal of Cardiovascular Surgery
1995-2002	Video Journal of Cardiothoracic Surgery
1997- 1998	Society of Thoracic Surgeons Committee on Nomenclature and Coding
1998-2000	Joint Committee on Nomenclature and Coding, American Association of Thoracic Surgery/Society of Thoracic Surgery
2007-2008	Society of Thoracic Surgery Council on Health Policy-Workforce on International Relationships
2016-	The Scientific Pages of Anesthesia and Pain Management

**Original, Peer Reviewed Articles - Chapters**

- Holcomb WG, **Anagnostopoulos CE**, Glenn WWL. A New Method of Determining Tissue Resistance by the Reflectometer Principle, for Use With Implanted RF Pacemakers; Laboratory and Clinical Observation on Cardiac, Bladder, and Phrenic Nerve pacemakers. *Trans NY Acad Sci*; Ser. II, 27:894-908, 1965.
- Anagnostopoulos CE\***, Glenn WWL, Holcomb WG, Van Heeckeren DW. Epicardial Radiofrequency Cardiac Pacemaker Implant. *Cardiovasc Surg* 1965: Suppl. I to *Circulation* Vols. XXXIII and XXXIV: I 99-106, 1966.
- Anagnostopoulos CE\***, Glenn WWL. Electronic Pacemakers of the Heart, Gastrointestinal Tract, Phrenic Nerve, Bladder, and Carotid Sinus: Current Status. *Surgery*; 60: 480-494, 1966.
- Anagnostopoulos CE\***, Holcomb WG, Glenn WWL. Pacemaker Synchronization. *Science*; 153:1636-1637, 1966.
- Anagnostopoulos CE\***, Hume M. Idiopathic Hypertrophic Subaortic Stenosis: Transventricular Infundibulectomy Under Cardiopulmonary Bypass. *Acta Chir Helen*; 633-644, 1967.
- Anagnostopoulos CE\***, Kabemba JM, Stansel HC Jr. Control of a bleeding intercostalaneurysm with the aid of partial pump-oxygenator bypass. *Ann Thorac Surg.* 1969Oct;8(4):358-60.
- Shapiro DH, **Anagnostopoulos CE\***, Dineen JP. Decortication and pleurectomy for the pleuropulmonary complications of pancreatitis. *Ann Thorac Surg.* 1970 Jan;9(1):76-80.
- Anagnostopoulos CE\***, DeLeuchtenberg N, Talner NS. Trans-position of the Great Arteries. *Conn Med*; 34:573-577, 1970.
- Anagnostopoulos CE\***, Patel B, Fenn JE, Stansel HC. Transvenous Coronary Sinus Pacemaker: A New Primary Approach to Heart Block in Patient with Tricuspid Prostheses. *Ann Thorac Surg*; Mar;9(3):248-52. 1970
- Anagnostopoulos CE\***, Kittle CF. The surgical aspects of acute myocardial infarction. Current status of infarctectomy, ventricular septal defect closure, mitral valve replacement, and revascularization. *Surg Clin North Am.* 1971 Feb;51(1):69-84.
- Anagnostopoulos CE\***, DeLeuchtenberg N, Talner NS, Stansel HC Jr. Transposition of the great arteries. Two successful open-heart corrections with the Mustard operation. *Conn Med.* 1970 Aug;34(8):573-7.
- Prabhakar MJ, Redding ME, **Anagnostopoulos CE\***, Kittle CF. Gas gangrene complicating aortic dissection. Report of a case. *Arch Surg.* 1971 Jul;103(1):96-7
- Redding ME, **Anagnostopoulos CE**, Ultmann JE. The possible value of mediastinoscopy in staging Hodgkin's disease. *Cancer Res.* 1971 Nov;31(11):1741-5.
- Altman DB, **Anagnostopoulos CE**, Kittle CF Hypoplasia of the left first rib in a child with Down's syndrome and an endocardial cushion defect. *Thorax.* 1972 Jan;27(1):100-1.
- Kittle CF, **Anagnostopoulos CE**. Chest Wall. In: Nora PF ed. *Operative Surgery, Principles and Techniques.* Philadelphia: Lea & Febiger; 257-270, 1972.

16. **Anagnostopoulos CE.\*** The Autologous Rectus Sheath Cardiac Valve Graft. *Surgical Forum*; 23:164-166, 1972.
17. **Anagnostopoulos CE\***, Athanasuleas CL, Kittle CF. The Autologous Rectus Sheath Valve, II: Pulmonary Valve and Artery Replacement in the Calf. *J Thorac Cardiovasc Surg*; 63:665-673, 1972.
18. **Anagnostopoulos CE\***, Kittle CF Penetrating wounds of the heart and great vessels: a report of 30 operated patients, six with ventricular wounds. *Proc Inst Med Chic.* 1972 Mar;29(2):83-4.
19. **Anagnostopoulos CE\***, Prabhakar MJ, Kittle CF. Aortic dissections and dissecting aneurysms. *Am J Cardiol.* 1972 Aug;30(3):263-73..
20. Redding ME, **Anagnostopoulos CE**, Wright HK Cholecystopyloric fistula with gastric outlet obstruction: a rare form of gallstone ileus and its management. *Ann Surg.* 1972 Aug;176(2):210-2.
21. **Anagnostopoulos CE\*** Direct coronary artery surgery. *Med Clin North Am.* 1973 Jan;57(1):219-30.
22. Athanasuleas CL, **Anagnostopoulos CE\***, Kittle CF. The Autologous Rectus Sheath Valve, III Design and Physical Properties. *J Thorac Cardiovasc Surg*; 65:118-123, 1973.
23. **Anagnostopoulos CE\***, Kittle CF. Penetrating Wounds of the Heart and Great Vessels. *Thorax*; 28: 142-146, 1973.
24. **Anagnostopoulos, CE.\*** A Proposed New Technique for Correction of Transposition of the Great Arteries. *Ann Thorac Surg*; 15:565-569, 1973.
25. Coleman PG, Martini DJ, Resnekov L, **Anagnostopoulos CE** Forty-two month follow-up of a semilunar valve homograft to the mitral area. Report of a case. *J Thorac Cardiovasc. Surg.* 1973 Jun;65(6):887-9
26. Campbell DP, **Anagnostopoulos CE\***, Glenn WWL. Selection of Patients with Portal Hypertension for Splendorenal Shunt. *Ann Surg*; 178:70-74, 1973.
27. **Anagnostopoulos CE\***, Coleman PG, Taussig HB, Resnekov L, Cassels DE Single ventricle and pulmonary stenosis. Surgical management in a patient over a period of 25 years. *Am J Cardiol.* 1973 Nov;32(6):855-9. No abstract available.
28. **Anagnostopoulos CE\***, Athanasuleas CL, Arcilla RA. Toward a Rational Operation for Transposition of the Great Arteries. *Ann Thorac Surg*; 16:458-463, 1973.
29. Campbell DP, Parker D, **Anagnostopoulos CE.\*** Survival Prediction in Portacaval Shunts: A Computerized Statistical Analysis. *Am J Surg*; 126:748-751, 1973.
30. Balderman SC, Athanasuleas CL, **Anagnostopoulos CE\***. The atrial baffle operation for transposition of the great arteries. A review of 591 reported cases. *Ann Thorac Surg.* 1974 Feb;17(2):114-21.
31. Balderman SC, Athanasuleas CL, **Anagnostopoulos CE.\*** Coronary Artery Anatomy in Transposition of the Great Vessels in Relation to Anatomic Surgical Correction. *J Thorac Cardiovasc Surg*; 67:208-212, 1974.
32. Stratoudakis AC, Kittle CF, **Anagnostopoulos CE.** Haemobilia from ruptured right hepatic artery aneurysm. A complication after aortic valve replacement. *J R Coll Surg Edinb.* 1974 Sep;19(5):305-9.
33. Wang T, **Anagnostopoulos CE**, Resnekov L Aneurysm of the body of the left atrium presenting with chest pain. *Chest.* 1975 Feb;67(2):226-8.
34. Record 38 of 50 Author(s): Russell, Ro; Moraski, Re; Kouchoukos, N; Karp, R; Mantle, Ja; Rackley, Ce; Resnekov, L; Falicov, Re; Alsadir, J; Brooks, H; **Anagnostopoulos, CE**; Lamberti, J; Wolk, M; Gay, W; Killip, T; Ebert, P; Rosati, R; Oldham, N; Mittler, B; Peter, R; Conti, Cr; Ross, Rs; Brawley, Rk; Plotnick, G; Gott, VI; Donahoo, Js; Becker, Lc; Hutter, Am; Desanctis, Rw; Gold, Hk; Leinbach, Rc; Mundth, Ed; Buckley, Mj; Austen, Wg; Hodges, M; Biddle, Tl Deweese, Ja; Yu, Pn; Schroeder, J; Stinson, E; Silverman, J; Willman, V; Cornfield, J; Reeves, Tj; Frommer, Pl; Kaplan, E; Gilbert, Jp; Newell, J Title: Unstable Angina-Pectoris - National Cooperative Study-Group To Compare Medical And Surgical Therapy .1. Report Of Protocol And Patient Population Source: *American Journal Of Cardiology*, 37 (6): 896-902 1976
35. Lamberti JJ, **Anagnostopoulos CE**, Al-Sadir J, Gupta DS, Lin CY, Replogle RL, Resnekov L, Skinner DB. Mechanical circulatory assistance for the treatment of complications of coronary

- artery disease. *Surg Clin North Am.* 1976 Feb;56(1):83-94.
36. Toscano M, Demos SS, Athanasuleas CL, Moraldi A, **Anagnostopoulos CE**.\* Treatment of Experimental Acute Myocardial Ischemia by Arterialization of the Coronary Veins. *Il Policlinico: Sezione Chirurgica*; 83(1-2):385-390, 1976.
  37. Kampman K, Lamberti JJ Jr, Lyons RT, **Anagnostopoulos CE**. Myocardial depression following acute decrease in serum ionized calcium. *Surg Forum.* 1977;28:252-4.
  38. Lamberti JJ, Gupta DS, Falicov R, **Anagnostopoulos CE** An unusual form of late stenosis after aortic valve replacement with a cloth-covered Starr-Edwards prosthesis. *Chest.* 1977 Jan;71(1):89-90.
  39. Balderman SC, Bates RJ, Toscano M, , **Anagnostopoulos CE**. The cardiac veins and retrograde coronary venous perfusion. *Ann Thorac Surg.* 1977 Jan;23:83-90.
  40. Balderman SC, Bates RJ, **Anagnostopoulos CE**.\* Cardiac Valve Replacement: Improved Survival Related to Air Exclusion and Myocardial Protection. *Illinois Med J*; 2:113-116, 1977.
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  68. Constantine E. Anagnostopoulos, Ioannis K. Toumpoulis, Stavros N. Siminelakis, Demosthenes G. Katritsis, John P.A. Ioannidis, Cliff P. Connery, Daniel G. Swistel. What Is The Mortality and Recuperative Difference of Bilateral versus Single Thoracic Artery Coronary Revascularization in Patients with Reoperation or Over 80 Years of Age? 14<sup>th</sup> Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery, October 9-12, Rhodes, Greece 2002.
  69. Ioannis K. Toumpoulis, Constantine E. Anagnostopoulos, George E. Drossos, Vassiliki D. Malamou-Mitsi, Lina S. Pappa and Demosthenes G. Katritsis. Early Ischemic Preconditioning Prevents Spinal Cord Injury Due to Descending Thoracic Aortic Occlusion. 14<sup>th</sup> Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery, October 9-12, Rhodes, Greece 2002.
  70. Petros V. Anagnostopoulos, Ioannis K. Toumpoulis, George E. Drossos, Alexander D. Shepard, Agathoclis Tsatsoulis, Demosthenes G. Katritsis, Constantine E. Anagnostopoulos. Temporary Adrenal Dysfunction with Descending Thoracic Aortic Occlusion. 14<sup>th</sup> Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery, October 9-12, Rhodes, Greece 2002.
  71. Toumpoulis IK, Anagnostopoulos CE, Shennib H, DeRose JJ, Swistel DG. Influence of innovative techniques on mid-term results in off-pump coronary artery bypass. Cardiothoracic Technologies and Techniques, 9<sup>th</sup> Annual Meeting, March 19-22, Miami, FL, United States 2003.
  72. Toumpoulis IK, Connery C, Siminelakis S, Anagnostopoulos C. How to demonstrate superiority of mitral valve repair over replacement: five to ten-year results with isolated and combined operations. 3<sup>rd</sup> International Meeting, 10<sup>th</sup> Anniversary of the Onassis Cardiac Surgery Center, April 10-13, Athens, Greece 2003.
  73. Anagnostopoulos CE, Toumpoulis IK, Swistel DG, DeRose JJ, Ioannidis JPA. Late superiority of double artery coronary revascularization. 3<sup>rd</sup> International Meeting, 10<sup>th</sup> Anniversary of the Onassis Cardiac Surgery Center, April 10-13, Athens, Greece 2003.
  74. Anagnostopoulos CE, Toumpoulis IK, DeRose JJ, Siminelakis SN, Katritsis DG. What is the mortality and recuperative difference of bilateral versus single thoracic artery coronary revascularization in patients with reoperation or over 80 years of age? 3<sup>rd</sup> International Meeting, 10<sup>th</sup> Anniversary of the Onassis Cardiac Surgery Center, April 10-13, Athens, Greece 2003.
  75. Toumpoulis IK, Anagnostopoulos CE, Shennib H, DeRose JJ, Swistel DG. Influence of innovative techniques on mid-term results in patients with OPCAB and MIDCAB surgery. ISMICS 6th Annual Meeting, June 19-21, San Francisco, United States 2003.
  76. Anagnostopoulos CE, Toumpoulis IK, Swistel DG, DeRose JJ. What is "best practice in patients undergoing coronary artery bypass grafting? Perceived early advantages may not constitute late superiority. European Society of Cardiology Congress 2003, August 30 to September 3, Vienna, Austria 2003.
  77. DeRose JJ, Toumpoulis IK, Anagnostopoulos CE, Belsley SJ, Ashton RC, Hillel Z, Shaw R, Swistel DG. Long-term survival following coronary artery bypass grafting for ischemic cardiomyopathy. European Society of Cardiology Congress 2003, August 30 to September 3, Vienna, Austria 2003.
  78. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. EuroSCORE predicts long-term

- survival in patients with CABG. 2nd EACTS/ESTS Joint Meeting, October 12-15, Vienna, Austria 2003.
79. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. The impact of deep sternal wound infection on long-term survival after coronary artery bypass grafting. American College of Cardiology Annual Meeting, March 7-10, New Orleans, LA, USA 2004.
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  81. Toumpoulis IK, Papakostas JC, Matsagas MI, Malamou-Mitsi VD, Pappa LS, Anagnostopoulos CE. Early ischemic preconditioning is superior to late ischemic preconditioning in spinal cord protection after descending thoracic aortic occlusion. AATS 84th Annual Meeting, April 25-28, Toronto, Ontario, Canada 2004.
  82. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. Early and midterm outcome after off-pump coronary artery bypass grafting in patients with left ventricular dysfunction. ISMICS 7th Annual Meeting, June 23-26, London, United Kingdom 2004.
  83. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. The impact of diabetes mellitus on long-term survival after coronary artery bypass grafting. European Society of Cardiology Congress 2004, August 28 – September 1, Munich, Germany 2004.
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  86. Toumpoulis IK, Anagnostopoulos CE, Ashton RC, Connery CP, DeRose JJ, Swistel DG. Risk factors for respiratory failure and long-term survival following coronary artery bypass grafting. Chest 2004 Congress, October 23-28, Seattle, WA, USA 2004.
  87. Toumpoulis IK, Anagnostopoulos CE, Katritsis DG, DeRose JJ, Swistel DG. Preoperative thrombolysis improves long-term survival after coronary artery bypass grafting. American Heart Association, Scientific Sessions 2004, November 7-10, New Orleans, LA, USA 2004.
  88. Toumpoulis IK, DeRose JJ, Balaram S, Ioannidis JP, Belsley S, Ashton RC, Swistel DG, Anagnostopoulos CE. Preoperative prediction of long-term survival following coronary artery bypass grafting in patients with low left ventricular ejection fraction: the HAVOC score. American Heart Association, Scientific Sessions 2004, November 7-10, New Orleans, LA, USA 2004.
  89. Toumpoulis IK, Anagnostopoulos CE, Balaram S, Swistel DG, Ashton RC, DeRose JJ. Does bilateral internal thoracic artery grafting increase long-term survival in diabetic patients? 41st Annual Meeting of the Society of Thoracic Surgeons, January 24-26, Tampa, FL, USA 2005.
  90. Toumpoulis IK, Anagnostopoulos CE. Superiority of early relative to late ischemic preconditioning in spinal cord protection. The 4th Athens Exchange of Cardiovascular Research Ideas. February 3-5, Athens, Greece 2005.
  91. Toumpoulis IK, DeRose JJ, Swistel DG, Anagnostopoulos CE. The impact of chronic obstructive pulmonary disease on long-term survival following coronary artery bypass grafting. 9th State-of-the-Art Interdisciplinary Review Course on Pulmonary Diseases Critical Care Emergency Medicine & Nursing Care, April 22-24, Athens, Greece 2005.
  92. Toumpoulis IK, Ioannidis JP, Toumpoulis SK, DeRose JJ, Swistel DG, Anagnostopoulos CE. Does EuroSCORE predict long-term mortality after cardiac surgery? 6th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke, May 14-16, Washington, DC, USA 2005.
  93. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. Risk factors for sepsis and endocarditis and long-term survival following cardiac surgery. 6th Scientific Forum on Quality

- of Care and Outcomes Research in Cardiovascular Disease and Stroke, May 14-16, Washington, DC, USA 2005.
94. Toumpoulis IK, Anagnostopoulos CE, Balam SK, Rokkas CK, Swistel DG, Ashton RC, DeRose JJ. Assessment of independent predictors for long-term mortality between women and men following coronary artery bypass grafting: are women different than men? Western Thoracic Surgical Association 31st Annual Meeting, June 22-25, Victoria, British Columbia, Canada 2005.
  95. Toumpoulis IK, Anagnostopoulos CE, Chamogeorgakis T, Swistel DG, DeRose JJ. The impact of left ventricular hypertrophy on early and long-term survival following coronary artery bypass grafting. 7th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke, May 6-8, Washington, DC, USA 2006.
  96. Toumpoulis IK, Anagnostopoulos CE, Chamogeorgakis T, Swistel DG, DeRose JJ. Independent predictors for early and long-term mortality after heart valve surgery. 7th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke, May 6-8, Washington, DC, USA 2006.
  97. Toumpoulis IK, Anagnostopoulos CE, Rokkas CK, Chamogeorgakis T, Swiste DG, DeRose JJ. CAB or OPCAB? Common and unique independent predictors affect midterm survival differently in patients with on-pump and off-pump coronary artery bypass. International Society for Minimally Invasive Cardiothoracic Surgery, Annual Scientific Meeting, June 7-10, San Francisco, CA, USA 2006.
  98. Toumpoulis IK, Anagnostopoulos CE, Swistel DG, Chamogeorgakis T, Connery CP, DeRose JJ. Does reexploration for bleeding affect long-term mortality after coronary artery bypass grafting? 16th World Congress of the World Society of Cardio-Thoracic Surgeons, August 17-20, Ottawa, Ontario, Canada 2006.
  99. Anagnostopoulos CE, DeRose JJ, Rokkas CK, Chamogeorgakis T, Swistel DG, Toumpoulis IK. The calcified aorta revisited: a 13-year experience. 16th World Congress of the World Society of Cardio-Thoracic Surgeons, August 17-20, Ottawa, Ontario, Canada 2006.
  100. Toumpoulis IK, Anagnostopoulos CE, Chamogeorgakis T, Rokkas CK, DeRose JJ, Swistel DG. Risk factors for stroke and long-term survival after coronary artery bypass grafting. International Stroke Conference 2007, February 7-9, San Francisco, CA, USA 2007.

### Selected Presentations

1. Epicardiac RF Pacemaker. Presented to the American Heart Association. Miami Beach, Florida; Nov. 1965.
2. Pulmonary Embolism. Round-table discussion at the American College of Chest Physicians meeting. Chicago, Illinois; Oct. 1969.
3. Results of Cooperative Study on Cardiac Surgery. Presented to the American College of Chest Physicians meeting. Chicago, Illinois; Oct. 1969.
4. Cardiac Pacemakers. Guest lecturer to the Vermillion County Heart Association meeting. Danville, Illinois; Feb. 1971.
5. Cardiac Pacemakers. Presented to the European Society for Experimental Surgery. Amsterdam, Holland; Apr. 1972.
6. Surgery for Valvular and Coronary Artery Disease. Lecture to the Chicago Medical Society. Chicago, Illinois; March 1972.
7. Rectus Sheath Valve. Paper presented to the European Society for Experimental Surgery. Amsterdam, Holland; Apr. 1972.
8. Autologous Rectus Sheath Grafts. Presented at the Surgical Forum Sessions, American College of Surgeons. San Francisco, California; Oct. 1972.
9. Surgery and Mechanical Assist Devices for Patients with Severe Coronary Heart Disease. Presented to the Hellenic Medical Society Meetings. Oakbrook, Illinois; Nov. 1973.
10. Acute Aortic Dissections: A Statistical Analysis. Presented to the Chicago Cardiology Club,

- Swedish Club. Chicago, Illinois; Nov. 1973.
11. Acute Aortic Dissections, Experimental Model of Transposition. Aneurysms of Sinus of Valsalva in Marfan's. Anomalous Coronary Arteries. Papers and film presented at the VII World Congress of Cardiology. Argentina; Sept. 1974.
  12. Transposition of the Great Arteries. Panel discussion in VII World Congress of Cardiology. Argentina; Sept. 1974.
  13. Cardiogenic Shock Symposium. Chicago Heart Association. Chicago, Illinois; Nov. 1974.
  14. Expanding Indications for Intra-Aortic Balloon. Presented at Tenth Congress of European Society for Experimental Surgery. Paris, France; Apr. 1975.
  15. Acute Aortic Dissections. Lecture given at University of Athens. Athens, Greece; Apr. 1975.
  16. Surgery Research. First Congress. Rome, Italy; 1975.
  17. Anomalous Coronary Arteries, Bacterial Endocarditis, Surgery for Aortic Dissections. Papers and film presented at the International College of Surgeons meeting. Athens, Greece; May 1976.
  18. Left Atrial Myxoma and Discussion of Acute Aortic Dissection. Visiting professor presentation at Mercy Hospital. Pittsburgh, Pennsylvania; Jan. 1977.
  19. Surgical Management of Dissecting Aneurysms. Chicago Lung Association. Chicago, Illinois; Apr. 1977.
  20. Ventriculographic Prognostic Features in Ventricular Aneurysms. Presented to the International Cardiovascular Society meeting. Athens, Greece; June 1977.
  21. Acute Aortic Arch Dissections and Special Problems with Dissecting Aortic Aneurysms in Marfan's Syndrome. German Cardiac Surgical Society. Munich, Germany; Oct. 1977.
  22. Aortic Dissection. Texoma Medical Center Conference of Advances in Cardiac Surgery. Denison, Texas; Nov. 1977.
  23. Urgent Coronary Revascularization Without Hospital Mortality. European Society of Cardiovascular Surgery. 1977.
  24. Surgical film session. Panelist at the American College of Surgeons 64th Annual Clinical Congress. San Francisco, California; Oct. 1978.
  25. Urgent Coronary Revascularization. The Cardiac Surgery session of the 11th Greek Surgical Society annual meeting. Salonica, Greece; Oct. 1976.
  26. Acute Aortic Dissections. Lecture at the Cook County Graduate School of Medicine. Cook County Graduate School of Medicine. Cook County, Illinois; Jan. 1979.
  27. Surgery for Coronary Artery Disease. Panelist for the Frontiers of Medicine Program entitled "A Day in Cardiology". The University of Chicago; June, 1979.
  28. Effect of Atrial Pacing on Coronary Bypass Flow. Paper by Lin C-Y, Cheng MS, Myerowitz D, Anagnostopoulos CE. Presented by C-Y Lin at the XIV World Congress of the International Cardiovascular Society for the Society of University Surgeons. San Francisco, California; Sept. 1979.
  29. Myocardial Rupture and Infarct Expansion. Paper presented by PA Beere. Panelist for the American Heart Association's 52nd Annual Scientific Session. Anaheim, California; Nov. 1979.
  30. Acute Aortic Dissections. Lecture at the Thoracic Surgery Postgraduate Course. Dec. 1979.
  31. Arrhythmias, "Inoperable" Coronary Heart Disease and Transplantation. Lecturer and discussant for the Center for Continuing Education Annual Retreat entitled "Investigative and Surgical Management of Coronary Heart Disease. The University of Chicago; Feb. 1980.
  32. Magnesium Cardioplegia in 500 Patients. By JL Levett. Lecture at the Society of University Surgeons residents' conference. Feb. 1980.
  33. Medical and Surgical Treatment of Dissecting Aneurysms of the Aorta. Panelist for the American College of Cardiology 29th Annual Scientific Session. Houston, Texas; March 1980.
  34. Delayed Complications Following Heterograft Valve Replacement. Chicago Cardiology Group, Rush Pres  
 yte ian St. Luke's Hospital. Chicago, Illinois; May 1980. 35. Myocardial Protection During Cardiac Surgery. Panelist for the Fr

- ntiers of Medicine Program entitled "Controversies in Coronary Heart Disease." May 1980.
36. Surgery for the Acutely Failing Myocardium. Lecture for the Medical Horizons Conference at the Center for Continuing Education. June 1980.
  37. Propranolol, Potassium and Cardiac Surgery. Lin C-Y, Little AG, Shian L, Fang V, Anagnostopoulos CE. Presented by A Little at the Scientific Program of the 42nd Annual Meeting of the Society of University Surgeons. March 1981.
  38. Aortic Dissection. Panelist for the Society for Vascular Surgery meeting. Dallas, Texas; June 1981.
  39. Anatomic Correction of Transposition of the Great Vessels. Symposium panelist at the XV World Congress of the International Cardiovascular Society meeting. Athens, Greece; Sept. 1981.
  40. Total Protection from Embolism in Left Ventricular Aneurysm Surgery. Lecture at the regional AMSECT meeting. Chicago, Illinois; Nov. 1981.
  41. Growth of Rectus Sheath Aortic Grafts in Puppies. Scientific exhibit presented at The American College of Surgeons 67th Annual Clinical Congress. San Francisco, California; Oct. 1981 - (By Dr. Bilfinger).
  42. Growth of Rectus Sheath Aortic Grafts in Puppies. Scientific Exhibit presented at The International College of Surgeons Meeting. Coronado, California; Nov. 1981 - (By Dr. Bilfinger).
  43. Surgical Treatment of Aortic Coarctation in Infancy. Abstract presented at DeBakey International Cardiovascular Society meeting. Buenos Aires, Argentina Apr. 1982 - (By Dr. Wernly).
  44. Measurement of Extravascular Lung Water with Short-Lived Tracers. Abstract presented at the Society of Nuclear Medicine. Miami Beach, Florida; June 1982 - (By Dr. Bilfinger).
  45. Anterior Rectus Sheath as Growing Cardiovascular Graft. Abstract presented at the Society of University Surgeons Tripartite Meeting. Salsburg, Austria; Sept. 1982 - (By Dr. Bilfinger).
  46. Operations for Aortic Coarctation in Infancy: Determinants of Survival and Postoperative Hemodynamics. Presented at Samson Thoracic Surgical Society. February, 1983 - (By Dr. Wernly)
  47. Coronary Bypass Surgery. Presented at Quarterly Medical Conference. Hempstead, New York; April 1983.
  48. Current Status of Coronary Artery Bypass Graft Surgery. Presented at Cardiology 1983. Coronary Artery Disease Update. Plainview, New York; Oct. 1983.
  49. New Aspects of Valvular Heart Disease. Presented at Cardiology Conference. Port Jefferson, New York; 1983.
  50. New Surgical Aspects in Congenital Heart Disease. Presented at conference on Heart Disease. East Meadow, New York; 1984.
  51. Cardiac Surgery: Reflections and Expectations. Presented at Tenth Annual Family Medicine Update. Stony Brook, New York; March 1984.
  52. Potential Use of Rectus Sheath in Single Ventricle and Pulmonary Outflow. Discussant at 64th Annual Meeting of American Association for Thoracic Surgery. New York, New York; May 1984.
  53. Surgery for Congenital Heart Disease. Presented at Pediatric Cardiology Grand Rounds. Stony Brook, New York; May 1984.
  54. Aortic Coarctation in Infancy-Determinants of Surgical Survival and Postoperative Hemodynamics. Abstract presented at XXXIII International Congress of the European Society for Cardiovascular Surgery. Madrid, Spain; Sept. 1984.
  55. The Left Ventricle in Transposition: Ventriculographic and Anatomic Variations Possible Contraindicating Anatomic Correction. Abstract presented at XXXIII International Congress of the European Society for Cardiovascular Surgery. Madrid, Spain; Sept. 1984.
  56. Acute Aortic Dissection-Long-Term Cardiac and Vascular Consequences in Sixty Patients. Abstract presented at XIV Panhellenic Surgical Congress. Athens, Greece; Oct. 1984.
  57. Update on Congenital Heart Surgery. Presented at Athens Pediatric Cardiology Society meeting. Athens, Greece; Oct. 1984.

58. Recent Advances in Treatment of Acute Aortic Dissection. Lecture at University of Salonica. Salonica, Greece; Oct. 1984.
59. Medical and Surgical Therapy of Acute Aortic Dissection. Presented at Evangelismos Hospital Department of Cardiology Grand Rounds. Athens, Greece; Oct. 1984.
60. Newest Advances in Infant Heart Surgery. Lecture at First Surgical Clinic of Policlinico Rome. Rome, Italy; Oct. 1984.
61. Acute Aortic Dissection. Lecture at Catholic Hospital of Rome. Rome, Italy; Oct. 1984.
62. Acute Aortic Dissection. Presentation at Ninth Annual Symposium on Vascular Surgery. Castle Point, New York; Oct. 1985.
63. Acute Aortic Dissections. Lecture at Surgery Grand Rounds, Hippocrates Hospital. Athens, Greece; Feb. 1986.
64. Newer Aspects of Surgery for Transposition of the Great Vessels. Lecture at Surgery Conference, Hippocrates Hospital. Athens, Greece; Feb. 1986.
65. Diastolic Dysfunction in Coronary Patients with and without Revascularization. Presented at the 59th Annual Scientific Sessions of the American Heart Association, Washington, D.C., November, 1986 - (By Dr. Lawson).
66. Fontan Procedure for Congenital Heart Disease-Results at Stony Brook University Hospital. Lecture at Pediatric Grand Rounds, University Hospital. Stony Brook, New York; May 1987.
67. Five Years of Cardiac Surgery. Lecture at Grand Rounds, Veterans Administration Hospital. Northport, New York; March 1988.
68. Pediatric Cardiac Surgery at University Hospital, Stony Brook. University Hospital, Stony Brook. Stony Brook, New York; August 1988.
69. Surgery for Acquired Heart Disease. Grand Rounds-University Hospital, Stony Brook, New York: April 1988.
70. Recent Advances in Cardiovascular Grafts and Their Growth Potential. Research Seminar, SUNY at Stony Brook, April 1989.
71. Discussant of Papers on Descending Aortic Dissections and Ventricular Aneurysms. Annual Meeting of The Society of Thoracic Surgeons. San Francisco, California, Feb. 1991.
72. Acute Aortic Dissections. Stony Brook University Hospital Vascular Surgery Seminar. SUNY at Stony Brook, NY, Nov. 1991
73. Cardiovascular Grafts with Potential for Growth. Memorial Lecture to Athens Children's Hospital, St. Sophia, Jan. 1992
74. Cardiovascular Grafts with Potential for Growth. Grand Rounds in Cardiac Surgery, Schneider Children's Hospital, Long Island Jewish Medical Center. New York, New York, Feb. 1992.
75. Discussant of Papers on Retrograde Cardioplegia and Anastomotic Growth. Annual Meeting of the Society of Thoracic Surgeons. Orlando, Florida, March 1992.
76. Risk Stratification in Cardiac Surgery and a Review of Developments in Acute Aortic Dissections. Hellenic Medical Society, New York Athletic Club. New York, New York. Dec. 1991 & Apr. 1992
77. NYS - STS, Risk Stratification in 180 St. Luke's Cardiac Surgery patients. Roosevelt Hospital, Cardiology Grand Rounds. New York, New York. May 1992
78. "Starting of New Cardiac Surgery Programs" Onassis Foundation Heart Hospital Center, Athens, Greece. Aug. 1992 & Oct. 1992
79. "50 Years of Progress in Cardiac Surgery" St. Regis Hotel, New York, New York. Dec. 1992
80. Acute Aortic Dissections. Lecture to Cardiac Surgery Grand Rounds, Albert Einstein School of Medicine, Wyler Center, New York, New York. Dec. 1992
81. Aortic Disease and Risk Stratification. Lecture to Cardiology Conference, Roosevelt Hospital, New York. Feb. 1993
82. Diseases of the Aorta, Results of Treatment (1990-1992). Lecture to Cardiology Conference, St. Luke's Hospital, New York. Feb. 1993

83. Protection of Myocardial, Brain and Spinal Cord during Aortic Surgery. Stony Brook University Hospital, Vascular Seminar, SUNY, New York. Feb. 1993
84. Acute Catastrophe of the Aorta in a Male. Symposium presentation to Special Grand Rounds, Roosevelt Hospital, New York. May 1993
85. Acute Aortic Dissections. Presentation to Thoracic Surgery Seminar, Albert Einstein School of Medicine, New York. Mar 1993
86. Pre-clamp Cardioprotection by Protein C Kinase Inhibitor. Presentation to Sphinx Pharmaceuticals Corporation, North Carolina.
87. Congenital Heart Disease Update 1995. Proceedings of the Second Cardiology International Conference. Onassis Cardiac Surgery Center. February 1995.
88. Chair Sessions of the Proceedings of the First International Cardiac Surgery Conference. Onassis Cardiac Surgery Center, Athens, Greece; December 1994.
89. Discussant three papers at the Thirty First Annual Society of Thoracic Surgeons meeting Palm Springs, CA. January 28 - February 1, 1995.
90. Chair session of the First Panhellenic Meeting of Surgery of the Thorax-Heart- Great Vessels. November 30 - December 3, 1995.
91. Discussant two papers at the Thirty Second Annual Society of Thoracic Surgeons Meeting, Orlando, FL. January 29 - 31, 1996.
92. Congenital Heart Disease - 1996, an Update. First International Cardiology Conference, University of Patras, Greece. June 4, 1996
93. 260 Operations for Congenital Heart Disease. The Two Year Experience of a New Cardiothoracic Center. First International Meeting - MEDICINE IN THE 21ST CENTURY Lagonisi, Greece. July 5, 1996.
94. Indications, Techniques and Results of Extra-anatomic Thoracic Aortic Bypass Grafts. International Congress of Thorax Surgery, Athens, Greece, July 1997.
95. "Band-Aid Surgery - Upper Sternal Split Incision for Valve Surgery in Adults: a modified Technique. Medical Developments for the New Millennium, Rhodes, Greece. August 1997.
96. Congenital Heart Surgery Combined conference Ioannina University and Tirana University, October 1997.
97. Aneurysms of the Aortic Arch University of Salonica, Salonica, Greece. November 1997.
98. Acute Aortic Dissections. 10th International Cardiology Symposium, Athens Greece, January 10, 1998.
99. Cardiovascular Rectus Sheath Grafts. Presented to the W.W.L. Glenn Symposium, Yale University School of Medicine, June 1998.
100. Acute Aortic Dissections. Presented during Visiting Professorship to BI Deaconess Hospital - Harvard Medical School, Department of Cardiothoracic Surgery, November 1998.
101. "Problems with New York State Risk Stratification - Discussion of Paper Burack et al", Society of Thoracic Surgeons Annual Meeting, January 1999. Ann Thor Surg 68: 1202-203, 1999.
102. Autologous Valve Conduits – Discussion of Paper by Okita et al, Society of Thoracic Surgeons Annual Meeting, January 1999. Ann Thor Surg 68: 1592, 1999.
103. Discussant, "The Effect of Public Reporting of Surgical Mortality on the Practice of Cardiothoracic Surgery; A Survey of Surgeon's Attitudes in New York State." JH Burack et al. February 4, 1999, New York Society for Thoracic Surgery.
104. Thoracic Aortic Aneurysm and Dissections: From Cradle to grave. Presentation. Part of "Science and Art of Medicine" Medical Board. St. Luke's-Roosevelt Hospital Center.
105. Speaker in round table " Aortic Surgery", Annual Meeting of the Greek Society of Cardiology, Crete- Greece, October 1999.
106. Lecture as invited speaker " Aneurysm surgery", Annual Meeting of the Northern Greek Society of Surgery, Ioannina- Greece, November 1999.
107. Lecture as invited speaker " Mitral Valve Repair", Annual Meeting of the Hepirus Greek Society of Cardiology, Arta- Greece, December 1999.

108. Invited lecture Annual Meeting of Greek Surgical Society “Aortic Arch surgery – an Experience with Forty Patients”. Grande Bretagne Hotel, Athens February 2000.
109. A Novel approach for the treatment of paroxysmal adrenergic, atrial fibrillation by catheter ablation of extracardiac and intracardiac component of ligament of Marshall tissue. XXII Congress of the European Society of Cardiology, Amsterdam August 2000
110. White Cell Filtration of Transfused Blood and/or Blood Products Reduces Infections in Cardiopulmonary Bypass Patients Undergoing Revascularization. ACCP San Francisco, October 25, 2000. Chair, section on Aneurysms of the Aorta Second international Meeting of the Onassis Cardiac Surgery Center. Athens December 7, 2000. Presenting Author, Early Mortality and Morbidity of Bilateral vs. Single internal thoracic artery revascularization: Propensity and risk modeling. American College of Cardiology Annual Meeting March 2001.
111. Toumpoulis IK, **Anagnostopoulos CE**, Shennib H, DeRose JJ, Swistel DG. Influence of innovative techniques on mid-term results in off-pump coronary artery bypass. Cardiothoracic Technologies and Techniques, 9<sup>th</sup> Annual Meeting, March 19-22, Miami, FL, USA 2003.
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113. Toumpoulis IK, Connery C, Siminelakis S, **Anagnostopoulos C?**. How to demonstrate superiority of mitral valve repair over replacement: five to ten-year results with isolated and combined operations. 3<sup>rd</sup> International Meeting, 10<sup>th</sup> Anniversary of the Onassis Cardiac Surgery Center, April 10-13, Athens, Greece 2003.
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122. Toumpoulis IK, **Anagnostopoulos CE**, DeRose JJ, Swistel DG. Early and midterm outcome

- after off-pump coronary artery bypass grafting in patients with left ventricular dysfunction. ISMICS 7th Annual Meeting, June 23-26, London, United Kingdom 2004.
123. Toumpoulis IK, **Anagnostopoulos CE**, DeRose JJ, Swistel DG. Effect of gastrointestinal complications on long-term survival after coronary artery bypass grafting. European Society of Cardiology Congress 2004, August 28 – September 1, Munich, Germany 2004.
  12. Toumpoulis IK, **Anagnostopoulos CE**, DeRose JJ, Swistel DG. The impact of diabetes mellitus on long-term survival after coronary artery bypass grafting. European Society of Cardiology Congress 2004, August 28 – September 1, Munich, Germany 2004.
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# Efficacy of percutaneous transluminal coronary angioplasty compared with single-vessel bypass

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The use of percutaneous transluminal coronary angioplasty has been increasing rapidly. When the procedure is successful, the clinical relief of symptoms is similar to that achieved with direct coronary artery bypass. It has been suggested that the angioplasty procedure, however, can accomplish these results with potentially less morbidity and mortality, along with a shorter hospital stay. In order to evaluate the results of percutaneous transluminal coronary angioplasty with single-vessel coronary artery bypass, we performed a retrospective review. From January, 1982, to December, 1983, a total of 198 angioplasty procedures were performed. They were successful in 142 patients (71.7%). Emergency bypass was performed in 21 (10.6%) of the 56 patients who had undergone unsuccessful angioplasty procedures. Perioperative myocardial infarction occurred in eight of these patients (38.1 %). There were no operative deaths but there was one death after angioplasty. Elective bypass was performed in 28 of the patients who had angioplasty procedures, with no perioperative myocardial infarctions or operative deaths. Recurrent symptoms developed in 31 (21.8 %) of the 142 patients who had undergone initially successful angioplasty. From 1982 to 1983, single-vessel bypass was performed in 143 patients. The internal mammary artery was utilized in 102 patients and the autogenous saphenous vein in 41 patients. There were no perioperative myocardial infarctions or deaths. No patients developed recurrent symptoms during the study interval. Percutaneous transluminal coronary angioplasty is an acceptable alternative to coronary artery bypass in patients with localized lesions that are sufficiently serious to cause symptoms and warrant surgical bypass. However, the angioplasty procedure, when compared to single-vessel coronary artery bypass, may result in an increased incidence of acute myocardial infarction and in a significantly ( $p < 0.001$ ) increased incidence of early recurrence of symptoms.

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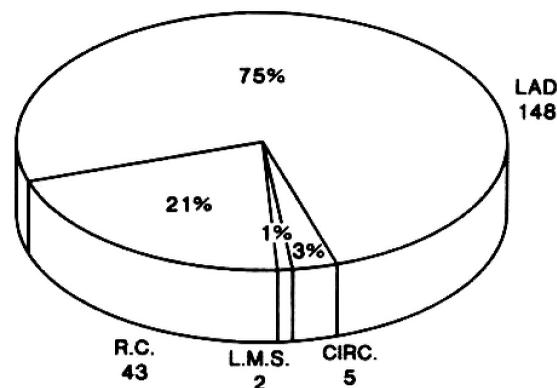
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The use of percutaneous transluminal coronary angioplasty (PTCA) in patients with coronary artery disease has been increasing rapidly throughout the world. When successful, PTCA can produce clinical relief of symptoms similar to that achieved with direct coronary artery bypass grafting (CABG).<sup>1,2,6</sup> The increasingly widespread utilization of PTCA has been attributed to its ability to achieve satisfactory results with potentially less morbidity and mortality and a shorter hospital stay than can be achieved with CABG.<sup>2</sup> In order to test this hypothesis, we evaluated our results with PTCA and compared them to our results with single-vessel CABG during a similar time interval.

### Patients and Methods

Between January, 1982, and December, 1983, a total of 198 PTCA (119 male and 79 female patients) were performed at St. Vincent's Medical Center, New York City, and Maimonides Medical Center, Brooklyn. Indications for PTCA were standardized according to strict institutional guidelines. A standard femoral or brachial technique for PTCA was performed. During the PTCA procedure, an operating room was always on standby. Patients in whom the PTCA was unsuccessful, but who remained hemodynamically stable and had no chest pain, were either electively scheduled for CABG or treated medically. If PTCA was unsuccessful, patients were considered to have an urgent need for CABG (1) if the vessel was acutely occluded, (2) if the patient had persistent pain despite intracoronary nitroglycerin, intravenous nitroglycerin, and/or sublingual nifedipine, or (3) if the patient had electrocardiographic evidence of acute myocardial ischemia. An intra-aortic balloon was inserted preoperatively<sup>8,9</sup> if the patient had evidence of hemodynamic instability (mean arterial blood pressure less than 60 mm Hg, pulmonary artery wedge pressure greater than or equal to 20 mm Hg, or cardiac index less than or equal to 2.0 L/min/m<sup>2</sup>).

Patients who required urgent operation were expeditiously transferred from the cardiac catheterization laboratory to the operating room (range 20 to 60 minutes). The mean time from onset of ischemia to completed revascularization was 48



**Fig. 1.** Schematic diagram of anatomic locations of 198 attempted percutaneous transluminal coronary angioplasty procedures from January, 1982, to December, 1983. LAD, Left anterior descending artery. RC, Right coronary artery. LMS, Left main stenosis. Circ, Circumflex artery.

**Table I.** Comparison of patients undergoing PTCA and single-vessel CABG

	PTCA		CABG × 1		p Value
Age (yr)	52.6 ± 8.3		59.7 ± 8.7		<0.001
	(33-65)		(34-75)		
Sex					
Male	119	60.1%	94	65.7%	NS
Female	79	39.8%	49	34.3%	NS
Total	198	100 %	143	100 %	
Hypertension	62	31.3%	49	34.3%	NS
Diabetes mellitus	24	12.1%	20	14.0%	NS
Previous MI	41	20.7%	53	37.1%	<0.001
Previous CABG	2	1.0%	3	2.1%	NS
LVEDP > 20 mm Hg	24	12.1%	28	19.6%	NS
EF ≥ 60%	128	64.6%	29	20.3%	<0.001
EF 40%-50%	65	32.8%	79	55.2%	<0.001
EF <40%	5	2.5%	35	24.5%	<0.001

*Legend:* PTCA, Percutaneous transluminal coronary angioplasty. CABG × 1, Single-vessel coronary artery bypass graft. MI, Myocardial infarction. LVEDP, Left ventricular end-diastolic pressure. EF, Ejection fraction.

minutes. Standard CABG was performed to the unsuccessfully angioplastied vessel and additionally to any other significantly diseased vessel.

Evidence of perioperative myocardial infarction was determined by a new Q wave greater than or equal to 3 mm in depth and greater than or equal to 0.4 second in duration or an elevation of the creatine kinase (CK) MB fraction of more than three times the normal level.<sup>1</sup>

During the same period of time, 143 patients (94 male, 44 female) underwent single-vessel CABG. Indications for operation were either chronic stable angina that was refractory to medical therapy or unstable angina. The internal mammary

**Table II. Results of percutaneous transluminal coronary angioplasty according to anatomic location**

Location	Successful		Unsuccessful		Total	
	No.	%	No.	%	No.	%
LAD	113	76.4	35	23.6	148	74.7
RCA	26	60.5	17	39.5	43	21.7
Circumflex	2	40.0	3	60.0	5	2.5
Left main	1	50.0	1	50.0	2	1.0
Total	142	71.7	56	28.3	198	100.0

Legend: LAD, Left anterior descending coronary artery. RCA, Right coronary artery.

artery was utilized whenever possible (102 patients), primarily for grafts to the left anterior descending coronary artery. A reversed segment of autogenous saphenous vein was employed in all other patients.

All bypass grafts were constructed while the patients were on cardiopulmonary bypass. Moderate systemic hypothermia (25° C) was employed during aortic occlusion, and cardioplegia by means of cold blood (6° to 8° C) with potassium (30 mEq/L) was utilized for myocardial protection.

All patients have been contacted within the last 6 months either by the authors or by the referring physicians.

All values are recorded as mean  $\pm$  standard deviation. Statistical analysis was performed with the use of Student's *t* test and Fisher's exact test.

## Results

Mean characteristics of the two patient groups are summarized in Table I. As can be seen, the mean age of patients undergoing CABG was greater than that of patients undergoing PTCA (59.7 versus 52.6;  $p < 0.001$ ). CABG patients had a significantly higher preoperative incidence of myocardial infarction ( $p < 0.001$ ; 37.1% versus 20.7%). Similarly a significantly greater number of patients who underwent PTCA had a normal ejection fraction compared with the number of patients undergoing CABG (64.6% versus 20.3%;  $p < 0.001$ ). In addition, more patients undergoing CABG had an ejection fraction under 40% (24.5% versus 2.5%;  $p < 0.001$ ).

PTCA was successful in 142 patients (71.7%). This procedure was successful for lesions in the left anterior descending artery in 113 of 148 patients (76.4%), for lesions in the right coronary artery in 26 of 43 patients (60.5%), for lesions in the circumflex coronary artery in two of five patients (40%),

**Table III. Results of PTCA**

	No.	%
Total No. of patients	198	
Successful PTCA	142	71.7
Emergency surgery	21	10.6
Elective CABG	28	14.1
Medical therapy	7	3.5
Perioperative infarction	8/21	38.0
Total No. of myocardial infarctions	11	5.5
Mortality*	1	0.5

Legend: PTCA, Percutaneous transluminal coronary angioplasty. CABG, Coronary artery bypass grafting.

\*Death occurred in a patient who was not operated on.

and for lesions of the left main coronary artery in one of two patients (50%) (Tables II and III; Fig. 1). There was one death after PTCA (0.5%).

A total of 142 patients underwent single-vessel CABG. The graft was to the left anterior descending coronary artery in 112 patients, to the right coronary artery in 28 patients, and to the circumflex coronary artery in three patients. There were no operative deaths nor perioperative myocardial infarctions in this group of patients (Fig. 2). The mean duration of hospitalization for patients undergoing PTCA was  $6.8 \pm 3.6$  days, compared with  $9.5 \pm 4.7$  days for bypass patients ( $p < 0.001$ ).

Mean follow-up time for patients undergoing successful PTCA is  $9.3 \pm 4.1$  months, compared with  $11.8 \pm 5.4$  months in patients undergoing single-vessel CABG (no statistical significance). Recurrent symptoms have developed in 31 (21.8%) of the 142 patients who had successful angioplasty within 1 year of the PTCA. Repeat angioplasty was performed in 20 patients and was successful in 17.

No patients who have undergone single-vessel CABG have developed recurrent anginal symptoms ( $p < 0.001$ ; Fig. 3).

## Discussion

Successful CABG is generally defined as resulting in a patent bypass graft, alleviation of anginal symptoms, and preservation or improvement of left ventricular function.<sup>10-14</sup> Successful PTCA is defined as a reduction of the degree of diameter narrowing by 20% or more, with alleviation of anginal symptoms.<sup>2,6</sup>

Since Gruentzig introduced PTCA in 1977, strict guidelines have been established in most institutions for the selection of patients.<sup>1-4</sup> Recent studies from Hail and Gruentzig<sup>2-4</sup> now indicate an initial success rate of 87% for patients who undergo PTCA. In contrast, the recent multi-institution report from the National Heart, Lung, and Blood Institute (NHLBI), summarizing data of 1,500 patients from 73 institutions, indicated an initial success rate for PTCA of only 63%.<sup>1</sup> Total mortality in this group was 1.1%. Emergency CABG was required in 6.8% of the patients; of the patients who required

emergency operation, 6.9% died. An additional 35% of patients who required emergency operation had a non-fatal perioperative myocardial infarction. The data contained in the NHLBI registry are consistent with our data. Our initial success rate of 72% is comparable to the NHLBI success rate of 63%. Emergency CABG was performed in a higher percentage of our patients (11%), compared with the NHLBI registry (6.8%). This difference may represent a more aggressive attempt on our part to surgically revascularize patients with myocardial ischemia than in other institutions. In addition, the lower operative mortality observed in our patients who required emergency bypass grafting (0% versus 6.9%) may represent an ability to initiate cardiopulmonary bypass and revascularize ischemic myocardium more rapidly by having an operating team and room readily available. Nevertheless, the incidence of perioperative myocardial infarction in these patients (38% in our group and 35% in the NHLBI registry) is relatively high.

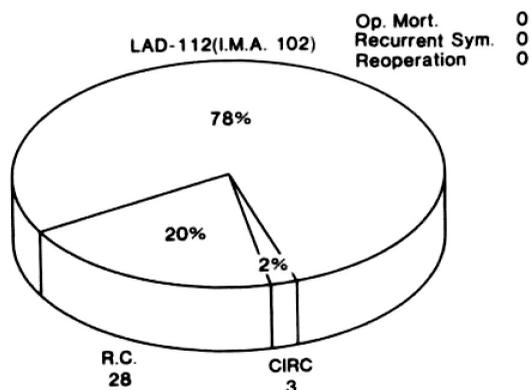


Fig. 2. Anatomic location and results of single-vessel coronary artery bypass surgery from January, 1982, to December, 1983. LAD. Left anterior descending artery. IMA. Internal mammary artery. RC, Right coronary artery. CIRC. Circumflex artery.

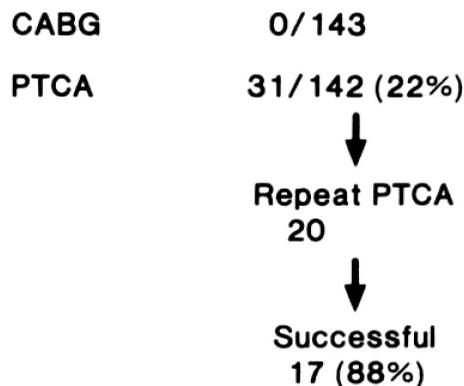


Fig. 3. Outcome of treatment for patients who develop recurrent symptoms following initially successful percutaneous transluminal coronary angioplasty (PTCA) and single-vessel coronary artery bypass grafting (CABG).

**Table IV. Comparative results of patients undergoing PTCA, single-vessel CABG, and multi-vessel CABG**

	PTCA	CABG × 1	CABG > 1	p <sub>1</sub> Value	p <sub>2</sub> Value
Total No.	198	143	1,234		
Mortality	1 (0.5%)	0	12 (1.2%)	NS	NS
MI	11 (5.5%)	0	16 (1.3%)	<0.05	<0.01
Hospital stay (days)	6.8 ± 3.6	9.5 ± 4.7	11.5 ± 6.7	<0.001	<0.001
Recurrent symptoms	31/142 (22%)	0	12 (1.2%)	<0.001	<0.001

Legend: PTCA, Percutaneous transluminal coronary angioplasty. CABG × 1, Single-vessel coronary artery bypass grafting. CABG > 1, Multivessel CABG. p<sub>1</sub>, A p value comparing PTCA with CABG × 1. p<sub>2</sub>, A p value comparing PTCA with CABG > 1. MI, Myocardial infarction.

Finally, the early recurrence of anginal symptoms, which was experienced by 31 patients (21.8%) who underwent successful PTCA, is troublesome. No patients in our single CABG series have developed early recurrence of symptoms. Most other institutions have experienced a similarly low recurrence rate of symptoms in the patients who have undergone CABG.<sup>10-14</sup>

If one considers that most patients who undergo PTCA generally have a short history of angina (usually less than 1 year), single-vessel disease with a proximal concentric, noncalcified lesion, a good distal vessel, and good left ventricular function, it can be seen that they are also ideal surgical candidates.<sup>1,15</sup> Although not all patients who undergo PTCA are "ideal candidates," it is still distressing that such a high percentage of patients from our study and also from the NHLBI registry experienced myocardial infarction and recurrent symptoms, compared with patients who have undergone CABG.

During the same time interval in which we compared PTCA with single-vessel CABG, multiple-vessel CABG procedures were performed on 1,234 consecutive patients. The operative mortality rate in this group was 12%, perioperative infarction rate was 1.2%, and recurrence of symptoms occurred in 1.2% (within 2 years of operation). Thus it is evident that patients who undergo multiple bypass grafting have a lower incidence of myocardial infarction, as well as a lower incidence of recurrent symptoms, than patients who undergo PTCA.

Although there may be an initial decrease in the duration of hospitalization and overall cost to the patients who undergo PTCA,<sup>7</sup> one must also

consider the incidence of restenosis (30%) and the need for repeat angioplasty.<sup>1,2,16,17</sup> The initial duration of the hospital stay in our series was lower in the PTCA patients (6.8 versus 9.5 days); however, 20 patients required readmission for a second procedure, which additionally required 3 or 4 days of hospitalization. In addition, most institutions require follow-up coronary arteriography in 6 months in patients who have undergone successful PTCA.<sup>1,2,4</sup> This requirement will further increase the total number of patient-days and the total medical expense. Therefore, although the initial cost of PTCA may be less than the cost of the operation, one must consider the additional cost that may be incurred if repeat PTCA is required or the patient subsequently undergoes CABG.

Clearly our data and the data from the NHLBI registry represent early results for PTCA. This technique is obviously undergoing transition and development. Cardiologists are gaining additional experience and refining their criteria for selecting angioplasty candidates. As many studies have well demonstrated, there is a dramatic learning curve for PTCA, and with increased investigator experience and improved PTCA techniques, overall results will improve considerably.<sup>2,18,19</sup> By comparison, the techniques and results of CABG have become standardized, consistent, and reproducible.<sup>11,14</sup> It is necessary, however, to critically appraise the results of PTCA, and in this regard, CABG for both single- and multiple-vessel disease, in comparison with PTCA, has a lower incidence of acute infarction and appears to alleviate symptoms for a significantly longer time.

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## Discussion

DR. DANIEL J. ULLYOT  
*San Francisco Calif.*

In an editorial entitled «Randomization and Coronary Artery Surgery», published in 1972, Tom Chalmers wrote:

*The only way to avoid the distorting influences of uncontrolled pilot trials is to begin randomization with the first patient... The possibility that the new treatment may turn out to be worse than the old makes randomization a most ethical procedure; ipso facto, postponement of a randomized trial until the technique of the new therapy has been developed is a most unethical procedure, because it implies sacrifice of the first*

*few patients while the surgeon is learning and perfecting his technique in order to be better able to demonstrate efficacy in a subsequent randomized Trial... Those in the forefront of surgical advances*

*should recognize that the scientific and ethical principles behind the development of modern clinical trials are sound and are in the best interest of the patient entering the trial, as well as of all mankind. Plans for the trial of new operations should undergo the same rigorous peer review procedures as are now routine in the development of drug therapy.\**

\* Chalmers TC: Randomization and Coronary Artery Surgery. *Ann Thorac Surg* 14:323-327,1972, by permission of Little Brown and Company.

So wrote Dr. Chalmers in 1972, lecturing surgeons on the way to conduct themselves in the introduction of new surgical techniques.

The voices calling for randomization have been conspicuously silent in regard to percutaneous transluminal coronary angioplasty (PTCA). It is as if, when a surgical procedure is performed by nonsurgeons, carefully conducted trials are perhaps less compelling or less necessary.

Many of us recall that only a few years ago, «single-vessel disease», did so well with contemporary medical therapy that surgical intervention was rarely necessary. At present there seems to be an acknowledgment that medical therapy may not be the best treatment for these patients, now that angioplasty is on the scene, even though there have been no prospective randomized studies comparing single-vessel PTCA either with the natural history of medically managed patients or with management by means of coronary bypass grafting.

It is noteworthy that the first presentation on the program of The Western Thoracic Surgical Association in an attempt, by surgeons, to critically examine two surgical procedures, both attempting to improve myocardial blood flow: one by balloon dilatation of atherosclerotic segments and the other by bypass grafting. Regrettably, the study presented here was neither prospective nor randomized. Unfortunately, the follow-up period was short (only 6 months), no patency data are provided, the concept of morbidity was not carefully defined, and cost was not considered.

Nonetheless, I believe that the authors have raised important questions about PTCA, a procedure that has achieved uncritical acceptance as an alternative to both medical and coronary bypass management.

When I read the manuscript, I wished that the authors had been somewhat stronger in making their point. However, in today's presentation, the authors were appropriately restrained in discussing the conclusions of their study; that is, it is perhaps premature to accept some of the claims being made for PTCA, since it is a technology in evolution, much the same as coronary bypass was 10 to 15 years ago. The authors made a strong case that there

is still a need for continuing data to compare the two approaches. This recent study was conducted over a 2 year period, and presumably the developmental phase of PTCA was behind us. If anything, even though the patients were not randomly assigned, the surgical patients had much worse left ventricular function. The statistics were not provided, but I am sure that there was no difference between mortality rates and perioperative infarction rates. Until data over a longer follow-up period show objective evidence of the advantages of treating single-vessel disease by PTCA, we should urge restraint in accepting this method of therapy. Basically, the point that I want to emphasize here is that surgeons are being asked to provide surgical standby for these procedures. Many of us in this audience have personal experience with hundreds and thousands of patients with coronary atherosclerosis and should play an influential role both in the selection of patients for angioplasty and in evaluation of results. Efforts such as those of Dr. Acinapura and his colleagues will help place PCTA in perspective alongside other means of management.

I have two questions, First, was there a learning curve embodied in the PTCA experience, at St. Vincent's? Second, would the inclusion of other indices of morbidity, such as neurological complications, wound or pericardial complications, or infectious complications, have made a case for substantially less morbidity with PTCA over coronary bypass?

DR. NEAL W. SALOMON

*Portland, Ore.*

I wish to share with you our experience at Good Samaritan Hospital in Portland, Oregon. Our results are almost identical to those just presented.

Over a 2.5 year period, a total of 180 patients have undergone PTCA. For the first 150 patients for whom there is a reasonable follow-up, we have already operated on 27%, or 40 patients. Half of these, or a total of 13% (20 patients), underwent operation on the day of dilatation, and half again, or 6% of the total (10 patients), truly represented emergencies, with arrest in the catheterization laboratory or something very similar. Three of these

patients died, one in the catheterization laboratory and two in the operating room. All were patients who had had previous operation and were extremely tenuous candidates for dilatation, with their only open vessel being dilated; they were obviously a very high-risk group. The other 13%, or 20 patients, were operated on either later during that same hospitalization or during a subsequent one.

I wish to suggest that perhaps the overall analysis of PTCA follow-up would be a worthwhile project for either this society, the Society of Thoracic Surgeons, The American Association for Thoracic Surgery, or another surgical society, since, for obvious reasons, it would be difficult to do such a project on either a local or a regional basis. If the information could be obtained on a national basis, it would be valuable.

One other point is that any analysis of PTCA must take into account not only mortality, morbidity, and the short- long-term follow-up but ultimately the overall cost to the patient, insurance carriers, and society. For example, our our hospital the total average cost of PTC A (professional fees plus hospital fees) for an average of 2 or 3 days' hospitalization is \$8,500. This contrasts with an average total cost of hospital fees, plus professional fees for a routine coronary bypass procedure and 6 or 7 days' average hospitalization, of approximately \$20,000. This, of course, does not take into account the time of return to gainful employment, which has to be figured in. It may be that if a relatively large proportion of PTCA patients eventually do come to operation, the overall cost to society may actually increase, and I think this may be one of the bottom lines, like it or not.

Would the authors comment on the duration of hospital stays, which seem unusually long in comparison with the usual hospital stay on the West Coast?

DR. DOUGLAS MURPHY

*Atlanta, Ga.*

I am a little skeptical as to whether the authors' presentation, although well done, will have a serious impact on the growth of angioplasty. At Emory University we are currently doing nearly eight such procedures a day. A very important aspect of

the authors' data is the fact that they were able to accomplish urgently needed revascularization in 21 acutely ischemic patients without any deaths. Cardiologists across the country have been reporting excellent results with angioplasty, and I think they often forget to give the surgical services credit for rescuing a significant proportion of their patients from what would otherwise be a significant myocardial infarction or, perhaps, death.

Across the country a big effort is now being made to extend angioplasty to patients with more advanced forms of coronary artery disease, such as multivessel disease and previously injured ventricles, and the assumption is being made that the surgeons will continue to be able to rescue that percentage of patients who are made acutely ischemic by the angioplasty procedure.

Our recent results over the last year suggest that perhaps the surgical rescue will not be as good in cases of more advanced disease. A certain subgroup that we have been able to identify involves patients with previous transmural myocardial infarctions in the distribution of an artery other than the one undergoing angioplasty. We have had four patients, three with previous inferior infarctions and one with a lateral infarction, who then had acute closure of the left anterior descending artery and developed profound, refractory cardiac arrest despite intra-aortic balloon pumping and maximum pharmacologic support. None of these patients had significant myocardial injury, but noncardiac complications were very high, and one patient died. Thus I bring to your attention the subgroup of patients undergoing angioplasty with previous injury in the distribution of another major coronary artery.

In answer to a question from Dr. Ulliyot about a randomized study, we are currently undertaking an exhaustively planned, prospective, randomized study of multivessel angioplasty versus surgery at Emory University. The results will not be available for at least 5 years.

DR. ACINAPURA

*(Closing)*

I wish to thank all the discussants for their comments. I will respond to Dr. Ulliyot's and Dr. Murphy's comments. I agree with both that randomi-

zation and follow-up are absolutely essential. All cardiologists have been after us for the past 10 years to randomize everything we do, including inserting a Foley catheter. I think it is imperative that we have randomization, and I know of the efforts that are currently being carried out in Atlanta to randomize treatment of single-vessel, double-vessel, and multivessel disease in patients undergoing both operation and angioplasty.

In regard to the learning curve, there is not much question that there was a learning curve at St. Vincent's and Maimonides, and currently the success rate is in the range of 82% to 83%, but there is still a great deal of room for improvement.

In regard to the total complication rate for surgical patients, including neurological complications (1.1%), major wound infection rate was 2.4%, and the total complication rate for all other ancillary complications was 12.5%, which is still less than (and I cannot tell you whether this is particularly significant) the 21% total complication rate in the National Heart, Lung, and Blood Institute Registry data.

In regard to emergency operations. I believe that the key—and I am sure all of you maintain the same policy—is to have an operating room readily

available, with an operating team waiting, in case patients do have trouble. I think the area of concern here is that the angiographer must decide to terminate his attempted angioplasty early, rather than waiting for the patient to start showing signs of hemodynamic instability. The use of percutaneous and intra-aortic balloon counterpulsation would be helpful in determining whether angioplasty should be terminated.

In regard to Dr. Salomon's comments regarding costs and a hospital stay of 6.8 days, our data on hospital stays include the patients who required operation and 1 or 2 days' preoperative stay while awaiting angioplasty in the catheterization laboratory. The other area of importance, as far as cost is concerned, is the 2 day initial hospital stay. Patients are going to be coming back at the rate of about 30% for repeat angioplasty. In addition, since randomization will be necessary in order to obtain a good idea about what angioplasty is doing, these randomly assigned patients will require repeat angiography within 6 months. When the cost of repeat angioplasty is compared with the cost of repeat angiography, although I have no specific data but just concern, I think the costs will not differ significantly.



# Ανοικτό ωειδές τρήμα: Tips and Tricks στην διαγνωστική και θεραπευτική προσέγγιση

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## Εισαγωγή

Το ανοικτό ωειδές τρήμα (PFO) είναι μια σχισμοειδής ή σηραγγώδης υπολειμματική επικοινωνία στο μεσοκοιλιακό διάφραγμα που παραμένει στην ενηλικίωση όταν το πρωτογενές και το δευτερογενές μεσοκοιλιακό διάφραγμα αποτυγχάνουν να συντηχτούν πλήρως μετά τη γέννηση. Το ένα τέταρτο του ενήλικου πληθυσμού έχει αυτό το έλλειμμα, το οποίο συνήθως ανευρίσκεται ως τυχαίο εύρημα χωρίς κλινικές επιπτώσεις.

Παρ' όλα αυτά, τα PFOs σχετίζονται με αυξημένο κίνδυνο παράδοξης εμβολής, δηλαδή θρόμβων αίματος που προέρχονται από τις συστηματικές φλέβες (συνηθέστερα από το εν τω βάθει φλεβικό σύστημα των ποδιών) που μπορούν να διασχίσουν την καρδιά από την δεξιά προς την αριστερή πλευρά της και τελικά να δημιουργήσουν απόφραξη στη συστηματική αρτηριακή κυκλοφορία. Η παράδοση εμβολή είναι ο πιο αποδεκτός μηχανισμός για να εξηγήσει μια σειρά παθολογικών καταστάσεων που σχετίζονται με την παρουσία ανοικτού ωειδούς τρήματος, όπως το κρυπτογενές αγγειακό εγκεφαλικό επεισόδιο (CS). Το PFO έχει επίσης συνδεθεί με διάφορες άλλες κλινικές καταστάσεις συμπεριλαμβανομένων των ημικρανιών, περιφερικών εμβολών (συμπεριλαμβανομένων εμφράγματος του

μυοκαρδίου και νεφραγγειακής απόφραξης), την νόσο εξ αποσυμπιέσεως ή νόσο των δυτών, το σύνδρομο οικονομικής θέσης του αεροπλάνου, το πνευμονικό οίδημα μεγάλου υψομέτρου και την νόσο Alzheimer (άνοια). Η δεξιά προς τα αριστερά επικοινωνία μέσω του PFO μπορεί επίσης να επιδεινώσει τα συμπτώματα σε χρόνιες υποξικές πνευμονικές παθήσεις, όπως σε αποφρακτική υπνική άπνοια ή άλλες διαταραχές αναπνοής στον ύπνο ή στο σύνδρομο platypnea-orthodeoxia<sup>1</sup>.

Για τους ασθενείς με PFO, η αξιολόγηση συγκεκριμένων κλινικών χαρακτηριστικών τους επιπρόσθετα στις ανατομικές και αιμοδυναμικές πληροφορίες που προκύπτουν από την ηχοκαρδιογραφία, μπορεί να βοηθήσει σημαντικά στην εκτίμηση της πιθανότητας παράδοξης εμβολής. Μία υποομάδα αυτών των ασθενών μπορεί να επωφεληθεί και από διαδερμική σύγκλειση του PFO<sup>2,3</sup>. Η επισκόπησή μας έχει ως στόχο να δώσει μια γενική εικόνα των ανατομικών και απεικονιστικών χαρακτηριστικών των PFOs καθώς και της θεραπευτικής αντιμετώπισής τους. Η εμβρυολογία και ανατομία του PFO θα παρουσιαστούν πρώτα, ακολουθούμενες από την απεικονιστική αξιολόγησή του και τις φαρμακευτικές ή επεμβατικές θεραπευτικές στρατηγικές διαχείρισής του.

## Εμβρυολογία PFO

Ξεκινώντας από την τέταρτη βδομάδα της κύησης, ο αρχέγονος μονόχωρος κόλπος χωρίζεται σε δεξί και αριστερό τμήμα με σχηματισμό και σύντηξη δύο διαφραγμάτων: του πρωτογενούς και δευτερογενούς διαφράγματος. Το πρωτογενές διάφραγμα είναι αρχικά ημισελινοειδές, δημιουργώντας ένα μεγάλο παράθυρο που συνδέει το αριστερό και δεξιό κόλπο. Αναπτύσσεται από την αρχέγονη κοιλιακή οροφή προς τα ενδοκαρδιακά επάρματα. Στη δεξιά πλευρά του πρωτογενούς διαφράγματος, μια άλλη ημισελινοειδής μεμβράνη αναπτύσσεται από το κοιλιοκρανιακό τοίχωμα: το δευτερογενές διάφραγμα. Σταδιακά αναπτύσσεται και επικαλύπτει μέρος του δευτερογενούς τρήματος, σχηματίζοντας ένα διαφραγματικό παράθυρο ωοειδούς σχήματος. Αυτό το παράθυρο είναι το ωοειδές τρήμα. Το πρωτογενές διάφραγμα σχηματίζει μία βαλβίδα τυπου περυγίου-πάνω από το ωοειδές τρήμα, η οποία κλείνει τυπικά με σύντηξη με το δευτερογενές διάφραγμα μετά τη γέννηση. Αυτή η σύντηξη έχει ολοκληρωθεί από την ηλικία των δύο ετών σε περίπου 75% των ενηλίκων ατόμων, αλλά άλλοτε παραμένει ατελής στο υπόλοιπο 25%. Οι λόγοι της αποτυχίας σύγκλισης του PFO είναι άγνωστοι, αλλά κατά πάσα πιθανότητα σχετίζονται με πολυπαραγοντική κληρονομικότητα (για παράδειγμα σε γονίδια όπως το Notch 3)<sup>2-4</sup>.

## Απεικόνιση και διάγνωση του PFO

Το υπερηχοκαρδιογράφημα είναι ο στυλοβάτης της απεικόνισης των PFOs, καθώς βοηθά στον καθορισμό της ανατομίας τους και στην ποσοτικοποίηση του shunt μέσω του διαφραγματικού ελλείμματος. Η c-TTE (διαθωρακική ηχοκαρδιογραφία αντίθεσης) είναι συνήθως το πρώτο βήμα στην ανίχνευση τους καθώς είναι προσιτή και εύκολη στην εκτέλεση. Η ειδικότητα της είναι παρόμοια με της c-TEE (διοισοφάγειος ηχοκαρδιογραφία αντίθεσης) (≈100%), ωστόσο, η ευαισθησία της είναι χαμηλότερη (87% έναντι 98% αντίστοιχα), ιδίως στην ανίχνευση των μικρών shunt. Λόγω φτωχότερης απεικονιστικής ανάλυσης, η

c-TTE δεν μπορεί να παρέχει τόσο λεπτομερείς πληροφορίες σχετικά με την μορφολογία του μεσοκοιλιακού διαφράγματος όσο η c-TEE<sup>5</sup>.

Η c-TEE παραμένει ο «χρυσή» απεικονιστική τεχνική για την άμεση απεικόνιση του shunt και της ανατομίας ενός PFO. Ο κύριος περιορισμός της είναι ο παρεμβατικός της χαρακτήρας. Για να πραγματοποιηθεί ολοκληρωμένα η μελέτη ενός PFO, η TEE θα πρέπει να περιλαμβάνει Doppler ροής. Η ενδοφλέβια χορήγηση αναδευμένου αλατούχου διαλύματος ή παράγοντα αντίθεσης κατά τη διάρκεια δοκιμασίας Valsalva ή με εξωτερικούς χειρισμούς όπως εξωτερική κοιλιακή συμπίεση μπορεί να αυξήσει την δεξιά προς τα αριστερά ροή μέσω του μεσοκοιλιακού διαφράγματος. Με αυτό τον τρόπο αυξάνεται η διαγνωστική ευαισθησία της μεθόδου με την ενίσχυση της υπερηχοκαρδιογραφικής ανίχνευσης μιας ασήμαντης, διαλείπουσας δεξιά προς τα αριστερά ροής σε ένα τυπικό PFO, δεδομένου ότι η μελέτη έγχρωμου Doppler ανιχνεύει μόνο το 5-10% των shunts. Επιπλέον, η έλευση των τριών διαστάσεων διοισοφάγειας ήχοκαρδιογραφίας (3D-TEE) επέτρεψε την καλύτερη κατανόηση της PFO μορφολογίας. Τα 3D TEEs είναι ιδιαίτερα χρήσιμα για την οριοθέτηση της σχέσης του PFO με τις γύρω δομές αλλά και κατά τη διάρκεια της διαδικασίας διαδερμικής σύγκλισής τους.

Το διακρανιακό Doppler αντίθεσης(c-TCD) είναι ένα ευαίσθητο, εύκολο εφικτό και ακριβές διαγνωστικό εργαλείο. Ο κύριος περιορισμός του είναι χαμηλότερη ειδικότητα λόγω της δυσκολίας στη διαφοροποίηση του ενδοπνευμονικού shunt από το ενδοκαρδιακό (ευαισθησία 97% - ειδικότητα 93%)<sup>5</sup>.

Κατά συνέπεια, τα c-TCD και c-TTE μπορούν να θεωρηθούν συμπληρωματικές διαγνωστικές μελέτες πρώτης γραμμής για τη διάγνωση ενός PFO. Αν μια καταγραφή απεικονίζει πειστικά μικροφουσαλίδες να εμφανίζονται στον αριστερό κόλπο αμέσως μετά την άφιξή τους στο δεξιό κόλπο, τότε η παρουσία ενός PFO μπορεί να θεωρηθεί πιθανή. Αν φουσαλίδες εμφανίζονται στον αριστερό κόλπο μετά από 5παλμούς αφότου εμφανιστούν στο δεξιό κόλπο, τότε θα πρέπει να εξεταστεί το ενδεχόμενο της ανώμαλης φλεβώδους επικοινωνίας με το αριστερό κόλπο ή της

πνευμονικής αρτηριοφλεβώδους δυσπλασίας<sup>4</sup>.

Μια θετική πρώτη διαλογή που θα καθορίσει την παρουσία μιας δεξιάς προς τα αριστερά επικοινωνίας, θα πυροδοτήσει την ανάγκη για περαιτέρω εκτίμηση με TEE. Η TEE συνιστάται επίσης εάν τα ευρήματα της TTE είναι αρνητικά ή ασαφή, αλλά υπάρχει μεγάλη υποψία PFO ιδιαίτερα σε εκείνους που βιώνουν επαναλαμβανόμενα αγγειακά εγκεφαλικά επεισόδια. Η TEE (αντίθεσης ή εάν είναι διαθέσιμη η 3D) θα μπορούσε επίσης να πραγματοποιηθεί α) σε ασθενείς με ανεύρυσμα του μεσοκοιλιακού διαφράγματος (ASA) και / ή διαπιστώσεως ενός μεγάλου παράδοξου shunt στο c-TCD β) σε ασθενείς που είναι προγραμματισμένοι για διαδερμικό καθετηριασμό σύγκλεισης του PFO και γ) σε ασθενείς στους οποίους πρέπει να διερευνηθεί μια εναλλακτική πηγή καρδιακής εμβολής. Ένας αλγόριθμος ανεύρεσης ενός πιθανού PFO με την βοήθεια απεικονιστικών τεχνικών φαίνεται στην Εικόνα 1.

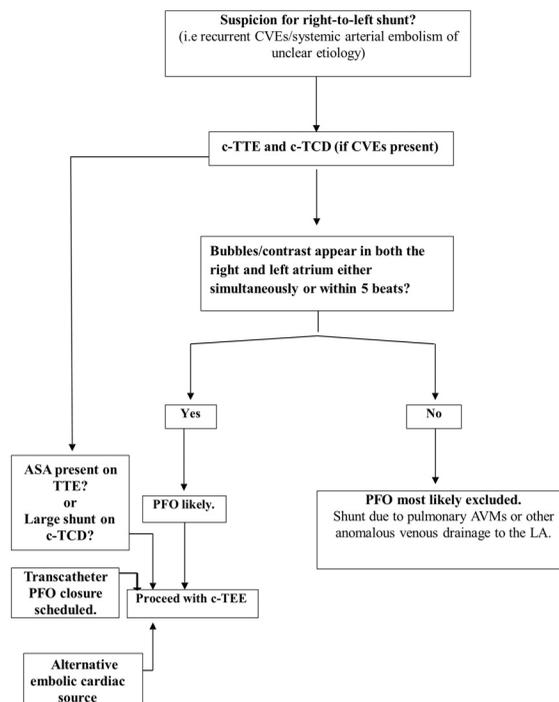
Θα πρέπει να σημειωθεί, ωστόσο, ότι η πιο ακριβής δοκιμασία για τον προσδιορισμό της παρουσίας ενός PFO είναι ο δεξιός καρδιακός καθετηριασμός, με τεκμηρίωση από ένα οδηγό σύρμα να διασχίζει το κοιλιακό διάφραγμα<sup>3,4</sup>.

## PFO ανατομία

Το PFO (Εικ.2) είναι μία λοξή σχισμή ή σήραγγα στο μεσοκοιλιακό διάφραγμα με το πλάτος της να κυμαίνεται σε ενήλικες από 1 έως 19 mm (μέση τιμή 4,9 mm). Το άνοιγμα στην αριστερή κοιλιακή πλευρά τείνει να είναι σχήματος ημισελήνου<sup>2</sup>.

– *PFO μέγεθος*: Η μέτρηση της μέγιστης απόστασης μεταξύ του πρωτογενούς και του δευτερογενούς διαφράγματος προς τον αριστερό κόλπο είναι η πιο συχνά χρησιμοποιούμενη παράμετρος για την αξιολόγηση του μεγέθους ενός PFO και η συνήθης πρακτική<sup>4</sup>. Η μέτρηση πρέπει να γίνεται αμέσως μετά την δοκιμασία Valsalva κατά τη μέγιστη αύξηση της πίεσης στο δεξιό κόλπο σε σχέση με την πίεση στον αριστερό. Κατά συνέπεια, το PFO μπορεί να χαρακτηριστεί ως μεγάλο =4mm, 2-3.9mm μεσαίες και μικρές <2 χιλιοστών<sup>4</sup>.

– *PFO μήκος*: Το μήκος της επικαλυπτόμενης

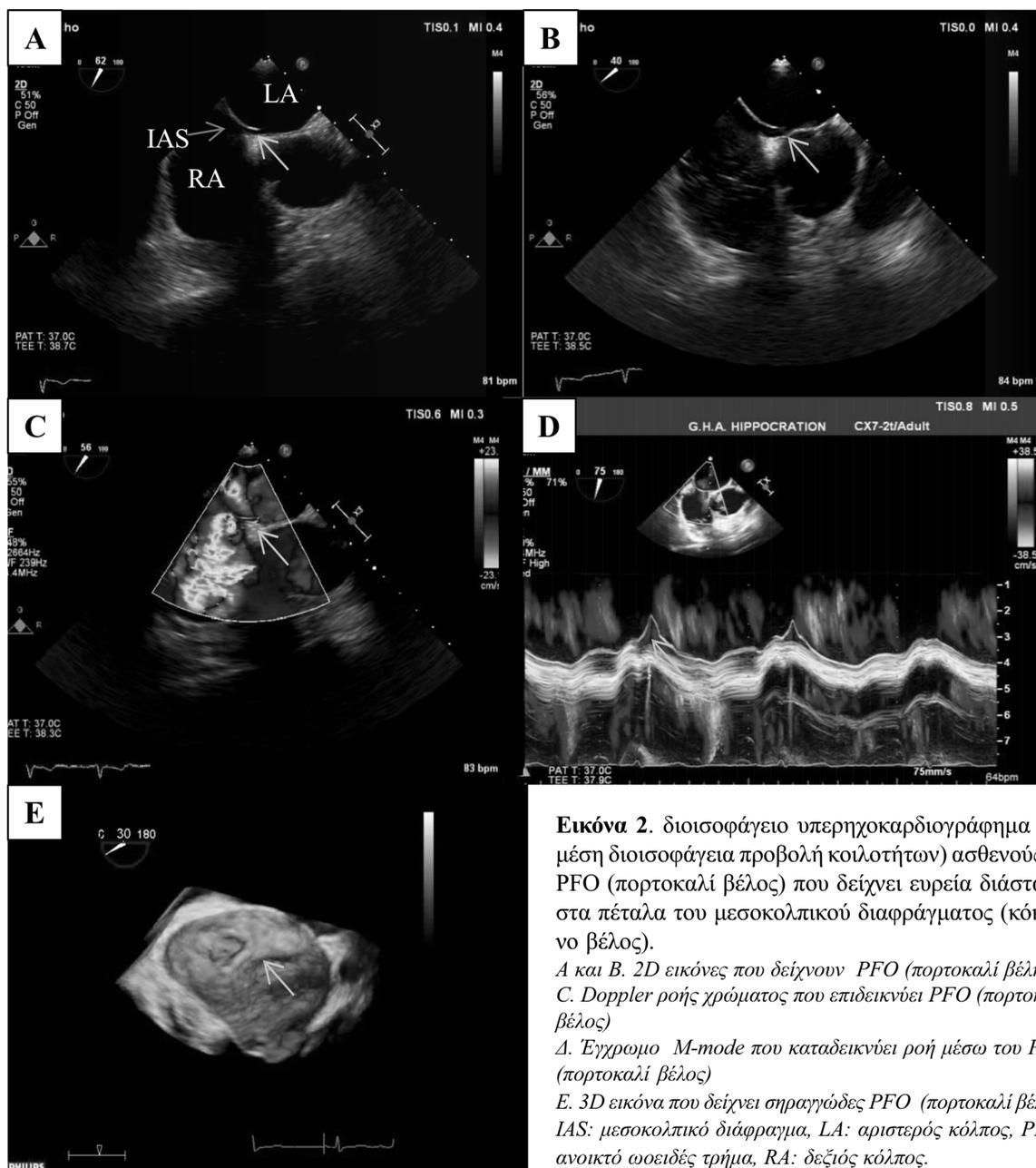


**Εικόνα 1.** αλγόριθμος ανεύρεσης πιθανού PFO με απεικονιστικές μεθόδους

ASA: ανεύρυσμα μεσοκοιλιακού διαφράγματος, AVM: αρτηριοφλεβώδεις δυσπλασίες, c-TCD: διακρανιακό Doppler αντίθεσης, c-TEE: διοισοφάγιο υπερηχοκαρδιογράφημα αντίθεσης, c-TTE: διαθωρακικό υπερηχοκαρδιογράφημα αντίθεσης, CVEs: αγγειακά εγκεφαλικά επεισόδια, LA: αριστερός κόλπος, PFO: ανοικτό ωοειδές τρήμα

περιοχής που παρεμβάλλεται μεταξύ του πρωτογενούς και δευτερογενούς διαφράγματος είναι ευρέως μεταβλητή, κυμαινόμενη από ένα μικρό εικονικό κανάλι (που δύσκολο να διαφοροδιαγνωσθεί από το δευτερογενές μεσοκοιλιακό έλλειμμα) έως ενός σηραγγώδους PFO<sup>4</sup>.

– *Χείλη ωοειδούς τρήματος*: Το κοιλιακό διάφραγμα αποτελείται από το λεπτό κεντρικό τμήμα που προέρχεται από το πρωτογενές διάφραγμα (και αντιπροσωπεύει την βάση του ωοειδούς τρήματος) και ένα παχύτερο όριο που προέρχεται από το δευτερογενές διάφραγμα, το οποίο σχηματίζει το μεγαλύτερο μέρος της δεξιάς πλευράς του μεσοκοιλιακού διαφράγματος της καρδιάς. Τα χείλη που οριοθετούν το ωοειδές τρήμα χωρίζονται σε πέντε περιοχές (κατώτερο, οπίσθιο, ανώτερο, αορτικό, άνω κοίλης φλέβας). Το πιο σημαντικό είναι το κατώτερο, το οποίο χωρίζει το



**Εικόνα 2.** διοισοφάγειο υπερηχοκαρδιογράφημα (σε μέση διοισοφάγεια προβολή κοιλότητων) ασθενούς με PFO (πορτοκαλί βέλος) που δείχνει ευρεία διάσταση στα πέταλα του μεσοκοιλιακού διαφράγματος (κόκκινο βέλος).

A και B. 2D εικόνες που δείχνουν PFO (πορτοκαλί βέλη)

C. Doppler ροής χρώματος που επιδεικνύει PFO (πορτοκαλί βέλος)

Δ. Έγχρωμο M-mode που καταδεικνύει ροή μέσω του PFO (πορτοκαλί βέλος)

E. 3D εικόνα που δείχνει σπυραγώδες PFO (πορτοκαλί βέλος)

IAS: μεσοκοιλιακό διάφραγμα, LA: αριστερός κόλπος, PFO: ανοικτό ωοειδές τρήμα, RA: δεξιός κόλπος.

ωοειδές τρήμα από την κάτω κοίλη φλέβα. Το πάχος των χειλέων που περιβάλλουν το ωοειδές τρήμα είναι ένας σημαντικός και καθοριστικός παράγοντας στην επιλογή της κατάλληλης θεραπείας<sup>4</sup>. Η παρουσία χειλέων του ωοειδούς τρήματος ιδιαίτερου πάχους αποτελεί παράγοντα κινδύνου για την μη ιδανική τοποθέτηση και σταθερότητα μιας συσκευής σύγκλισης. Έχει αναφερθεί ότι ένα πάχος =10mm μπορεί να αντιπροσωπεύει ένα πιθανό εμπόδιο στην πλήρη και ορθή απελευθέρωση μιας συσκευής σύγκλισης ενός PFO (Σχήμα 3).

### Συνυπάρχουσες καρδιακή δομές ή ελλείματα

– **Ανεύρυσμα μεσοκοιλιακού διαφράγματος:** Το ASA ορίζεται ως μια εντοπισμένη σακκοειδής δυσμορφία του μεσοκοιλιακού διαφράγματος στο επίπεδο του ωοειδούς τρήματος, η οποία προεξέχει προς τα δεξιά ή τον αριστερό κόλπο ή αμφότερα<sup>6</sup>. Τα κριτήρια που χρησιμοποιούνται για τη διάγνωση του ASA περιλαμβάνουν μια παρέκκλιση =10mm στο δεξιά ή αριστερό κόλπο ή ένα συνολικό άθροισμα των αμφοτέρων παρεκκλίσεων > 10 mm<sup>7</sup>. Ο Olivares Reyes και οι συν.<sup>7</sup> ταξινομούν τα ASA με βάση την κατεύθυνση της

παρέκκλισης τους σε πέντε τύπους: Τύπος 1R, εάν η παρέκκλιση είναι προς τον δεξιό κόλπο μόνο, τύπος 2L εάν η παρέκκλιση είναι μόνο προς τον αριστερό κόλπο, τύπου 3RL εάν η κύρια παρέκκλιση είναι προς τον δεξιό κόλπο και μικρότερη προς τον αριστερό, τύπος 4LR εάν η μέγιστη παρέκκλιση είναι προς το αριστερό κόλπο με μικρότερο αυτήν προς το δεξιό κόλπο και τύπος 5, αν η ανευρυσματική κίνηση του μεσοκοιλιακού διαφράγματος είναι αμφίδρομη και σε ίση απόσταση προς τους δύο κόλπους κατά τη διάρκεια του καρδιοαναπνευστικού κύκλου. Η αναφερόμενη συχνότητα εμφάνισης του ASA είναι 1,9% με μια αναλογία γυναίκες / άνδρες 1: 2<sup>7</sup>, και μπορεί να βρεθεί σε περίπου 35% των ασθενών με PFO<sup>3,4</sup> (Εικ.4).

– *Atrial septal pouch*: μια εσοχή /οδόντωση του κοιλιακού διαφράγματος είτε στην αριστερή είτε στην δεξιά πλευρά αυτού που προκαλείται από μια ατελή σύντηξη του πρωτογενούς με το δευτερογενές διάφραγμα. Το RASP μπορεί να οδηγήσει σε λίμανση αίματος εντός του δεξιού κόλπου και ως εκ τούτου μπορεί να είναι θρομβογόνο<sup>8</sup>.

– *Ευσταχιανή βαλβίδα / δίκτυο Chiari και Eustachian ridge*: Η ευσταχιανή βαλβίδα (EV) είναι ένα εμβρυολογικό κατάλοιπο της βαλβίδας της κάτω κοίλης φλέβας. Κατά τη διάρκεια της εμβρυϊκής ζωής, η δομή αυτή κατευθύνει τη ροή του αίματος που προέρχονται από το κατώτερο φλεβικό σύστημα μέσω προς το ωειδές τρήμα προκειμένου να παρακάμψει την πνευμονική κυκλοφορία<sup>4</sup>.

Το δίκτυο Chiari (Σχήμα 4) έχει την ίδια προέλευση και είναι παρόμοιο με την EV, αλλά είναι πιο εκτεταμένο και νηματοειδές.

Η Eustachian ridge επίσης γνωστή ως φλεβώδες διάφραγμα βρίσκεται σε προνομιακή θέση μεταξύ του ωειδούς τρήματος και του στομίου του στεφανιαίου κόλπου. Το μεσαίο τμήμα της EV εισέρχεται στην δομή αυτή και συνεχίζει στον τένοντα Todaro, το οποίο συνεχίζει προς το κεντρικό ινώδες σώμα.

– *Υβριδικό ελαττώματα*: είναι ένας συνδυασμός ενός PFO με άλλα ελαττώματα του μεσοκοιλιακού διαφράγματος της καρδιάς. Αυτά μπορεί να παρουσιαστούν είτε ως διακριτές πρόσθε-

τες οπές ή ως πολλαπλές οπές του πρωτογενούς διαφράγματος (θυριδωτό διάφραγμα) σε μία άλλοτε διαφορετική απόσταση από το PFO στον αριστερό κόλπο. Ένα παράδειγμα ενός υβριδικού ελαττώματος που περιλαμβάνει ένα δευτερογενές μεσοκοιλιακό έλλειμμα -ASD σε συνδυασμό με PFO και απεικονίζεται στο Σχ.5.

## Παράδοξη εμβολή και PFO

Η πλειοψηφία των PFOS θεωρούνται καλοήθειες, ωστόσο, η κύρια κλινική σημασία τους πηγάζει από τη σύνδεσή τους με αυξημένο κίνδυνο παράδοξης εμβολής<sup>1</sup>. Το PFO είναι μια πιθανή οδός για τη διέλευση συσσωρεύσεων αιμοπεταλίων, θρόμβων, φυσαλίδων αερίων ή άλλων σωματιδίων από τη συστηματική φλεβική κυκλοφορία στον εγκέφαλο, εάν η πίεση στον δεξιό κόλπο υπερβεί την πίεση στον αριστερό. Αυτό μπορεί να προκληθεί από το βήχα, το γέλιο, το φτέρνισμα, την βαθιά εισπνοή ή μετά από δοκιμασία Valsalva.

## Εντοπισμός και διαχείριση των χαρακτηριστικών υψηλού κινδύνου για παράδοξη εμβολή

Μετά την ανίχνευση ενός PFO, πρέπει να πραγματοποιηθεί μια συνολική εκτίμηση για την αναγνώριση ορισμένων χαρακτηριστικών, που συνδέονται με υψηλό κίνδυνο για παράδοξη εμβολή. Ένας ενδεδειγμένος έλεγχος του μεσοκοιλιακού διαφράγματος στο σύνολό του είναι επίσης απαραίτητος για να πραγματοποιηθεί μια επιτυχημένη σύγκλιση του PFO όταν αυτή συνίσταται. Τα πιο σημαντικά στοιχεία που πρέπει να αντιμετωπιστούν είναι τα εξής:

α) Μέγεθος του PFO = 3 mm: Αυτό έχει αποδειχθεί ότι είναι ο πιο ισχυρός προγνωστικός παράγοντας υποτροπής αγγειακού εγκεφαλικού επεισοδίου εντός 3 ετών<sup>9</sup>. Παρόμοια αποτελέσματα, που αποκαλύφθηκαν και σε άλλες μελέτες, αναφέρουν ότι η παρουσία ενός μεγάλου μεγέθους PFO σχετιζόταν με αυξημένη υποτροπή ενός ισχαιμικού εγκεφαλικού επεισοδίου<sup>4, 10, 11</sup>.

β) το μέγεθος του shunt: Αυτό μπορεί να μετρηθεί έμμεσα με μέτρηση του αριθμού των φυσαλίδων που διέρχονται από το PFO στον αρι-

στερό κόλλο μετά από ενδοφλέβια έγχυση σκιαγραφικού στην TEE ή TTE. Σε αυτή τη βάση, το shunt μπορεί να οριστεί ως μικρό όταν περνούν =5 φυσαλίδες, μέτριο όταν περνούν 6-25 φυσαλίδες ή σοβαρό όταν περνούν > 25 φυσαλίδες (Σχήμα 6). Θα πρέπει να σημειωθεί ότι δεν υπάρχει κοινή συμφωνία για αυτές τις τιμές.

Το μέγεθος του shunt μπορεί επίσης να αξιολογηθεί με τη χρήση του TCD το οποίο έχει δείξει καλή συσχέτιση με δεδομένα που προέρχονται από TEE<sup>5</sup>. Ένα μεγάλο shunt ορίζεται από την ανίχνευση > 10 μικροεμβολικών σημάτων που συχνά συνδέονται με μια σχεδόν συνολική επικάλυψη στο φάσμα Doppler (φαινόμενο κουρτίνας-curtain effect). Μεγαλύτερο PFO συνδέεται συνήθως με ένα πιο σοβαρό shunt.

Συμπτωματικοί ασθενείς βρέθηκαν να έχουν μεγαλύτερα PFOs και shunts συχνότερα σε σχέση με ασθενείς με σιωπηρά PFOs<sup>4</sup>. Επιπλέον, τα αποτελέσματα της μελέτης RESPECT έδειξαν ότι οι ασθενείς με ένα μεγάλο shunt και συνυπάρχον ASA ωφελήθηκαν περισσότερο από διαδερμική σύγκλιση του PFO αντί αποκλειστικά της φαρμακευτικής θεραπείας<sup>3</sup>. Η χρήση των δοκιμασιών αύξησης της πίεσης στον δεξιό κόλλο, ιδιαίτερα της δοκιμασίας Valsalva, είναι ζωτικής σημασίας για να εκτιμηθεί με ακρίβεια το μέγεθος και η σοβαρότητα του shunt.

γ) παρουσία σημαντικού shunt σε κατάσταση ηρεμίας: Σημαντικό shunt διαμέσου ενός PFO σε κατάσταση ηρεμίας (χωρίς δοκιμασίες πρόκλησης) έχει συνδεθεί με αυξημένο κίνδυνο υποτροπής αγγειακών εγκεφαλικών επεισοδίων-CVEs<sup>5</sup>. Η παρουσία εν ηρεμία του από δεξιά προς αριστερά shunt-RLS συνδέεται με τον υψηλότερο κίνδυνο υποτροπής<sup>3</sup>.

δ) Παρουσία ανευρύσματος του μεσοκοιλιακού διαφράγματος-ASA: Ανίχνευση ενός ASA συσχετίζεται με υψηλότερη πιθανότητα παρουσίας ενός PFO (περίπου 60%)<sup>4</sup>. Το ASA συνδέεται με μεγάλου μεγέθους PFOs και κάποιοι συγγραφείς το θεωρούν ως χαρακτηριστικό γνώρισμα ενός δυναμικά σοβαρού shunt<sup>4</sup>. Σε ασθενείς που εμφανίζονται με κρυπτογενές αγγειακό εγκεφαλικό επεισόδιο-CS και PFO, η παρουσία ASA είναι ένας ανεξάρτητος προγνωστικός δείκτης υποτροπής νευρολογικών εκδηλώσεων<sup>9</sup>. Ο Meisser

και οι συν. ανέφεραν κίνδυνο CVE σχεδόν τέσσερις φορές υψηλότερο σε ασθενείς με ASA ανεξάρτητα της διάγνωσης PFO<sup>12</sup>. Παρουσία ενός ASA έχει επίσης συσχετισθεί με χαμηλότερα ποσοστά επιτυχών συγκλίσεων PFOs και μεγαλύτερη πιθανότητα υπολειμματικών shunt κατά την μετέπειτα παρακολούθηση των ασθενών πιθανώς λόγω της σχετικής αστάθειας της εμφυτευμένης συσκευής<sup>4</sup>.

ε) Σηραγγώδες-Tunneled PFO (Εικ.2, 4, 5): PFOs με μορφή σήραγγας =8mm έχουν συσχετιστεί με αυξημένο κίνδυνο επαναλαμβανόμενων CVEs, με υψηλότερη συχνότητα ατελούς σύγκλισης τους διαδερμικά με συσκευή, καθώς και με υπολειμματικό shunt μετά από διαδερμική σύγκλιση<sup>4</sup>. Έχει διατυπωθεί η υπόθεση ότι στροβιλώδης ροή του αίματος διαμέσου ενός PFO με την μορφή ενός μακρού σωλήνα, προάγει την θρομβογένεση<sup>4</sup>. Οι θρόμβοι αυτοί θα μπορούσαν να προκαλέσουν εμβολή στο περιφερικό αρτηριακό δίκτυο, αυξάνοντας τον κίνδυνο CVEs, ωστόσο η θεώρηση αυτή δεν έχει σαφώς αποδειχθεί<sup>4</sup>. Η διαδερμική σύγκλιση των μακρών-σήραγγωδών PFOs είναι συχνά δύσκολη, διότι οι συσκευές σύγκλισης με σχετικά στενό αυχένα δεν «κάθονται» καταλλήλα στην περιοχή του ελαττώματος και η συσκευή μπορεί να παραμείνει μερικώς ξεδιπλωμένη<sup>13, 14</sup>.

στ) συνυπάρχον RASP: Είναι μια πιθανή πηγή κρυπτογενούς εμβολής, όταν συνδέονται με μια οδό δεξιάς προς αριστερά επικοινωνίας, όπως στο PFO<sup>6</sup>.

ζ) Παρουσία ενός υβριδικού ελλείμματος: Το πιο σημαντικό θέμα στην παρουσία ενός υβριδικού ελλείμματος, είναι η ανάγκη να κλείσουν όλα τα ελλείμματα κατά τη διάρκεια της διαδερμικής παρέμβασης, ώστε να αποφευχθεί η παραμονή ενός σημαντικού υπολειμματικού shunt.

η) Ευσταχιανή βαλβίδα /δίκτυο Chiari: Ο Ingleliss και οι συν. ανέδειξε ότι προγνωστικός παράγοντας υποτροπιαζόντων CVEs ήταν η παρουσία μιας εμφανούς EV<sup>15</sup>. Μια συνυπάρχουσα EV ή ένα δίκτυο Chiari μπορεί επίσης να επηρεάσει την τοποθέτηση μιας συσκευής σύγκλισης, εμποδίζοντας τη διέλευση των συρμάτων και μειώνοντας το διαθέσιμο χώρο στο δεξιό κόλλο. Η ακριβής αξιολόγηση αυτών των δομών είναι

ζωτικής σημασίας, προκειμένου να σχεδιάσει την πιο κατάλληλη θεραπευτική στρατηγική.

θ) Eustachian ridge: Μια υπερβολικά εξέχουσα Eustachian ridge μπορεί να επηρεάσει τη σωστή τοποθέτηση και έκπτυξη μιας συσκευής σύγκλισης<sup>4</sup>. Επιπλέον, αν ο δίσκος στηρίζεται σε αυτή τη δομή, η προκύπτουσα τάση τόσο στη συσκευή όσο και το πρωτογενές διάφραγμα μπορεί να οδηγήσει στην μη αποτελεσματική σύγκλιση του PFO και παραμονή shunt<sup>4</sup>.

### **Κλινικά χαρακτηριστικά υψηλού κινδύνου παράδοξης εμβολής που δεν σχετίζονται με PFO**

α) Ηλικία: οι νεαροί ασθενείς με PFOs θεωρούνται ότι είναι σε αυξημένο κίνδυνο για CS. Περίπου το ήμισυ των ασθενών <60 ετών με κρυπτογενές εγκεφαλικό επεισόδιο έχουν PFO, σχεδόν διπλάσιο δηλαδή επιπολασμό σε σχέση με το γενικό πληθυσμό<sup>16</sup>.

β) Εν τω βάθει φλεβική θρόμβωση: Η υπόθεση της παράδοξης εμβολής μέσω ενός PFO προϋποθέτει την παρουσία εν τω βάθους φλεβικής θρόμβωσης<sup>17</sup>.

γ) νευροαπεικονιστικά χαρακτηριστικά: Ταυτοποίηση κενотоπιωδών εγκεφαλικών έμφράκτων (lacunar strokes) συνδέεται συνήθως με εγγενή παθολογία των μικρών εγκεφαλικών αγγείων παρά με εμβολή<sup>4</sup>. Η διεξοδική αξιολόγηση νευροακτινολογικά με μαγνητική τομογραφία πρέπει να γίνεται πριν αποφασιστεί η διαδερμική παρέμβαση για σύγκλιση ενός PFO.

δ) προθρομβωτική κατάσταση: η υπερπηκτικότητα μπορεί να διευκολύνει το σχηματισμό θρόμβων στο φλεβικό σύστημα και να έχει σχέση με παράδοξη εμβολή<sup>4</sup>.

ε) Το RoPE score: είναι ένα κλινικά προερχόμενο score που βασίζεται στην Risk of Paradoxical Embolism μελέτη και μπορεί να βοηθήσει γιατί παρέχει την πιθανότητα ένα CS να σχετίζεται με την παρουσία ενός PFO<sup>18</sup>. Μπορεί επίσης να παρέχει την πιθανότητα επανάληψης ενός εγκεφαλικού επεισοδίου ή παροδικού εγκεφαλικού επεισοδίου σε ασθενείς με προηγούμενο CS<sup>18</sup>. Με βάση τη μελέτη RoPE, οι μεταβλητές που αυξάνουν την πιθανότητα εύρεσης ενός PFO σε ασθενείς με CS είναι: η νεαρότερη ηλικία, η παρου-

σία ενός εγκεφαλικού επεισοδίου στο φλοιό του εγκεφάλου κατά τη νευροαπεικόνιση και η απουσία διαβήτη, υπέρτασης, χρήσης καπνού και προηγούμενου εγκεφαλικού επεισοδίου ή παροδικού ισχαιμικού εγκεφαλικού επεισοδίου<sup>18</sup>.

### **Κρυπτογενές αγγειακό εγκεφαλικό επεισόδιο και PFO**

Η πιο αποδεκτός μηχανισμός για να εξηγήσει τη σχέση μεταξύ CS και PFO είναι η παράδοση εμβολής. Περίπου το 35% των εγκεφαλικών ισχαιμικών επεισοδίων ορίζονται ως κρυπτογενή διότι είναι αδύνατον να προσδιοριστεί μια σαφής αιτιολογία τους<sup>4</sup>. Η διάγνωση του CS μπορεί να γίνει μόνο αποκλείοντας άλλες πηγές εγκεφαλικού επεισοδίου, όπως η καρωτιδική νόσος ή εμβολή εκ της καρδιάς<sup>3, 4, 12</sup>. Η TTE ή η TEE μπορούν να χρησιμοποιηθούν για την αξιολόγηση των λοιπών πηγών των εκ της καρδιάς εμβολών (ενδοκαρδιακών θρόμβων, όγκων) ή να αποκαλύψουν αθηρώματα στην ανιούσα αορτή του ή /και το τόξο, αποκλείοντας τη διάγνωση του CS<sup>19</sup>. Η παρουσία φλεβικών θρομβοεμβολικών υποστρωμάτων θα πρέπει να αξιολογείται με μελέτη Doppler ή τεχνικές μαγνητικού συντονισμού ή υπολογιστική τομογραφία απεικόνισης του φλεβικού συστήματος. Επιπλέον, θα πρέπει να εκτελούνται δοκιμασίες ελέγχου πήκτικότητας, όπως ο χρόνος προθρομβίνης, ο χρόνος ενεργοποιημένης μερικής θρομβοπλαστίνης, τα αντιφωσφολιπιδικά αντισώματα, το ινωδογόνο, οι πρωτεΐνες C και S, η αντίσταση στην ενεργοποιημένη πρωτεΐνη C, η αντιθρομβίνη<sup>3, 4</sup>.

Σε ασθενείς με CS ο επιπολασμός του PFO είναι 40% και η ανακάλυψη πολλών εξ αυτών είναι τυχαία ευρήματα<sup>1</sup>. Πρόσφατες μεγάλες προοπτικές μελέτες κατέδειξαν ότι το PFO δεν είναι δείκτης πιθανότητας πρόβλεψης ενός εγκεφαλικού επεισοδίου ή σιωπηλού αγγειακού εγκεφαλικού επεισοδίου<sup>4</sup>. Ως εκ τούτου η διαχείριση με αντιπηκτική (συνήθως βαρφαρίνη) ή αντιαιμοπεταλιακή αγωγή (συνήθως ασπιρίνη) συστήνεται ως δευτερογενής προφύλαξη για τους ασθενείς με προηγούμενο θρομβοεμβολικό συμβάν για να μειωθεί ο κίνδυνος για υποτροπιάζουσα παράδο-

ξης εμβολής<sup>4</sup>. Πρόσφατα η διαδερμική σύγκλιση του PFO έχει εισαχθεί ως ενδεχόμενη πιθανή θεραπευτική επιλογή για τους ασθενείς με προηγούμενο CS<sup>4</sup>. Χειρουργική σύγκλιση ενός PFO διενεργείται συνήθως ως συμπληρωματική παρέμβαση σε εγχείρηση ανοιχτής καρδιάς που διενεργείται για άλλη αιτία, αλλά που σπάνια γίνεται από μόνη της αποκλειστικά για σύγκλιση ενός PFO, λόγω της νοσηρότητάς της<sup>4</sup>. Οι ασθενείς με PFO και CS που αντιμετωπίζονται φαρμακευτικώς, δεν έχουν υψηλότερο κίνδυνο για υποτροπιάζον κρυπτογενές CVE σε σύγκριση με εκείνους χωρίς PFO (2-4% ετησίως)<sup>3, 20, 21</sup>. Επιπλέον, οι μελέτες WARSS και PICSS ανέδειξαν μη σημαντική επίδραση της από του στόματος αντιπηκτικής αγωγής σε σχέση με την από του στόματος αντιαμοπεταλιακή σε ασθενείς με PFO και CS<sup>3, 1</sup>.

Οι μελέτες, CLOSURE που διερεύνησε την σύγκλιση του PFO με συσκευή STARFLEX-ομπρέλα σύγκλισης<sup>22</sup>, PC<sup>23</sup> και RESPECT που διερεύνησαν τον AMPLATZER-δίσκο σύγκλισης ενός PFO<sup>6, 24</sup> ανέδειξαν μια τάση της διαδερμικής σύγκλισης να είναι πιο ευεργετική σε σχέση με αποκλειστικά την φαρμακευτική θεραπεία<sup>4</sup>. Πρόσφατα παρουσιάστηκαν και τα τελικά αποτελέσματα της εκτεταμένης παρακολούθησης (Αύγουστος 2003- Μάιος 2016) της μελέτης RESPECT που έδειξαν ότι η διαδερμική σύγκλιση του PFO ήταν πιο ευεργετική από την φαρμακευτική αποκλειστικά διαχείριση για τη μείωση των υποτροπών σε αγγειακά εγκεφαλικά επεισόδια (62% μείωση του σχετικού κινδύνου 95% CI-0,18- 0,79)<sup>25</sup>. Η διαδερμική σύγκλιση ενός PFO θα μπορούσε να θεωρηθεί ως μία κατάλληλη θεραπευτική επιλογή για τους ασθενείς με CS για να μειώσουν τον κίνδυνο υποτροπής, αλλά η συνεργασία μεταξύ καρδιολόγων και νευρολόγων είναι σημαντική για τη κατάλληλη επιλογή των ασθενών που μπορεί να ευεργετηθούν με την συγκεκριμένη θεραπευτική παρέμβαση<sup>26</sup>. Η μελέτη RESPECT έδειξε σημαντική μείωση των σχετικού κινδύνου για ασθενείς με CS και PFO κάτω των 60 ετών που υποβλήθηκαν σε διαδερμική σύγκλιση αυτού(HR 0,42 > 95% CI 0.21 0-81)<sup>25</sup>.

Στις 28 Οκτωβρίου 2016 η Αμερικανική Υπηρεσία Τροφίμων και Φαρμάκων ενέκρινε την

St. Jude Medical συσκευή σύγκλισης PFO Amplatzer, ως τη μόνη διαθέσιμη συσκευή για την πρόληψη του εγκεφαλικού επεισοδίου με μια αξιόλογη παροχή ασφάλειας και αποτελεσματικότητας<sup>27</sup>. Αλλά, επισημαίνεται ότι «οι ασθενείς θα πρέπει να αξιολογούνται προσεκτικά από έναν καρδιολόγο και έναν νευρολόγο για να αποκλειστούν άλλες γνωστές αιτίες ενός εγκεφαλικού επεισοδίου.» Οι ασθενείς μπορεί να δραστηριοποιηθούν χωρίς περιορισμούς, ήδη από λίγες ώρες μετά την διαδερμική παρέμβαση. Συνήθως μια TTE μελέτη διενεργείται για να επιβεβαιώσει την ορθή τοποθέτηση της συσκευής προ του εξιτηρίου του ασθενούς. Η χορήγηση αντιβιοτικής αγωγής κατά τη διάρκεια της επέμβασης είναι κοινός τόπος και η πρόληψη της ενδοκαρδίτιδας συνιστάται για μερικούς μήνες μέχρι η συσκευή να καλυφθεί εντελώς από επιθηλιακό ιστό. Η μετά το εξιτήριο θεραπεία περιλαμβάνει ακετυλοσαλικυλικό οξύ (80-300 mg ημερησίως), με την προσθήκη της κλοπιδογρέλης (75 mg ημερησίως) για 1-6 μήνες. Σε 3-6 μήνες μετά από την διαδερμική σύγκλιση του PFO, θα πρέπει να επαναλαμβάνεται μια c-TEE μελέτη, για την αξιολόγηση παρουσίας ή μη υπολειμματικού shunt και αποκλεισμού θρόμβωση της συσκευής. Εάν το PFO αποδεικνύεται ότι έχει κλείσει εντελώς, η αντιθρομβωτική αγωγή μπορεί να διακοπεί, εκτός αν αυτό απαιτείται για κάποια άλλη ένδειξη π.χ. συνυπάρχουσα στεφανιαία νόσος ή προηγούμενο εγκεφαλικό επεισόδιο<sup>28</sup>.

Οι πρόσφατες δημοσιευμένες κατευθυντήριες οδηγίες (the practice advisory of the American College of Neurology, guidelines of American Heart and Stroke Association) είναι σε συμφωνία για ένδειξη της σύγκλισης του PFO περιορισμένα σε ασθενείς με PFO και CS και ειδικότερα σε εκείνους με εν τω βάθει φλεβική θρόμβωση και υψηλό κίνδυνο υποτροπής του CS<sup>4, 17</sup>. Σύμφωνα με τον European Stroke Organization<sup>29</sup> οι κλινικοί γιατροί θα μπορούσαν να εξετάσουν την διαδερμική σύγκλιση του PFO σε ασθενείς με CS / TIA και υψηλού κινδύνου PFO (συνυπάρχουσα ASA, δίκτυο Chiari, EV, μεγάλο shunt ή shunt στην ηρεμία) ή σε ασθενείς με επαναλαμβανόμενα περισσότερα από ένα εγκεφαλικά επεισόδια.

Προτείνουμε την ακόλουθη διαχείριση των α-

σθενών με εγκεφαλικό επεισόδιο που σχετίζονται με PFO:

– Μια αρχική ολοκληρωμένη και εμπειριστωμένη αξιολόγηση των ασθενών για καρδιοεμβολικές, νευρολογικές ή υπερπηκτικότητας αιτίες εγκεφαλικού επεισοδίου. Άλλες αιτίες εγκεφαλικού επεισοδίου θα πρέπει να αποκλειστούν πριν από την απόδοση του εγκεφαλικού επεισοδίου στην παρουσία ενός PFO.

– Επιθετική δευτερογενής αγωγή πρόληψης πρέπει να συσταθεί σε όλους τους ασθενείς με εγκεφαλικό επεισόδιο, εκτός αν υπάρχουν αντενδείξεις. Αυτό περιλαμβάνει και αλλαγές στον τρόπο ζωής, καθώς και φαρμακευτική αγωγή. Ελλείψει άλλης ένδειξης για αντιπηκτική αγωγή ή φλεβικής πηγής εμβολής (π.χ. εν τω βάθει φλεβική θρόμβωση), οι κλινικοί γιατροί μπορεί να συστήσουν αντιαιμοπεταλιακά φάρμακα αντί αντιπηκτικής σε ασθενείς με CS και PFO (ασπιρίνη ή κλοπιδογρέλη). Για τους ασθενείς με ισχαιμικό εγκεφαλικό επεισόδιο παροδικό ή μη και PFO και παρουσία φλεβικής πηγής εμβολής, όταν αντιπηκτική αγωγή αντενδείκνυται, μια λογική επιλογή είναι τοποθέτηση φίλτρου στην κάτω κοίλη φλέβα.

– Διαδερμική σύγκλιση του PFO με τη συσκευή AMPLATZER θα μπορούσε να θεωρηθεί ως εναλλακτική λύση έναντι αποκλειστικά της φαρμακευτικής αγωγής στην διαχείριση των ασθενών για την υποτροπιάζουσα πρόληψη εγκεφαλικού επεισοδίου, ιδιαίτερα σε εκείνους με υψηλού κινδύνου ανατομικά χαρακτηριστικά PFO και κλινικά χαρακτηριστικά που συνδέονται με αυξημένο κίνδυνο εγκεφαλικού επεισοδίου.

– Θα πρέπει να εξηγηθεί στους ασθενείς ο υψηλός επιπολασμός του PFO στο γενικό πληθυσμό, καθώς η δυσκολία να διευκρινισθεί εάν η κλινική συμπτωματολογία τους οφείλεται πραγματικά στην παρουσία του PFO ή όχι. Οι ασθενείς πρέπει επίσης να ενημερώνονται ότι αν και η διαδερμική σύγκλιση του PFO φαίνεται να είναι πιο ευεργετική από μόνη της για τη μείωση της υποτροπής αγγειακού εγκεφαλικού επεισοδίου σε ασθενείς με PFO και CS, το όφελος αυτό είναι πιο σημαντικό για εκείνους ιδιαίτερα που είναι κάτω των 60 ετών<sup>25,27</sup>. Επιπλέον, ορισμένες καταστάσεις συνδέονται τόσο με αυξημένο κίνδυ-

νο υποτροπών σε CVEs όσο και σε υψηλή συχνότητα εμφάνισης επιπλοκών κατά την διαδερμική σύγκλιση του PFO όπως η παρουσία ASA, υβριδικού ελλείμματος, το tunnel-like PFO και η παρουσία σημαντικού shunt στη ηρεμία<sup>4</sup>. Αυτό υπογραμμίζει τη σημασία της προσεκτικής εκτίμησης της σχέσης κινδύνου / οφέλους κατά την καθοδήγηση των ασθενών και την σωστή διαχείρισή τους. Επομένως πρέπει να προτρέπει η σωστή επιλογή των ασθενών που θα ευνοηθούν από την σύγκλιση του PFO για τη μείωση του κινδύνου υποτροπής εγκεφαλικού επεισοδίου σε σχέση με την πιθανότητα επιπλοκών που σχετίζονται με τη επεμβατική διαδικασία.

– Σε περιπτώσεις επαναλαμβανόμενων εγκεφαλικών επεισοδίων παρά την επαρκή φαρμακευτική αγωγή και αφού αποκλειστούν άλλοι πιθανοί μηχανισμοί πρόκλησης των εγκεφαλικών συμβαμάτων, οι κλινικοί γιατροί μπορούν να συστήσουν την διαδερμική σύγκλιση του PFO με την συσκευή AMPLATZER για την πρόληψη εγκεφαλικού επεισοδίου.

– Σε ασθενείς με υποτροπιάζον εγκεφαλικό επεισόδιο, παρά την επαρκή αντιαιμοπεταλιακή θεραπεία και όταν η διαδερμική σύγκλιση του PFO με τη συσκευή AMPLATZER δεν είναι εφικτή ή αντενδείκνυται, οι κλινικοί γιατροί μπορεί να συστήσουν αντιπηκτική αγωγή<sup>25-27, 29</sup>.

Θα πρέπει επίσης να σημειωθεί ότι για ορισμένες παθολογικές καταστάσεις, όπως στις ημικρανίες ή στην νόσο εξ αποσυμπίεσης δεν υπάρχει καμία ένδειξη για το συστηματικό έλεγχο για PFO και τα τρέχοντα στοιχεία σχετικά με την αποτελεσματικότητα της διαδερμικής σύγκλισης του PFO σε αυτές τις περιπτώσεις είναι ανεπαρκή. Παρ' όλα αυτά, λαμβάνοντας υπόψη τις συνέπειες ενός ισχαιμικού επεισοδίου η διαδερμική σύγκλιση ενός PFO πάντα μετά από κατάλληλο screening θα μπορούσε να συστηθεί σε ειδικές περιπτώσεις, όπως για επαγγελματίες δύτες<sup>25-31</sup>.

## Συμπέρασμα

Κλινικά χαρακτηριστικά των ασθενών και συγκεκριμένα ανατομικά και αιμοδυναμικά χαρακτηριστικά των PFOs που αντλούνται από την

υπερηχοκαρδιογραφία παρέχουν μεγάλη βοήθεια για την εκτίμηση της πιθανότητας παράδοξης εμβολής. Αυτά μπορούν να συμβάλλουν επίσης στη βέλτιστη επιλογή των ασθενών που θα ωφεληθούν από τη διαδερμική σύγκλιση του PFO. Η υπερηχοκαρδιογραφία διαδραματίζει κεντρικό ρόλο στην αξιολόγηση των ασθενών, τόσο για τη διάγνωση του PFO όσο και για τη διαχείρισή τους. Η 2D και 3D TEE σήμερα είναι ο στυλοβάτης στην απεικόνιση ακόμα και των πολύ μικρών

ελλειμμάτων και χρησιμοποιείται και κατά την διάρκεια των διαδερμικών επεμβάσεων σύγκλισης για την τεχνική καθοδήγηση της παρέμβασης και την εγγύηση της πλήρους σύγκλισης αυτών. Δεδομένου ότι αυτές οι τεχνικές βελτιώνονται, η χρήση τους στην ανίχνευση και τη διαχείριση των ασθενών με PFOs αναμένεται να αυξηθούν.

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# Long-Term P2Y<sub>12</sub>-Receptor Antagonists in Post-Myocardial Infarction Patients Facing a New Trilemma?

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## ABSTRACT

Physicians considering prescription of P2Y<sub>12</sub>-receptor antagonist for long-term (>1 year) protection of patients postmyocardial infarction face the trilemma of selecting between clopidogrel, prasugrel, or ticagrelor. Differential ischemic benefits derived from relevant trials may assist in tailoring treatment, although the different bleeding definitions applied make any meaningful comparison of each agent's bleeding potential very difficult. Considering the available data and recognizing the significant limitation of observations obtained thus far from subgroup analyses, prasugrel appears to provide higher anti-ischemic protection than clopidogrel. Ticagrelor seems to be an attractive option for patients with renal dysfunction, peripheral arterial disease, or following a brief P2Y<sub>12</sub>-receptor antagonist interruption, whereas clopidogrel may be advised in the presence of cost and availability issues. As head-to-head comparative trials between P2Y<sub>12</sub>-receptor antagonists are lacking, selection of a specific agent by the clinician should be made on the basis of critical appraisal of available large clinical datasets. (J Am Coll Cardiol 2016;68:1223–32)

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Dual antiplatelet treatment with a P2Y<sub>12</sub>-receptor antagonist in addition to aspirin for 1 year is considered mandatory in most patients with acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention (PCI) with stent implantation<sup>1-4</sup>. Based mainly on the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition

with Prasugrel–Thrombolysis In Myocardial Infarction 38) and PLATO (PLATElet inhibition and patient Outcomes) trial results<sup>5,6</sup>, and despite increased bleeding potential and cost, prasugrel and ticagrelor are preferentially suggested for use over clopidogrel, unless contraindications/special warnings and precautions exist<sup>1,3,4,7</sup>. Moreover, adverse events, availability, cost, adherence to treatment,

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and local reimbursement policies are among the factors that significantly influence selection of specific agents when prescribing P2Y<sub>12</sub>-receptor antagonists<sup>8</sup>. During the acute phase of ACS (in the pre-hospital setting or during hospitalization), at discharge or post-discharge, and during the recommended 1-year period of P2Y<sub>12</sub>-receptor antagonist administration, the practicing physician commonly faces the dilemma of the choice to prescribe either a novel agent or clopidogrel, or even a trilemma choice between clopidogrel, prasugrel, or ticagrelor. Of note, there is only a weak proposal for extending P2Y<sub>12</sub>-receptor antagonist administration beyond 1 year (Class IIb, Level of Evidence: A), and only after careful assessment of the patient's ischemic and bleeding risks<sup>3,4</sup>. Following the accrual of recent data, the potential beneficial role of prolonged P2Y<sub>12</sub>-receptor antagonist use beyond the first year has emerged and been re-emphasized.

The purpose of this review was to analyze the available data for the use of P2Y<sub>12</sub>-receptor antagonists for long-term protection of post-myocardial infarction (MI) patients in an effort to provide practical guidance for the clinician in selecting between clopidogrel, prasugrel, or ticagrelor.

#### INCREASED LONG-TERM RISK IN PATIENTS WITH A HISTORY OF MI

It has been well appreciated that patients with prior ACS are at heightened risk for recurrent ischemic events beyond the first year after the index event. In the GRACE (Global Registry of Acute Coronary Events) long-term study, 3,721 ACS patients were prospectively recruited and followed for a median period of 5 years; death occurred post discharge in 19% of ST-segment elevation myocardial infarction (STEMI) and 22% of non-STEMI patients, uncovering an under-recognized substantial late mortality, particularly in the NSTEMI ACS cohort<sup>9</sup>. A preliminary report of 140,887 1-year post-MI survivors drawn from unselected electronic health and administrative records in Sweden, the United States, England, and France showed the risk of further MI, stroke, or death remained high (approximately 1 in 5) across the 3 years and 4 countries studied, with fairly constant annual risks<sup>10</sup>. More recently, in a

retrospective cohort study of 97,254 MI patients who were alive 1 week after discharge, patients without a combined endpoint event (nonfatal MI, nonfatal stroke, or cardiovascular death) during the first 365 days carried a composite endpoint risk of 20.0% in the following 36 months<sup>11</sup>. This heightened late risk of ischemic events emphasizes the need for prolonged surveillance and intensive secondary prevention efforts. Of importance, the 3-year cumulative risk of hospitalized bleeding events also remains high, although with significant between-country variations<sup>10</sup>.

#### IMPACT OF LONG-TERM P2Y<sub>12</sub>-RECEPTOR ANTAGONISTS IN POST-MI PATIENTS

Long-term use of P2Y<sub>12</sub>-receptor antagonists in patients with prior MI has been studied in 3 major trials (Tables 1 to 3). In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, clopidogrel, 75 mg once daily (o.d.), was compared to placebo, added to low-dose aspirin therapy in a stable population with either established atherothrombotic disease or multiple risk factors for atherothrombotic events. No statistically significant benefit was found with clopidogrel in the overall population studied. However, in patients with documented prior MI, ischemic stroke, or symptomatic peripheral arterial disease (PAD) and over a follow-up period of 27.6 months, clopidogrel provided a lower rate (7.3%) of the primary efficacy endpoint (a composite of cardiovascular death, MI, or stroke) than placebo (8.8%), with a hazard ratio (HR) of 0.83 (95% confidence interval [CI]: 0.72 to 0.96; *p* = 0.01)<sup>12</sup>. Moderate bleeding was significantly increased with clopidogrel: 2.0% versus 1.3% (HR: 1.60; 95% CI: 1.16 to 2.20; *p* = 0.004). In a post hoc subgroup analysis of 3,846 patients with a history of MI (at a median time of 23.6 months earlier), the primary efficacy endpoint rates were 6.6% and 8.3% in the clopidogrel and placebo arms, respectively (HR: 0.774; 95% CI: 0.613 to 0.978; *p* = 0.031).

In the DAPT (Dual Antiplatelet Therapy) study, 9,961 patients who did not experience adverse events in the first year after PCI with drug-

eluting stent(s) (DES) were randomized to receive an additional 18 months of a thienopyridine therapy (clopidogrel, 75 mg o.d., or prasugrel, 10 mg o.d. [5 mg o.d. if <60 kg in weight]) or placebo in addition to aspirin, 75 to 162 mg o.d.<sup>13</sup>. Continued treatment with a thienopyridine compared with placebo reduced the rates of both stent thrombosis, 0.4% versus 1.4%, respectively (HR: 0.29; 95% CI: 0.17 to 0.48;  $p < 0.001$ ), and major adverse cardiovascular and cerebrovascular events (MACCE: a composite of death, myocardial infarction, or stroke), 4.3% versus 5.9%, respectively (HR: 0.71; 95% CI: 0.59 to 0.85;  $p < 0.001$ ). The rate of moderate or severe bleeding, as assessed according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) criteria, was increased with continued thienopyridine treatment: 2.5% versus 1.6%, respectively (HR: 1.61; 95% CI: 1.21 to 2.16;  $p = 0.001$ ). Among 11,648 DAPT patients treated with either DES or bare-metal stents, 3,576 patients (30.7%) presented with MI as the index event 1 year prior to randomization<sup>14</sup>. In this cohort, continued thienopyridine therapy for between 12 and 30 months reduced stent thrombosis compared with placebo: 0.5% versus 1.9%, respectively (HR: 0.27; 95% CI: 0.13 to 0.57;  $p < 0.001$ ). This effect was consistent in both the MI and non-MI cohorts ( $p$  interaction = 0.69). In the MI cohort, the MACCE rate was reduced with continued thienopyridine therapy for between 12 and 30 months, from 6.8% in the placebo group to 3.9% in the active treatment group (HR: 0.56; 95% CI: 0.42 to 0.76;  $p < 0.001$ ). The reduction in MACCE was greater for patients with MI than for those in the non-MI cohort ( $p$  interaction = 0.03). Moderate or severe bleeding was higher for continued thienopyridine therapy (1.9%) than with placebo (0.8%; HR: 2.38; 95% CI: 1.27 to 4.43;  $p = 0.005$ ), and this effect was consistent across patients with and without MI presentation ( $p$  interaction = 0.21).

In the PEGASUS–TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial, 21,162 participating patients with prior MI 1 to 3 years earlier were

randomized to receive ticagrelor at a dosage of 90 mg twice daily, ticagrelor at a dosage of 60 mg twice daily, or placebo in addition to aspirin, 75 to 150 mg o.d.<sup>15</sup>. At a median follow-up of 33 months, the composite of cardiovascular death, MI, or stroke was reduced (HR: 0.84; 95% CI: 0.76 to 0.94;  $p = 0.001$  for pooled ticagrelor dosages; HR: 0.85; 95% CI: 0.75 to 0.96;  $p = 0.008$  for 90 mg of ticagrelor; and HR: 0.84; 95% CI: 0.74 to 0.95;  $p = 0.004$  for 60 mg of ticagrelor vs. placebo). TIMI (Thrombolysis In Myocardial Infarction) major bleeding occurred more frequently with ticagrelor (2.60% with 90 mg of ticagrelor and 2.30% with 60 mg of ticagrelor) than with placebo (1.06%) with HR of 2.69 (95% CI: 1.96 to 3.70) and HR of 2.32 (95% CI: 1.68 to 3.21), respectively, and  $p$  value of  $< 0.001$  for each dose versus placebo. Cardiovascular mortality was 2.90% with ticagrelor (pooled doses) versus 3.39% with placebo (HR: 0.85; 95% CI: 0.71 to 1.00;  $p = 0.06$ ). Contrary to the PLATO findings, where use of ticagrelor (vs. clopidogrel) was followed by a higher rate of intracranial hemorrhage, no such difference was found among the 3 PEGASUS–TIMI 54 groups. Although both of the ticagrelor doses were associated with a similar magnitude of efficacy, the 60-mg dose was associated with numerically less bleeding and dyspnea and a lower rate of discontinuation than the 90-mg dose, implying a more attractive benefit–risk profile. The U.S. Food and Drug Administration recently approved a dosage of 60 mg twice daily for ticagrelor<sup>16</sup>.

In a meta-analysis of the 3 trials discussed previously, along with 3 other studies involving ACS patients, dual antiplatelet treatment beyond 1 year decreased the risk of MACCE (a composite of cardiovascular death, nonfatal MI, and nonfatal stroke) compared with aspirin alone (6.4% vs. 7.5%, respectively; risk ratio [RR]: 0.78; 95% CI: 0.67 to 0.90;  $p = 0.001$ )<sup>17</sup>. Cardiovascular death was reduced (2.3% vs. 2.6%, respectively; RR: 0.85; 95% CI: 0.74 to 0.98;  $p = 0.03$ ), whereas noncardiovascular mortality did not differ significantly (RR: 1.03; 95% CI: 0.86 to 1.23;  $p = 0.76$ ). The risk of major bleeding was increased (1.85% vs. 1.09%, respectively; RR: 1.73; 95% CI: 1.19 to 2.50;  $p = 0.004$ ) but the risk of fatal bleeding was not (0.14%

	<b>CHARISMA Subanalysis (n = 9,478)</b>	<b>DAPT Subanalysis (n = 11,648)</b>	<b>PEGASUS-TIMI 54 (n = 21,162)</b>
Study type	Post hoc analysis of a randomized, double-blind, placebo-controlled study	Post hoc analysis of a randomized, double-blind, placebo-controlled study	Randomized, double-blind, placebo-controlled study
Study objective	Assessment of the possible benefit of dual antiplatelet therapy	Assessment of the benefits and risks of 30 vs. 12 months of dual antiplatelet therapy	Assessment of the efficacy and safety of dual antiplatelet therapy with ticagrelor
Population	Documented prior MI, ischemic stroke, or symptomatic PAD Excluded: subjects on chronic medications, such as warfarin, high-dose aspirin, or NSAID	PCI with stenting (either DES or BMS) 1 yr before, and free from MI, stent thrombosis, stroke, repeat revascularization, moderate or severe bleeding, and adherent with thienopyridine Excluded: subjects on warfarin or similar anticoagulant therapy, or with planned surgery, index PCI with concomitant DES and BMS	MI 1-3 yrs before enrollment, age >50 yrs + 1 of the following additional high-risk features: age ≥65 yrs; diabetes; a second prior MI; multivessel CAD; CrCl <60 ml/min Excluded: subjects taking anticoagulants, with a bleeding disorder, prior ischemic stroke, or intracranial bleeding, GI bleeding within 6 months, or major surgery within 30 days
Number of patients with prior MI	3,846 (40.6%)	3,576 (30.7%)	21,162
Time from MI to randomization	23.6 months median	12 months	1-3 yrs 20.4 months median
Treatment groups	Clopidogrel vs. placebo	Thienopyridine vs. placebo	Ticagrelor 90 mg bid vs. ticagrelor, 60 mg b.i.d., vs. placebo
Follow-up period	27.6 months (median, for the whole study cohort)	18 months (months 12-30 after coronary stent treatment)	33 months (median)
Primary efficacy endpoint	The composite of CV death (including hemorrhagic death), MI, or stroke	Definite or probable stent thrombosis and MACCE* (coprimary endpoints)	The composite of CV death, MI, or stroke
Primary safety endpoint	GUSTO severe bleeding	GUSTO moderate or severe bleeding	TIMI major bleeding

\*MACCE were defined as the composite of death, MI, or stroke.  
b.i.d. = twice a day; BMS = bare-metal stent(s); CAD = coronary artery disease; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CrCl = creatinine clearance; CV = cardiovascular death; DAPT = Dual Antiplatelet Therapy; DES = drug-eluting stent(s); GI = gastrointestinal bleeding; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiovascular or cerebrovascular events; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54; TIMI = Thrombolysis in Myocardial Infarction.

vs. 0.17%, respectively; RR: 0.91; 95% CI: 0.53 to 1.58;  $p = 0.75$ ). Limitations of this metaanalysis (e.g., pooled trials with heterogeneous populations,

no evaluation of individual patient-level data, analysis of subgroups) are recognized.

Taken together, the results from the randomized studies discussed previously and meta-analysis suggest that in patients with a prior MI and features of high ischemia and low bleeding risk, physicians may consider reinitiating or extending treatment with a P2Y<sub>12</sub>-receptor antagonist beyond 1 year.

## WHICH P2Y<sub>12</sub>-RECEPTOR ANTAGONIST TO USE?

Physicians deciding on the use of long-term (>1 year) P2Y<sub>12</sub>-receptor antagonists are likely facing a dilemma: the choice between clopidogrel, 75 mg o.d. (used in CHARISMA and in 66.4% of patients in the MI cohort of DAPT); prasugrel, 10 mg o.d. or 5 mg o.d. for patients <60 kg (used in 33.6% of patients in the MI cohort of DAPT); or ticagrelor, 60 mg twice daily (used in one-half of the PEGASUS active comparator population) (Central Illustration). In fact, direct comparisons among the different

**TABLE 2 Baseline Characteristics of Patients Enrolled in Major Studies Evaluating Long-Term P2Y<sub>12</sub>-Receptor Antagonists Post MI**

	<b>CHARISMA Subanalysis</b>	<b>DAPT Subanalysis</b>	<b>PEGASUS-TIMI 54</b>	
	<b>Clopidogrel arm of Whole Study Cohort</b>	<b>Thienopyridine Arm of the MI Group</b>	<b>Ticagrelor, 90-mg Arm</b>	<b>Ticagrelor, 60-mg Arm</b>
Age	64 (56, 71)	57.9 ± 10.5	65.4 ± 8.4	65.2 ± 8.4
Female	27.3	22.4	23.9	23.6
Diabetes	30.8	20.8	31.8	32.8
Hypertension	68.3	59.8	77.5	77.5
Current smoker	21.6	41.8	16.8	17.1
CHF	6.3	3.0	NA	NA
Stroke or TIA	44.2	2.1	NA	NA
PAD	32.3	2.6	5.3	5.2
Prior MI	46.3	19.1	16.2	16.6
Prior PCI	25.5	16.4	83.0	83.5
Prior CABG	17.1	4.1	NA	NA
Indication for PCI				
STEMI	NA	46.8	53.4	53.4
NSTEMI		53.2	41.1	40.4
Renal insufficiency/failure	4.1 (diabetic nephropathy)	3.5	23.8*	22.2*
LVEF <30%	NA	2.6	NA	NA
DES	NA	72.4	NA	NA

Values are median (Q1, Q3), mean ± SD, or %. \*Renal dysfunction was defined as estimated glomerular filtration rate <60 ml/min/1.73 m<sup>2</sup>.  
CABG = coronary artery bypass graft; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NA = not applicable; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; other abbreviations as in Table 1.

**TABLE 3 Main Results of Studies Evaluating Long-Term P2Y<sub>12</sub>-Receptor Antagonists in Post-MI Patients**

	CHARISMA Subanalysis	DAPT Subanalysis	PEGASUS-TIMI 54
Primary efficacy endpoint	CV death (including hemorrhagic death), MI, or stroke; Clopidogrel, 6.6%, Placebo, 8.3%; HR: 0.774 (95% CI: 0.613-0.978); p = 0.031	Stent thrombosis; Thienopyridine,* 0.5%; Placebo, 1.9%; HR: 0.27 (95% CI: 0.13-0.57), p < 0.001; MACCE Thienopyridine,* 3.9%; Placebo, 6.8%; HR 0.56 (95% CI: 0.42-0.76), p < 0.001;	CV death, MI, or stroke; Ticagrelor, 90 mg: 7.85%; Ticagrelor, 60 mg: 7.77%; Placebo, 9.04%; • Ticagrelor 90 mg vs. placebo: HR: 0.85 (95% CI: 0.75-0.96), p = 0.008; • Ticagrelor, 60 mg vs. placebo: HR: 0.84 (95% CI: 0.74-0.95), p = 0.004
Safety endpoints (bleeding rates)	GUSTO severe No significant difference; GUSTO moderate Clopidogrel, 2.0%; placebo, 1.3%; HR: 1.60 (95% CI: 1.16-2.20); p = 0.004; For the whole study cohort	GUSTO moderate or severe Thienopyridine, 1.9%; placebo, 0.8%; HR: 2.38 (95% CI: 1.27-4.43), p = 0.005;	TIMI major Ticagrelor, 90 mg, 2.60%; ticagrelor, 60 mg, 2.30%; placebo 1.06%; HR: 2.69 (95% CI: 1.96-3.70) and 2.32 (95% CI: 1.68-3.21), p < 0.001 for each dose versus placebo

\*66.4% clopidogrel, 33.6% prasugrel.  
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

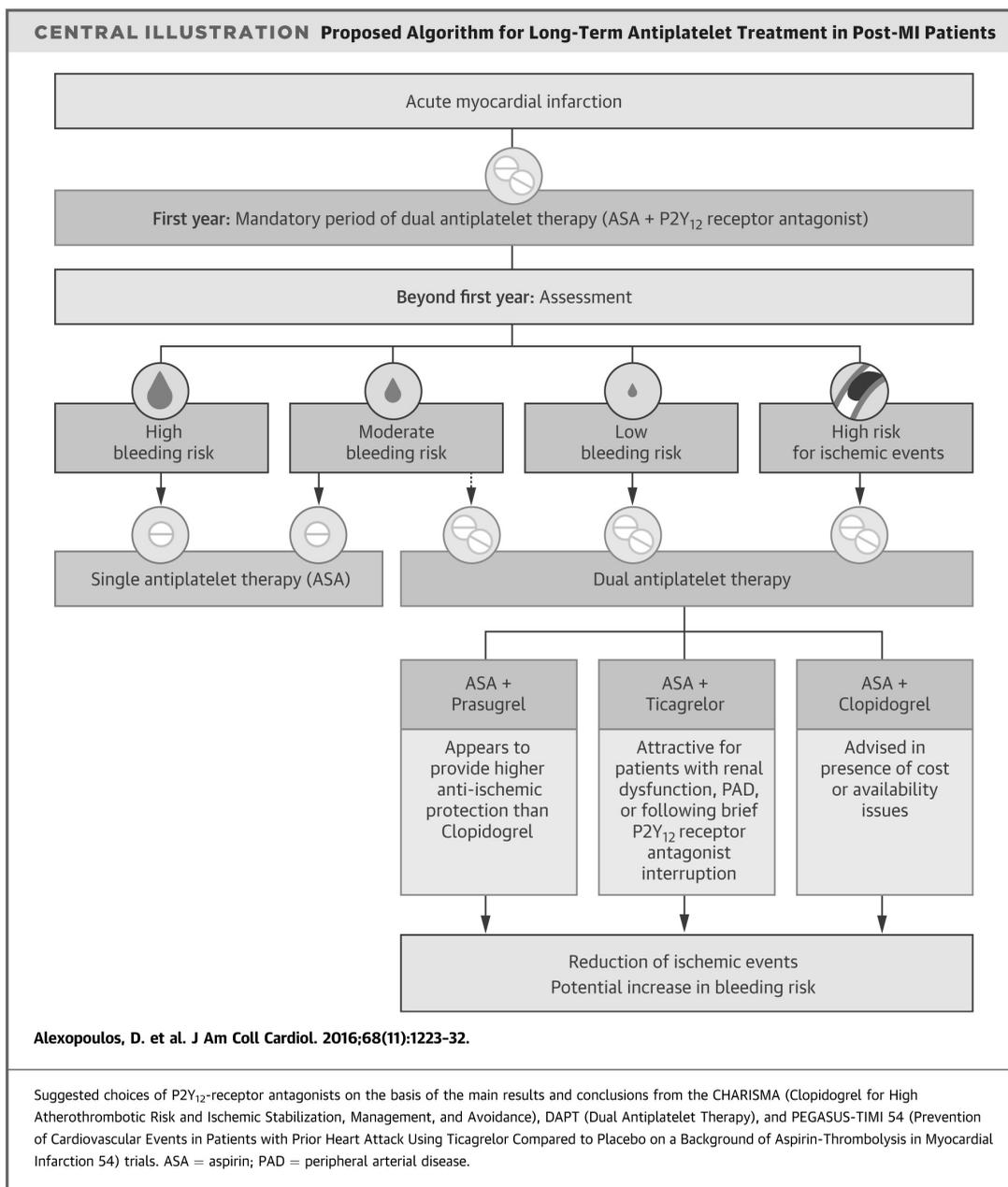
P2Y<sub>12</sub>-receptor antagonists with respect to efficacy, safety, and cost effectiveness for the long-term treatment of post-MI patients do not exist, creating the challenge of comparing trials like CHARISMA, DAPT, and PEGASUS–TIMI 54.

The first, obvious question is the choice between clopidogrel or a more potent agent like prasugrel or ticagrelor. Absolute risk reductions in the composite of cardiovascular death, MI, or stroke (defined as MACCE in DAPT and MACE in PEGASUS–TIMI 54) were 1.7%, 2.9%, and 1.27% for clopidogrel, thienopyridine, and ticagrelor, 60 mg twice daily, in CHARISMA, DAPT, and PEGASUS–TIMI 54, respectively (Table 3, Figure 1). Absolute risk increase in GUSTO moderate bleeding was 0.7%, in GUSTO severe/ moderate bleeding 1.1%, and in TIMI major bleeding 1.24% with clopidogrel, thienopyridine, and ticagrelor, 60 mg twice daily, in CHARISMA, DAPT, and PEGASUS, respectively (Table 3, Figure 2). Importantly, the time interval from the index event to randomization was 12 months in DAPT but 23.6 and 20.4 months in CHARISMA and PEGASUS–TIMI 54, respectively. Data from PEGASUS–TIMI 54 have convincingly shown a higher rate of MACCE in patients in the placebo arm who had discontinued their P2Y<sub>12</sub>-receptor antagonist within the previous 30 days (9.91% at 3 years) than that in those who had discontinued 30 days to 1 year previously (8.70%) and those who stopped more than 1 year before randomization (6.91%; p trend = 0.0097)<sup>18</sup>. Therefore, patients studied in DAPT may be considered to have had a higher ischemia risk than those in CHARISMA or in

PEGASUS–TIMI 54, as they were studied closer to their index event.

Clopidogrel is the most widely used P2Y<sub>12</sub>-receptor antagonist worldwide, available in generic form and with a lower bleeding potential<sup>5,6</sup>. Nevertheless, clopidogrel carries the drawback of a variable response, with approximately one-third of Caucasian patients having inadequate platelet inhibition by criteria that have been developed mostly from studies in the acute setting of ACS or PCI<sup>19</sup>. Of note, platelet function analysis was not used for treatment guidance in any of the long-term P2Y<sub>12</sub>-receptor antagonist post-MI studies and represents for this setting “navigation in unknown waters.” Although clopidogrel selection for cases without high on-clopidogrel platelet reactivity or categorized as rapid metabolizers by genetic testing may be attractive, it lacks supportive data and is absolutely speculative.

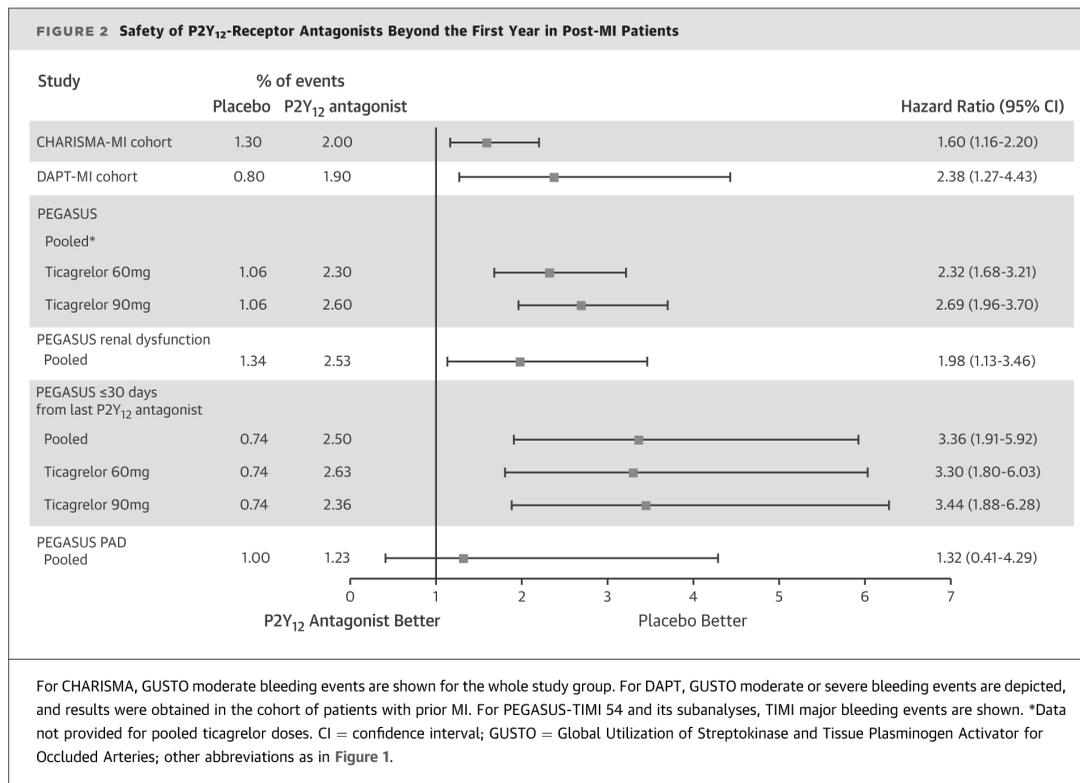
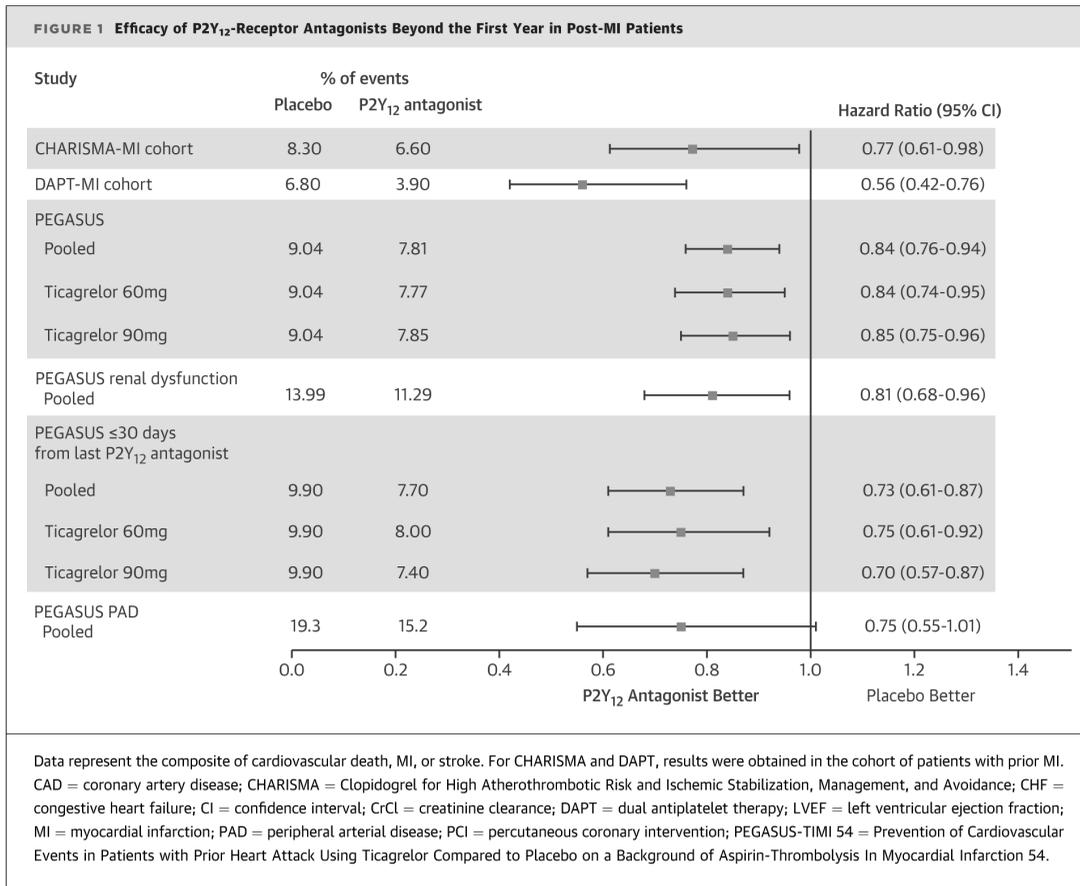
Regarding selection of clopidogrel versus prasugrel, some information is provided by the results of DAPT, in which the overall population treatment effect on MACCE was affected by the thienopyridine type, as prasugrel-treated patients had more benefit from extended treatment (continued prasugrel, 4.0% vs. placebo 7.3%; HR: 0.52; 95% CI: 0.38 to 0.71) than those treated with continued clopidogrel (4.5% vs. placebo, 5.2%; HR: 0.80; 95% CI: 0.64 to 1.01), p interaction = 0.03. However, in the MI cohort<sup>14</sup>, the benefit from extended P2Y<sub>12</sub>-receptor antagonist treatment was consistent across the thienopyridine type: the definite or probable stent thrombosis rate was 0.4% in the clopidogrel group versus 1.2% in the placebo



group (HR: 0.29; 95% CI: 0.10 to 0.90) and 0.9% in the prasugrel group versus 3.2% in the placebo groups (HR: 0.26; 95% CI: 0.10 to 0.69), with  $p$  interaction = 0.86. The MI rate was 2.3% in the clopidogrel versus 4.3% in the placebo group (HR: 0.52; 95% CI: 0.32 to 0.83) and 2.2% in the prasugrel versus 6.8% in the placebo group (HR: 0.32; 95% CI: 0.17 to 0.59), with  $p$  interaction = 0.22. Furthermore, the extended P2Y<sub>12</sub>-receptor antagonist treatment effects in GUSTO moderate or severe bleeding were consistent across thienopyridine type: 2.2% and 0.6% with clopidogrel and

placebo, respectively (HR: 3.60; 95% CI: 1.56 to 8.29) and 1.4% and 1.2% with prasugrel and placebo, respectively (HR: 1.14; 95% CI: 0.41 to 3.15), with  $p$  interaction = 0.09.

Long-term protection post MI might require a lower intensity of platelet inhibition than in the acute setting, and therefore the role of a lower dosage of prasugrel (e.g., 5 mg o.d.) could be considered. However, data from the small cohort of DAPT patients receiving 5 mg of prasugrel have not been provided. Of note, in the elderly cohort of medically managed ACS patients (78.4% presenting



with NSTEMI) treated with 5 mg of prasugrel, the cumulative risk of primary efficacy endpoint and non-coronary artery bypass graft-related TIMI major bleeding through 30 months were similar to those in the clopidogrel arm<sup>20</sup>.

In PEGASUS–TIMI 54, active treatment was compared to placebo, and we cannot speculate about the relative efficacy and safety of a ticagrelor-based versus a clopidogrel-based strategy in a similar population. Of note, a pharmacodynamic comparison study between clopidogrel, 75 mg o.d., and ticagrelor, 60 mg twice daily, in the chronic phase of stable post-MI patients with PEGASUS–TIMI 54-like characteristics is currently underway (NCT0266-3713).

### SPECIAL SUBGROUPS

In an effort to individualize treatment duration, a post hoc analysis of the DAPT population has proposed a decision tool to identify whether an individual patient is more likely to derive benefit or harm from extension of dual antiplatelet therapy beyond 1 year after PCI<sup>21</sup>. On the basis of a composite of individual patient characteristics and simultaneously accounting for patient risks of ischemia and bleeding events with continued therapy, a 9-item score was created, consisting of age ( $\geq 75$  years of age, 65 to 74 years of age), prior PCI or MI, stent diameter  $< 3$  mm, congestive heart failure or left ventricular ejection fraction  $< 30\%$ , MI at presentation, paclitaxel-eluting stent, smoking, and diabetes. In patients with a DAPT score  $< 2$ , continued thienopyridine therapy versus placebo was associated with no significant differences in stent thromboses or MI (1.7% vs. 2.3%, respectively;  $p = 0.07$ ) and MACCE rates (3.7% vs. 3.8%, respectively;  $p = 0.73$ ), whereas GUSTO moderate/severe bleeding occurred more frequently with continued thienopyridine (3.0%) than with placebo (1.4%;  $p < 0.001$ ). In contrast, patients with a DAPT score  $\geq 2$  had a favorable benefit-risk ratio with continued thienopyridine compared with placebo: the stent thrombosis or MI rates were 2.7% and 5.7%, respectively ( $p < 0.001$ ), whereas the MACCE rates were 4.9% and 7.6%, respectively ( $p < 0.001$ ). GUSTO moderate/severe bleeding did not differ

between the 2 treatment strategies (1.8% vs. 1.4%, respectively;  $p = 0.26$ ). Recognized limitations of the DAPT score are that it is the product of a post hoc analysis, not powered to examine differences in outcomes between subgroups, and that incomplete information on potential unmeasured confounders cannot be excluded. A recent exploratory analysis of the DAPT study by MI status and DAPT score described, in patients with any MI and a score  $\geq 2$ , a reduction in MI/stent thrombosis with continued thienopyridine versus placebo (2.7% vs. 6.0%, respectively;  $p < 0.001$ ) and bleeding rates of 1.5% vs. 1.1%, respectively ( $p = 0.24$ )<sup>22</sup>; the number needed to benefit was reduced from 39 to 31, and the number needed to harm was increased from 106 to 226. In contrast, among patients with DAPT scores  $< 2$ , continued thienopyridine therapy was associated with increased bleeding (3.2% vs. 1.2%, respectively;  $p = 0.01$ ) and no significant differences in ischemia rates.

Thus far, 2 pre-specified subanalyses of PEGASUS–STIMI 54 trial have likely contributed to the identification of subgroups that will derive the most benefit with long-term ticagrelor treatment. For MACCE, renal dysfunction did not modify ticagrelor's effect ( $p$  interaction = 0.44)<sup>23</sup>. However, the absolute risk reduction was 4 times higher in patients with renal dysfunction than in those without: 2.70% (95% CI: 0.49 to 4.93) versus 0.63% (95% CI: -0.32 to 1.57), respectively. These findings are in line with comparisons between ticagrelor and clopidogrel in the setting of ACS, where a 4-fold greater absolute risk reduction in MACCE was described in patients with renal dysfunction<sup>24</sup>. TIMI major bleeding events were increased with ticagrelor to a similar degree in patients with or without renal dysfunction ( $p$  interaction = 0.38), whereas the absolute increase in TIMI major bleeding with ticagrelor did not differ according to renal dysfunction (1.19% vs. 1.43%, respectively). Patients with renal dysfunction appear, therefore, to be good candidates for long-term treatment with ticagrelor.

In another subanalysis of 18,761 patients (88.7% of the total PEGASUS–TIMI 54 population with a recorded history of the timing of their last P2Y<sub>12</sub>-receptor antagonist dose prior to

randomization), results were reported for patients  $\leq 30$ ,  $>30$  to 360, and  $>360$  days from P2Y<sub>12</sub>-receptor antagonist withdrawal<sup>18</sup>. Regarding MACCE, patients who restarted ticagrelor versus placebo within 30 days had more benefit compared with those who restarted at a later time (HR: 0.73; 95% CI: 0.61 to 0.87;  $p = 0.0005$ ; HR: 0.86; 95% CI 0.71 to 1.04;  $p = 0.0853$ ; and HR: 1.01; 95% CI: 0.80 to 1.27;  $p = 0.9249$ , respectively;  $p$  trend for interaction  $< 0.001$ ). For the 7,181 patients (38%) who had their last dose within 30 days from randomization, the MACCE rate was 9.9% for placebo, 8.0% for the ticagrelor 60-mg arm (HR: 0.75; 95% CI: 0.61 to 0.92;  $p = 0.0064$ ), and 7.4% for the ticagrelor 90-mg arm (HR: 0.70; 95% CI: 0.57 to 0.87;  $p = 0.0009$ ). Both of the doses of ticagrelor increased TIMI major bleeding compared with placebo, regardless of time from the last dose of P2Y<sub>12</sub>-receptor antagonist ( $p$  interaction for 90 mg = 0.90; 0.62 for 60 mg). In the brief interruption group, the TIMI major bleeding rate was 0.74% in the placebo arm, 2.50% in the pooled doses (HR: 3.36; 95%CI: 1.91 to 5.92), 2.63% in the ticagrelor 60-mg arm (HR: 3.30; 95% CI: 1.80 to 6.03), and 2.36% in the ticagrelor 90-mg arm (HR: 3.44; 95% CI: 1.88 to 6.28;  $p < 0.0001$  for all versus placebo). These results suggest that the benefit of ticagrelor depends significantly on the time from the last dose, being more marked in patients continuing on or restarting after only a brief interruption of P2Y<sub>12</sub>-receptor antagonism. Physicians may strongly consider no interruption or early reinitialization of treatment with ticagrelor, rather than late reinitialization of treatment in patients who were stable for more than 2 years from their MI and without P2Y<sub>12</sub>-receptor antagonist therapy for more than a year.

Moreover, in a PEGASUS–TIMI 54 subgroup analysis by the presence of PAD at baseline, no heterogeneity in the relative risk reduction with ticagrelor for MACCE was described ( $p$  interaction = 0.41); a greater absolute risk reduction was seen for patients with PAD (4.1%; 95% CI:  $-1.07\%$  to 9.29%) than for those without (1.0%; 95% CI: 0.14% to 1.9%) (25). The ticagrelor-induced increase in TIMI major bleeding was consistent among groups ( $p$  interaction = 0.28). Patients with

PAD may therefore represent another clinical scenario, where ticagrelor administration appears appealing. Notably, a PEGASUS score analog to the DAPT score, which may assist in selection of the most beneficial long-term ticagrelor dose for the post-MI patient, has not yet been developed.

#### PRIOR STENTING AND TYPE OF STENT

In recent years and with the use of second-generation DES, very late stent thrombosis has become less of an issue, and events not related to the stent site appear to play the major role. In the overall population of DAPT, the rate of MI not related to stent thrombosis was 1.8% and 2.9% in the continued thienopyridine and placebo groups, respectively (HR: 0.59; 95% CI: 0.45 to 0.78;  $p < 0.001$ ), and accounted for 55% of the treatment benefit<sup>13</sup>. The DES type appeared to have an impact on the benefit obtained from continued thienopyridine therapy on lower MACCE with second- versus first-generation stents ( $p$  interaction = 0.048). In PEGASUS–TIMI 54 and in 16,891 stented patients (51% bare metal stents; 49% DES) the majority of events at 3 years (91%) were non–stent-related, supporting the significance of extended dual antiplatelet treatment as a secondary prevention measure for the post-MI patient, regardless of stent implantation<sup>26</sup>. Whether the choice of a P2Y<sub>12</sub>-receptor antagonist for the long-term treatment of the post-MI patient should be influenced by prior coronary stenting and the type of stent implanted has not been addressed thus far.

#### PRACTICAL CONSIDERATIONS

Studies in ACS patients undergoing PCI have shown a wider applicability of ticagrelor than prasugrel, mainly due to the relatively high prevalence of contraindications or warnings for the latter (e.g., history of stroke/ transient ischemic attack,  $>75$  years of age, weight  $<60$  kg)<sup>5,7,27</sup>. Nevertheless, ticagrelor is accompanied by a higher rate of dyspnea<sup>6</sup>. In DAPT, the discontinuation rate of the study drug did not differ significantly between the continued thienopyridine and placebo arms (21.4% and 20.3%, respectively;  $p = 0.18$ ). In contrast, in PEGASUS–TIMI 54, a higher proportion of patients

receiving active treatment discontinued the study: 32.0%, 28.7%, and 21.4% in the 90-mg ticagrelor, 60-mg ticagrelor, and placebo groups, respectively ( $p < 0.001$  for the comparison of each ticagrelor dose versus placebo). These differences were mainly caused by higher premature discontinuation rates in the 2 ticagrelor groups due to adverse events: 20.3%, 17.8%, and 11.1% in the 90-mg ticagrelor group, 60-mg ticagrelor group, and placebo group, respectively. The requirement for twice daily administration of ticagrelor might also affect the patient's adherence to long-term treatment. Therefore, when considering the choice between prasugrel and ticagrelor, it seems that more patients are eligible for prescription of ticagrelor, although with the likelihood of a higher rate of discontinuation due to adverse events.

Finally, the cost of novel agents, availability of generic clopidogrel, and reimbursement policies are likely to affect the long-term antiplatelet therapy choice for the individual patient. Even if a clinical trial comparing clopidogrel, prasugrel, and ticagrelor were undertaken and led to favorable results for the novel agents, one might still be left with the economic forces that drive physician usage. Notably, despite PLATO showing a clear net clinical benefit of ticagrelor over clopidogrel, there is moderate uptake of ticagrelor in most parts of the world.

## CONCLUSIONS

Physicians facing the trilemma of choice among P2Y<sub>12</sub>-receptor antagonists for long-term (>1 year) therapy of post-MI patients should mainly balance the antiischemic benefits obtained in trials of clopidogrel, prasugrel, and ticagrelor. Different bleeding definitions applied in different trials make any meaningful comparison of the relative bleeding potential of each agent practically impossible. Considering the available data, prasugrel appears to provide higher anti-ischemic protection than clopidogrel. Ticagrelor seems to be an attractive option for patients with renal dysfunction, PAD, or following brief P2Y<sub>12</sub>-receptor antagonist interruption. Clopidogrel may be advised in the presence of cost and availability issues. Of note, all relevant observations obtained so far have been on the basis of subgroup analyses. Prospectively designed and adequately powered clinical comparisons between P2Y<sub>12</sub>-receptor antagonists would be ideal to develop evidence-based recommendations on long-term antiplatelet treatment in post-MI patients. However, one would have to assume equipoise for a comparative study to be undertaken, and a head-to-head clinical trial is likely to require tens of thousands of patients, making it potentially prohibitively expensive. As it is unlikely that we will see such a study in the future, selection of a specific P2Y<sub>12</sub>-receptor antagonist by the clinician on the basis of the available clinical data appears to be a more pragmatic goal.

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# Pioneers and Buccaneers, Toilers and Spoilers. A Personal Retrospective on Cardiothoracic Transplantation

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Transplanting a heart had been the dream of surgeons from the beginning of the 20th century. In spite of Russian Vladimir Demikhov's brilliant techniques in the experimental laboratory in the 1950s, the problem remained unsolved: the invention of a simple yet reliable and reproducible method of implantation so the heart would immediately take over the circulation. All this concerned the technical part, since the problem of rejecting the "foreign" organ still had to be addressed<sup>(1)</sup>.

My first contact with the "father" of heart transplantation, Dr. Richard R. Lower, took place in the fall of 1977 when I was interviewing at the Medical College of Virginia (M.C.V.) in Richmond. I was then in my last year at Boston University repeating the general surgery training in order to qualify for the Boards. My strongest card in getting the job was a letter from my former chief, the legendary Dwight E. Harken of Harvard University, with whom I spent my first and most memorable year in the New World. Dr. Lower ran me up and down several flights of stairs of the 18-story M.C.V. tower to test my endurance but

to also show me two of his recent heart transplant recipients. I was mesmerized and knew my calling on that very day.

Lower came from Michigan, that is to say he was a Midwesterner, and as is usual with people from the middle American States, he was different: serious, a man of few words, with a very strong accent and simple manners. After doing a brief stint at Cornell University in New York, Dick, as he was known to his friends, moved to California and Stanford, where the Cardiac Surgery Unit under Norman Shumway was still in its infancy. Shumway came from the famous Minnesota School, which, under Owen Wangensteen, had made a name for pioneers in heart surgery, like C. W. Lillehei<sup>(2)</sup>. Shumway, another Midwesterner, divided his time between surgery and a primitive experimental laboratory. Genius, however, does not require luxury; on the contrary, it performs its miracles with want and deprivation.

In 1958 Lower was taken on as Shumway's first trainee and together they began to experiment on dogs, looking for a way to operate with the heart stopped and dry, but also without dam-

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aging myocardial function. Shumway created a bath in the pericardium in which a cold saline infusion continuously circulated as a preservative. They stopped the heart, therefore, clamping the aorta, and, after waiting an hour, opened it to let the blood again circulate in the myocardium. While they were waiting, they would sit idly around the table until Shumway had the idea that perhaps they could cut into the heart at the level of the ventricles and suture it together again before opening the aorta. They soon discovered that this procedure was extremely difficult, if not impossible, because there was no tissue left to stitch and furthermore it was so fragile that the animal died of hemorrhage. Then Lower had a brilliant idea: “Why don’t we use the heart of another dog so that there will be enough tissue for stitching?”<sup>(3)</sup> After the first failures, they started to have survivals. Several dogs survived for a week to ten days, at which point death was caused by tissue rejection. This was the first stable survival of the transplanted heart, by combining an ingeniously simple surgical technique with myocardial protection, solving once and for all the technical part of the procedure. The other part, survival using suitable anti-rejection drugs, would take some decades to solve.

The following year they reported to the American College of Surgeons, before an empty auditorium, the stable survival of five out of eight animals, from one to three weeks. It was obvious that their work was considered “utopian.” However, the publication that followed—concise and lucid like the one by Watson and Crick announcing in 1953 the discovery of the double helix of DNA, which won them a Nobel prize—is still today a landmark in the international bibliography<sup>(4)</sup>.

During the next seven years, the two researchers, Shumway at Stanford and Lower, now in Virginia, widened the field with innovative work and were considered by the experts, along with Adrian Kantrowitz of Maimonides Hospital in New York, to be the most likely to perform the first human heart transplant. Unfortunately, all three were hindered by the existing law: the possible donor was considered dead only after all heart activity had

ceased. What is more, a great opportunity for an ethical reward was lost to Lower in the fall of 1966, when there was the rare coincidence of a suitable donor and recipient. He did not proceed then for what proved later to be a secondary incompatibility of blood groups. Always conscientious and a perfectionist, he did not want to risk this historic operation with something that was *a priori* a negative factor on the scale of success, in spite of insistent urging to proceed by David Hume, chairman of the Department of Surgery at M.C.V., who was legendary for his drive and aggressiveness<sup>(5)</sup>.

This decision was fatal! A few months later the South African surgeon, Christiaan Barnard, came to watch Hume perform kidney transplants. Up to that point he had had no contact with heart transplants. A coincidence led him to the experimental cardiac surgery laboratory. He had popped in there simply because he was looking for Carl Gosen who had formerly been his pump technician. From Gosen, therefore, he learnt that in the next-door laboratory heart transplants were being carried out and through Lower’s pump technician, Lanier Allen, he asked if he could watch the procedure. Of course Lower, always the perfect teacher and all-unsuspecting, invited him and an hour later the South African was leaning against the wall watching, taking in every detail. When it was over he said to Gosen: “Was that all? It’s extremely simple.” Visiting Richmond for the second time, he couldn’t help saying to Gosen: “As soon as I get back to South Africa I shall try a human transplant. You here have too many prohibitions to negotiate before you can find a donor. We have no such obstacles.”

His motive was his outsized ambition to make his mark and surpass his former colleagues at the University of Minnesota, among whom was Shumway. His excuse for doing an operation for which he was not prepared was the inability of his American colleagues to proceed because of the prohibitive legislation. With great perspicacity he had realized his advantage: in South Africa only the agreement of two doctors was required to declare death in a case of irreversible brain injury, even before the heart had stopped. It was

the ace up his sleeve! With this advantage, on December 3, 1967, Barnard transplanted the heart of 25-year-old Denise Darvall, victim of a road traffic accident, into the chest of 53-year-old Louis Washkansky that caught the world completely unawares<sup>(6)</sup>. Surprise was succeeded by admiration and idol-worshipping of the protagonist, who became famous overnight. Newspapers and television channels competed to interview him and reputable scientific associations to recruit him as the principal speaker at their conferences. The jet-set of the time embraced him and famous movie stars adored him.

Shumway and Lower were wounded to the core. The former never forgave Barnard for what he considered to be the theft of his work. In the spring of 1981, in the M.C.V. amphitheater, as his second-year Resident, I heard Lower blame himself because he did not proceed then, adding sadly: "God never forgave me for that hesitation of mine and so fame and fortune went to Cape Town, South Africa, and not to Richmond, Virginia", expressing that we only regret those things we didn't do and not those we did. And as if this was not enough, when he performed his first heart transplant, in May 1968, he was accused of wrongful death action! His acquittal – and that of ten other M.C.V. doctors – in May 1972, established the acceptance of "brain death", which allows us to remove a heart before it has stopped working<sup>(7)</sup>.

This is the story of one of the most definitive and at the same time unjust developments in the history of medicine, which was decided by a minor donor/recipient incompatibility! Heart transplantation is the most famous operation of the 20<sup>th</sup> century and it is generally considered that the glory went to the doer and not to the thinker. People respect thought but adore action!

When I went to work with Lower he was already in his fifties. Always in his surgical garb and sports shoes, fit and flexible, he came and went silently. What he said, little and well-thought-out, confirmed his real genius, also betrayed by his eyes that flashed behind his spectacles for short sight. But somewhere there the connection with Lower ended. He never talked about

anything that was not strictly professional and did not have social contact with those he worked with. His enjoyments were his daily jogging and the week he went hunting with his friends on a lonely island off the coast of Virginia. He was in the hospital every day, and when there were emergencies, at the weekend. He was that rare combination of a surgeon who married his clinical work to the experimental laboratory. It was no accident that Shumway called Lower "the most important experimental surgeon after Alexis Carrel", who had been honored with the Nobel Prize for Medicine in 1912.

The other side of Lower was that of the teacher. In spite of being recognized as a leader in transplantation, his pride in his students was even greater. *For him it was almost a religious rite to sit on the left of the table and from there to help the Resident, with the simplest to the most complex procedures, only intervening when it was necessary.* Work etiquette was strictly enforced: the Resident opened the patient with the help of the general surgery Resident, and when all was ready to go on bypass, Dr. Lower was called. He helped the Resident for the main part of the operation until they came off bypass. He would then return to his office where he stayed until late studying, writing and dealing with administrative matters. Edna Jones, his African American secretary, could go without sleep to serve him faithfully, a model of serious dedication and professional dignity. He was never simply an observer during surgery, however, and when he intervened, always from his side, we saw the perfection of his technique. His hands went up and down like pistons and, without the least hesitation, placed the sutures with the ideal distance between them, as if they had not been put in by human hand. There was nothing spectacular or artistic in his movement, but the perfection of the result took our breath away. In this regard, he demanded similar operative behavior from his students, with no cutting of corners, theatrics or surgical tricks. He firmly believed in perfection and not in speed. His sarcastic comment to the first-year Resident who had just spent four months working with the exceptionally gifted Hungarian heart surgeon at

Veterans' Administration (V.A.) trained by Lower, yet combining accuracy with speed, says it all. The day that the Resident returned and started to sew, Lower observed: "I see, you too have taken the advanced course in cardiac surgery." Aghast, the Resident apologized and immediately went back to the "orthodox" technique, keeping the Hungarian's lessons for when he finished!

My relationship with Lower could be described as one of deep respect but not love. He lacked something of human warmth, the pat on the back, encouragement after failure, the "well done!" after a particularly difficult case. This was obviously foreign to him, without that meaning that he was unfeeling. The fact that he resigned at the age of fifty-nine and withdrew to a ranch in Montana, causing shock waves throughout the medical world, was probably due to the fact that he lost his younger son in a road traffic accident. It cost him a great deal more than he let on. When Edna tried to console him after the accident, he cut her short, saying: "That's over and done with now." Did he perhaps have some feelings of guilt that tortured him? We never knew...

After his withdrawal and having spent two or three miserable winters in Montana, Lower returned to Richmond where he volunteered his services to some foundation for down-and-outs. During the last year of his life, 2008, he was given the "Life Achievement Award" at the International Society's Congress in Boston. He was unable to attend because he was already suffering from pancreatic cancer. It was received on his behalf by a former student of his from Richmond. I asked for his telephone number and talked to him for the last time. His voice sounded fresh and full of life, as it always had, as if nothing unusual was happening. Shortly afterwards he stopped his chemotherapy and went back to his ranch, where he died surrounded by his children and grandchildren. I had time to send him the English publication with the intermediary results from the Onassis program and a little later I sent the final ones to his widow<sup>(26)</sup>. Ann Lower, very moved, wrote to me: "Dick would have been so glad if he had known of your new achievements".

He died as he had lived, quietly and with dig-

nity. He had tasted bitterness though because he was denied the world recognition for which he had worked harder than anyone else.

So, between 1978 and 1981, I did my cardiothoracic residency at M.C.V., including a year in the animal laboratory with another foreigner, Dr. Albert Guerraty from Canada, doing work on myocardial preservation and on a model of left ventricular assistance using an allograft. Both projects were subsequently published in reputable journals<sup>(8,9)</sup>. The second half of the year 1981 was spent in congenital heart surgery at the prestigious Great Ormond Street Hospital, in London. Then I moved a bit west, to Harefield Hospital where the great British surgeon, Sir Magdi H. Yacoub, was determined to transform an old sanatorium into the world's biggest transplant center.

I met Mr. Yacoub in his private consulting rooms near Harley Street, where the most celebrated doctors have their offices in London. He received me in a simple, friendly manner, sitting behind a large desk on which there was nothing. Knowing him better later on, I would say that he probably never used it. It was just that he had to receive me somewhere and he chose this virtually empty room. It was better like that because I was able to concentrate completely on his appearance without having my attention caught by a diploma or a photograph on the wall. The impression was astounding, as if some Pharaoh had risen from the grave! The same swarthy skin, the same ancient, calm gaze in a perfectly noble face, gave the impression that my interlocutor had lived and seen everything three thousand years before. As a surgeon I was impressed by his exceptionally delicate fingers, unusually flexible and dexterous as I could see when he inspected my papers. After two or three questions, he asked when I could start. The answer was "Immediately!"

Magdi Yacoub, Egyptian and a Christian Copt, was helped to get to England by Rosemary Radley-Smith, a pediatric cardiologist whom he was later to work with, since the Muslim regime in his country would not have allowed him to develop his talents in the same way. When Magdi went to London, he worked with Sir Russell Brock, well-known for his pulmonary valvoto-

mies at Guy's Hospital. The two most famous students of Sir Russell, afterwards Lord Bock, were Donald Ross, a South African surgeon and fellow-student of Christian Barnard, and Magdi Yacoub. As Ross wrote, their boss, although a genius in the introduction of new ideas, was technically not particularly good<sup>(29)</sup>. This is not an unusual occurrence since to the same category belong Owen Wangenstein, the famous professor of Minnesota, teacher of Lillehei and Shumway, and Alfred Blalock of Johns Hopkins, professor of Denton Cooley<sup>(29)</sup>. This bears an American colleague's pithy comment: "Great surgeons do not have 'good hands', they've got 'guts'". Apart from this, Brock had the reputation of being able to strike terror in the hearts of his coworkers with his eccentricities. He detested, for some unaccountable reason, the practice then in vogue of the assistant holding the end of the stitch so that the surgeon could tie the knots faster. He said: "Three things you do not do in this life! You do not kick a pregnant woman in the belly, you do not urinate in the sanctuary of a church and you do not hold the end of my suture!"

At the end of the '60s the historic Royal Brompton Hospital advertised the position of Consultant and Magdi rightly submitted his application. Unfortunately for the Brompton, they chose an unknown English surgeon but with a historic name. And so Magdi was limited to Harefield, west of London, which, owing to its position in the country, was also a sanatorium. It was built during the First World War for the Australian and New Zealand (ANZAC) casualties of Gallipoli, the catastrophic campaign in the Dardanelles, in 1915. It is a complex of small houses connected by long corridors. In this insignificant, anachronistic environment, therefore, Magdi Yacoub was to create the greatest Service for Heart and Lung transplants in the world, with more than two and a half thousand cases up to the end of his career. Of course, no one could have predicted his meteoric rise, not even the people he worked with. He once suggested to Sir Peter Morris, the famous Oxford professor and authority in kidney transplantation, that together they could create a program at Harefield, perhaps the largest in the

world, only to receive Morris's condescending reply: "Are you being serious, Magdi? Can you imagine *me* at Harefield?"

His industry and stamina were monumental. He could work days and nights on end, finishing at three in the morning, snatching a little sleep, usually a couple of hours, before starting the new day at one of the two hospitals, Harefield or the National Heart. Then in the evening, after more than fulfilling his obligations to the National Health Service, he would operate at the Harley Street Clinic or the Princess Grace (private hospitals). Always calm and with the utmost concentration, without making mistakes and without, as so often happens, losing his temper with his coworkers because of lack of sleep. And apart from that, he was able after two sleepless nights to examine and discuss data brought to him regarding some project that we were about to present. At two o'clock in the morning he could analyse them with absolute clarity and give the necessary guidance. His superhuman strength and tranquillity disarmed everyone and, of course, I was no exception.

Although he was absolutely calm in the operating room, he could not tolerate the slightest noise because, as he said, it stopped him "from thinking". You could see and sympathize with the fact that for him surgery was not a simple mechanical process. His brain worked continuously, sifting through details and predicting the possible outcome. It was not unusual to see him finish the operation before completing all the objectives we had set out. Releasing the aortic clamp to restore blood flow to the heart, he would say: "This patient won't tolerate any more. It's better for him to come out alive and never mind if the operation wasn't so perfect...", something that my perfectionist American teachers would not have espoused. Results proved him right.

Sir Magdi Yacoub practiced the whole gamut of cardiac surgery, adult, congenital and transplant, unattainable even for Denton Cooley. In spite of the latter's technical perfection, Magdi was undoubtedly the greater genius, not only because he introduced new concepts and new operations, especially in pediatric surgery, but be-

cause he could change the plan with the greatest skill if a different situation emerged, *tailoring the operation to the patient* and not, as so often happens, *bringing the patient "in line with" the procedure* that had been programmed. This is the supreme test of a really great surgeon!

In surgical dexterity Magdi's technique was unlike any other: it was completely his own. It was like looking at a painting of Michelangelo or Raphael that "shouts out" who the master is. His movements, without being in any way theatrical, had a princely grace and delicacy. When he operated, he created. You could not be unmoved by the perfection of what he was doing, especially when it was a child with congenital heart disease. I have never seen anyone else who could cut a circular patch to close a hole in the heart *looking at the hole and not at the patch!* He had a supernatural three-dimensional perception that enabled him to cut it the right size and shape without looking at it, his eyes glued to the hole! I did not exaggerate then and I do not exaggerate now when I call Sir Magdi Yacoub the real Leonardo da Vinci of heart surgery and I consider myself fortunate to have worked those two years with him. In the 1980s he was appointed a university professor and at the beginning of the 1990s he was knighted. The greatest honor came later when he became a member of the Royal Society of Great Britain.

Magdi never stayed on the beaten track. He immediately adopted mechanical support of the circulation as the alternative solution to transplantation and going more deeply into the matter of molecular cardiology than anyone else, he proved that hearts that are supported mechanically have a chance of recovering. At a lecture that he gave at the Hilton Hotel in Athens, we witnessed the impressive exchange of opinions, actually a duel, with the famous James Willerson, editor of the most respected cardiac journal, "Circulation". I do not think anyone understood what they were saying, but the ease with which the "surgeon" stood up to the "scientist" made a lasting impression.

During this period, 1982-1984, the heart transplants came thick and fast. When I first joined the team, a total of 40 transplants had been per-

formed and the survival rate, before the introduction of cyclosporine, was only 30%. The years 1982 and 1983 saw integration of cyclosporine into immunosuppressive protocols<sup>(10,11)</sup>. Complications, even disasters, were not uncommon. It was here that my American training for organization and efficiency was put to good use. In 1983 we did 34 cases with a spectacular rise in the rate of survival. It was then clear that there would be an increase in the next few years, and this is exactly what happened. Up to April 1984 when I left Harefield, a total of 95 transplants had been carried out. From the day I started we had done 55 cases with a short-term survival of 83%. Meanwhile, Magdi made the historic prediction: "Cyclosporine is not a substitute for clinical excellence." Future developments proved him right.

In the spring of 1984 I received several calls from Baylor to come and start the heart transplantation program. I felt that my previous stint as a Fellow in 1972-1973 was destined for this major undertaking. The enthusiasm was tempered, though, in the following couple of months because of two new developments. The first was the rumored and soon confirmed plan to start transplantation at B.U.M.C. with a liver program sponsored by Dr. Thomas Starzl of the University of Pittsburgh. The second development was the arrival of another cardiac surgeon, Dr. Ivan Crosby, who was an Australian with a very respectable associate professor's record at the University of Virginia. It was obvious that we were destined for a showdown and several months of indecisiveness and behind-closed-doors politics ensued. Eventually, I was named director with Ivan codirector, which were perceived as two equal appointments. The issue was resolved when Baylor's creator, Boone Powell Sr., met us in his office and in his booming voice said to me: "You are the director and he is your codirector! You are the pilot, he is the copilot!" That was it. We both got up, almost clicking our heels, and got to work!

The first case, performed on Alamo Day, March 6<sup>th</sup> 1986, was on a 39-year-old man with end-stage ischemic cardiomyopathy after back-to-back myocardial infarctions. The operation was performed under palpable pressure in all quarters,

because a few weeks earlier an attempted liver transplantation at Methodist Hospital, in Dallas, had failed, the patient dying on the operating table after a 24-hour ordeal. They never tried again, which proved the importance of a successful first attempt. Coming back from Atlanta with a heart we were delayed by adverse winds, yet the graft was one of the best ever. It started on its own as soon as the aortic cross-clamp was removed and the patient survived for the following seventeen years. Two more successful cases were performed in 1986, and the first case for 1987 was a 61-year old woman with dilated cardiomyopathy. This patient proved crucial for the program's development: from the very beginning she and her husband committed themselves to creating a support group and tirelessly saw it through for the following seven years, until she passed away. This support group, called "NewHearts and Lungs", enjoyed a membership in the hundreds organizing banquets, dinners and golf tournaments, providing day-to-day support for its new members.

Twenty transplants were performed in 1988, including the first combined heart/kidney transplant on a 42-year-old diabetic with end-stage cardiac and renal failure, which was also the world's fifth case. Two months later, B.U.M.C. performed the first bridge to heart transplantation in the U.S.A. using the Abiomed biventricular assist device, on a 48-year-old man in cardiogenic shock. He was discharged and survived for six months after his transplant, subsequently dying of a fulminant lymphoma.

Although lung transplantation was being developed in Toronto by Dr. Joel Cooper, up to that time the only available modality for end-stage lung disease was a combined heart and lung transplantation. I was marginally acquainted with the procedure, having assisted Mr. Yacoub in the first-ever such transplant performed in Europe. My friend from M.C.V. days, Albert Gueratty, was doing heart/lung transplants in the animal laboratory at McGill University, in Montreal, so I went there to learn the technique and twice a week we familiarized ourselves with it in the laboratory, in over 80 transplants in pigs. Just prior to our first attempt, Mr. Yacoub made headlines by introduc-

ing the concept of "domino" transplants. Given the fact that the lung transplant candidate was receiving a combined heart and lung graft and the healthy heart was discarded along with the diseased lungs, he decided to use it for another patient, whereupon the heart-lung recipient became a heart donor. We had already identified a 44-year-old man with terminal alpha-1 antitrypsin deficiency and at the same time a 64-year-old man with ischemic cardiomyopathy. Both were of the same, less frequent, blood group B.

In the early hours of March 9<sup>th</sup> 1989, a 32-year-old man became a donor (also of blood group B) thanks to his family's prompt decision and the wheels started turning. Three teams were needed in adjacent operating rooms, one for harvesting the combined heart-lung graft, another for the preparation of the heart-lung recipient and a third team for reopening the heart recipient's chest (he had had a previous coronary bypass procedure). Although the surgery went smoothly in both cases, the heart required an all-night resuscitation on bypass. The next day, exhausted after the 24-hour ordeal, we were still able to give a press conference, which made the national news and B.U.M.C. was in the limelight, because this was the first "domino" case in Texas and probably the second or third in the country. For the record, about 40 people were involved in the three operating rooms on that memorable day. After several weeks of close calls and many complications, both patients were released following another press conference.

By June 1990 the program had performed 70 transplants with a one-year survival of 84.5% and a three-year one of 80.3%. At that time it received the much-coveted Medicare endorsement, the first one in North Texas. A month later the first single lung transplant in our area was successfully performed on a 47-year-old South Carolinian, also with alpha-1 antitrypsin deficiency.

In July 1991 B.U.M.C. completed its 100th heart transplant, yet the competition for grafts among the three active programs in town, and a fourth one developing, was fierce. The concept of taking high-risk donors, therefore, fell onto receptive ears. A couple of years earlier, our German colleagues had proposed a new set of liberal

“extended donor criteria” in order to alleviate the shortage<sup>(12)</sup>. They suggested the acceptance of heretofore suboptimal grafts because of older donor age, presence of systemic disease, such as diabetes mellitus or hypertension, a compromised left ventricular contractility or the excessive administration of dopamine ( $>10\mu\text{g}/\text{kg}/\text{min.}$ ). Initial reports on the new policy were encouraging and after several discussions we decided to try. The Hospital Transplant Review Committee was kept informed. Then adversity came, swift and devastating. Between July and November 1991 five deaths were recorded, sometimes in succession, and everyone was left numb and indecisive. An impeccable audit was carried out and the verdict, issued in December 1991, stated that the deaths were due to the acceptance of high risk patients and consequently of high risk donors.

The road to recovery was long and arduous, even painful. A team reshuffling was followed by 30 consecutive heart transplants in the years 1992 and 1993 without a single postoperative loss. Additionally, two more combined heart-lung transplants and the first double lung transplant in the area, on a 30-year-old lady from Oklahoma with pulmonary hypertension, were successfully accomplished. Moreover, in the next three years (1993-96) a lung transplantation program was developed which provided the majority of cases – 44 out of 48 submitted – for the Medicare endorsement, which was granted in 1998. The 1991 calamity made a “dent” in the actuarial survival curve: in the first year it dropped to 70% and at five years to 60%. It would take four more years and 40 more transplants to rise again to 80% at one year and to 70% at five years by the time of my departure, in 1996, for Greece<sup>(13)</sup>.

This 1991 adversity deserves further scrutiny. Earlier reports on the use of two lists, one standard, the other alternate, focus on the use of older donors ( $>50$  years). It appears that these grafts, suboptimal by classical criteria, were assigned to patients on the waiting list without special regard for the recipient’s high or low risk. In a sense, these alternate lists were constructed retrospectively by putting together patients who received older grafts and then compared them to those who

were allocated standard donors. As it will be shown further on, it is a lower risk undertaking when one of the two – recipient or donor – meets standard criteria. Not surprisingly, those reports focusing on “age” as the discriminator for entrance into the alternate list, claim comparable operative mortality and long-term survival<sup>(14-16)</sup>, although others report a worse 90-day (82% vs. 91%) and 5-year (48.3% vs. 68.4%) survival<sup>(17-19)</sup>. There is agreement, however, that older donor use is associated with increased incidence (47% vs. 17%) and earlier development (6.5 years vs. 12.7 years) of cardiac allograft vasculopathy<sup>(14,15,18)</sup>.

The field looks considerably different when recipients with one or more risk factors are given marginal grafts, the standard donors being assigned to the better candidates. Later reports concern a high-risk recipient population, because of older age, renal dysfunction, diabetes m. and peripheral vascular disease matched with marginal donors due to age  $>50$  years, diabetes m., L.V. ejection fraction  $<45\%$ , high inotropic support or donor/recipient weight ratio  $<0.7$ . Combining those risks may bring the 5-year survival down to 50% compared to 75% for the standard list. The rationale for accepting this meager result is the 5.2 year median survival accorded to patients who do not qualify for a standard donor and consequently would live for less than a year without a transplant<sup>(20)</sup>. Due to the expected compromised result it is suggested the recipient give consent at the time of listing and not when the organ is offered<sup>(21)</sup>.

In spite of this information and the logic behind it, there are reports which claim that pairing high-risk recipients with high-risk donors yields results comparable to those of the standard list<sup>(22,12)</sup>. The controversy involves single-centered studies as opposed to multi-centered ones which report a postoperative mortality rate 42% higher when compared to the standard donor list<sup>(23)</sup>.

In an effort to better quantify donor risk, a 10-point scoring system was proposed based on actual discard rates for each risk factor, using Eurotransplant’s Registry. It was shown that hearts previously declined for donor related medical reasons were associated with a 1.85-fold higher risk of recipient death compared to those never turned

down. It is emphasized that the score helps identify high-risk donors before they are accepted and is by no means equivalent to an on-site graft inspection and assessment<sup>(21)</sup>. The issue of exercising extreme caution before accepting a previously refused donor was brought up in an earlier report (2005) suggesting that the heart is resuscitated carefully before being considered suitable<sup>(24)</sup>.

From all of the above it follows that alternate listing is associated with greater morbidity and resource utilization. Using United Network for Organ Sharing (UNOS) data, transplanted patients were separated into four distinct categories: standard, when both recipient and donor satisfy established criteria, alternate, when both recipient and donor are compromised, and two intermediate, when a high-risk recipient is paired with a standard donor or the reverse, a standard recipient is matched with a marginal donor (ST, ALT, HR:SD, SR:HD). As expected, survival was best in the standard category (75%) and worst in the alternate list (51.4%). However the two intermediate categories yielded an acceptable 67% survival at 5 years. *The important lesson is that pairing two high-risk components (recipient and donor) is associated with a very significant morbidity.* On the other hand, if one of the two meets the classical criteria, then the result is quite acceptable<sup>(20)</sup>.

Finally, there is another suggestion which may improve the outcome of this high-risk combination (HR:HD). Data point to a better outcome by as much as 13% at 5 years, when the transplant is performed at a high volume center, i.e. one doing >25 transplants per year vs. a low volume one, designated as such by the performance of <14 transplants per year<sup>(23)</sup>.

The conclusion is that marginal donors will continue to be used and matched with suboptimal recipients as good grafts are reserved for the better candidates. However, keeping in mind that pairing two outright high-risk components will increase the risk substantially, it may be prudent to modify it by allocating a marginal graft to a standard recipient. *This match demands considerable experience, therefore it is better left to high volume centers.*

Based on the above brief review it is evident

now that the outcome of our 1991 effort to maximally utilize donors was doomed from the outset. Without experience we combined high-risk recipients with high-risk donors, the worst case scenario, and the fact that the program did recover is a tribute to Baylor's resources, ethical, medical and administrative. The vicissitudes of that ten-year creative effort at B.U.M.C. were described in its institutional journal in 2008<sup>(25)</sup>.

Let us now move to Athens, Greece, and to the Onassis Cardiac Surgery Center. In the 1980s cardiac surgery was still going through its adolescence with many patients, if not the majority, seeking treatment abroad, especially in England. At that point the Alexander S. Onassis Public Benefit Foundation stepped in, constructing one of the most original and handsome buildings in Athens. From the start, in 1993, it was the institution's intention to provide Greece with a heart transplant program based on international specifications and I was chosen to be the leader of this important project.

The new program was constructed according to Baylor's philosophy and guidelines capitalizing on the experience acquired after 233 heart, heart-lung and lung transplants in the preceding ten years. The following points were stressed in particular:

- The program's success would be measured only by its long-term survival.
- Matching a qualified recipient with a suitable donor is the cornerstone of success.
- Patient monitoring would be for the recipient's lifetime.

At the same time it was repeatedly emphasized that the surgery was simple and should not be idolized. Survival should!

A word about the program's structure: it was to be accessible to everyone, with a fair graft allocation. Patient selection would be done by a committee in which, apart from the hospital staff, the specialty consultants and the essential transplant coordinators would take part. The criteria were those established internationally by the American Cardiology Societies and the International Society for Heart and Lung Transplantation. Similar strict specifications would also ap-

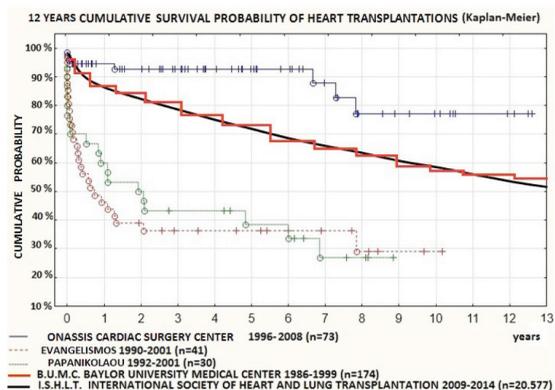
ply to the acceptance of a graft. Above all there would be team work and group decisions. The candidate would be thoroughly vetted by the twenty members of the Selection Committee. Thus the decision to accept a candidate was collective, the product of experience and the viewpoint of each of us.

From the outset the only aim of the program was to serve the candidates on the list. Our philosophy was simple: a transplantation procedure was carried out if the donor matched the recipient on the list without our having to manipulate things to bring him in line with the offered graft, purely and simply so that there would be “another operation”. As I was constantly reiterating: “*Our program does not just stitch hearts.*” If the graft is not suitable, let it go to another program, even to another country. In short, the program does not work like Procrustes’ bed! This “pairing” cannot be learnt from books but is knowledge acquired over the course of time and after painful failures.

*What did the Onassis program aim to offer?* The patient should come out of surgery with a new heart at least ninety percent of the time. He should be alive at the end of the first year in 85% of the cases and in 50% after ten years. We aimed high and the future would show whether our expectations were realistic.

After two years of preparation the first heart transplantation was successfully performed in 1995 and up until 2002 the program performed an average of four transplants annually, obviously not much. The reason for this frustratingly slow growth was two-fold: a lack of donors, due to an essentially non-existent infrastructure and a paucity of referrals, to some degree fuelled by heart transplantation’s already acquired controversial name. In the early 1990s, when there was a great deal of enthusiasm for what was then a novel procedure, two public hospitals performed 41 and 30 transplants respectively. The one year survival was only 50%, coming down to 30% at five years. Clearly, those numbers were turning prospective candidates away and nothing could be done until better outcomes were achieved. *And so the temptation was great to accept candidates who did not meet the international specifications, in order to*

*compile a waiting list.* Such candidates, even if they survived the surgery, *would not have survived long-term* because their other organs and systems were already irreparably damaged. However, the poor donation rate had to be addressed and very quickly.



**Diagram I:** Heart transplantation survival at the Onassis Cardiac Surgery Center compared to I.S.H.L.T., B.U.M.C., and two other Greek programs.

A committee appointed by the Ministry of Health under the chairmanship of a highly respected law professor and scholar – G. Koumantos – drafted new legislation regulating transplantations in line with the European Union’s directives. It made it mandatory for doctors in the Intensive Care Unit to proceed with the diagnosis of brain death and made it an offense to keep such persons on a respirator, until pneumonia and sepsis provided a convenient solution. The exact opposite happened and in the year 2000 only two heart transplants were performed! The new law was misinterpreted, vilified and ignored from all quarters – academia, “ethicists”, self-appointed psychologists and “legal experts”. Even the brain death criteria were challenged. Some transplant doctors joined the cacophony, as the new rules empowered the National Transplant Organization with the allocation of organs through a computerized system, taking away from the surgeon the prerogative of selecting the recipient of his “choice” on the waiting list. I wrote then an article on the subject for the *Kathimerini* daily (Oct. 1999), arguing that our law was more liberal than those imposed upon donation in some other countries and that the paucity of grafts was due to the

fact that a certain section of the medical community, for various reasons, refused to co-operate. I asserted that no regulation can force the doctors of an I.C.U. to arrive at the diagnosis of brain death if they, themselves, are not persuaded. *Corpses will continue to be ventilated* until it is certain that the heart has stopped, by which time the organs will not be suitable for transplantation. The furor raged, yet the spectacle of sparring officials didn't do any good for the public's trust, so organ donation plummeted. Consequently, the program was caught between the Scylla of inactivity due to the paucity of donors and the Charybdis of taking "any donor" in order to produce "numbers" to justify its existence. There was an additional reason why low output numbers should be avoided: it has been generally accepted since the early 1990s that programs performing less than ten transplants yearly are associated with a less favourable patient survival<sup>(27)</sup>. Unwilling to compromise donor criteria in view of the previous Baylor experience, we inevitably had to accept a high attrition rate on the patient waiting list. Therefore, in order to decrease losses, in 2003, our program performed its first left ventricular assist device (V.A.D.) implantation. This "bridging" to transplantation dramatically decreased the mortality on the waiting list from 47.2% to 15.3%, but not the time on it. The introduction of the V.A.D.s changed the philosophy and also the way in which the program functioned. Up to then candidate recipients who were in the last stages of heart failure faced certain death – if a donor did not appear – or the doubtful solution of accepting any graft, even one that was below standard, just to survive. The results of this second option were catastrophic, as shown by the 1991 Baylor experience. With a V.A.D. the patient can wait in relative safety for a suitable graft. Of course, mechanical support also has its dangers, but far fewer than those of the "Russian roulette" of an inferior graft.

By the end of the year 2008 the program had performed 74 heart transplants (one was a re-transplant) and six lung transplants. Of the seventy-four transplants performed at the Onassis, seventy went home, a record indeed, thanks to the successful matching up of recipient with a

suitable donor. It should be noted that survival at the Onassis during the first twelve years was substantially better than that of Baylor, in spite of the known superiority of the American system, because of the difference in long-term follow-up.

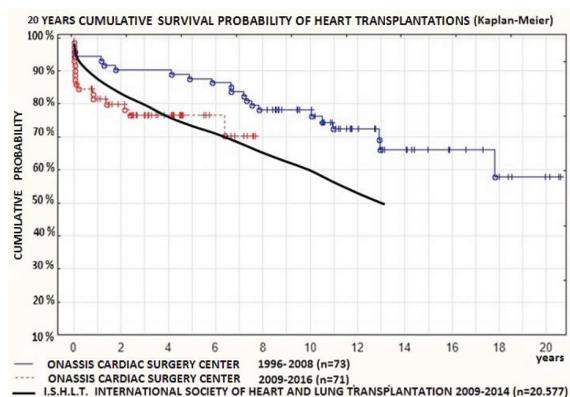
A year later we published our results in the journal "Transplantation Proceedings", presenting the Onassis program internationally<sup>(28)</sup>. The survival rate was 94% in the first year, 92% at five years and 70% at ten years, clearly above the standards of the International Society for Heart and Lung Transplantation<sup>(30)</sup>, refuting the association of infrequent transplant performance with suboptimal results<sup>(27)</sup>. In the fall of 2010 at the Center's International Conference, Dr. R. Kormos, head of the University of Pittsburgh program – one of the largest and most recognized in U.S.A. – congratulated us saying: "I didn't know that Greece had a program of such specifications. Your results are better than ours. Our survival rate never exceeded 85%."

In spite of these achievements, it has been said by certain critics that the Onassis did "easy" and "selected" transplants, hence the superb results. *If we look at the numbers, of the 74 transplants, 54 were high risk.* Twenty-two lived thanks to the continuous infusion of inotropes with a pump, six others with a combination of drugs and an intra-aortic balloon pump, whereas 26 had undergone the implantation of V.A.D., with the usual dangers associated with reoperation. So much for the "easy". As for the "selected" cases, the critics know that since the 1970s selection has been inextricably entwined with the graft.

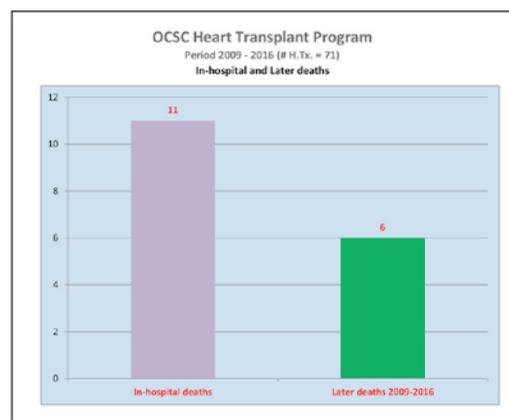
Even the non-specialist can understand, therefore, that acceptance or rejection of a graft is the most important link in the transplantation chain. That is why in the seventy-four cases I made the choice myself, going to the donor's hospital. It was not unusual for us to leave empty-handed since what we found did not tally with the description of the offer, even in cases where we had gathered the information by talking directly to the doctors in order to avoid the time-consuming and expensive trip by air. This was information that was not available to other teams from abroad that came for the graft. After doing the journey – and

paying the expenses – they would take the heart, regardless of whether they would use it as a graft or only as a source of valves. This fact reinforced the cacophony of protests about the “flight” of hearts out of the country!

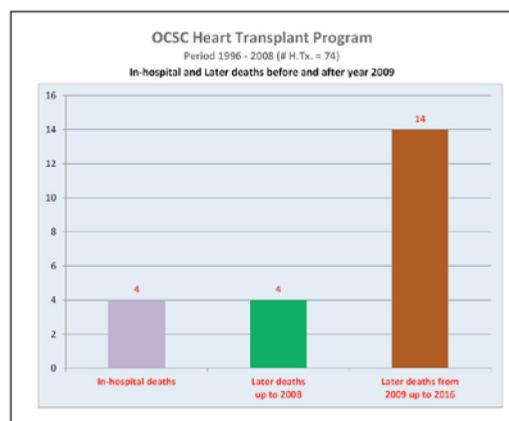
So in 2008, when the Onassis program was finally recognized and 19 heart and lung transplants had been performed in that year, the administration decided to implement a compulsory retirement age, non-existent in the hospital by-laws, at the same time promoting the candidacy of a Greek surgeon working in a major cardiac center in Germany. After time-consuming and painful negotiations and after insult was added to injury by telling the author that “the graveyards are full of indispensable people” – a quip attributed to General Charles de Gaulle – the administration accepted my suggestion to appoint my deputies as codirectors of the Division and the program. Unfortunately, the injudicious four-week vacation they awarded themselves in the summer of 2009, suspending all surgical activity, led to the loss of ten grafts (hearts and/or lungs) going to European programs, while there were 28 patients on the Onassis waiting list. Worse, over the next six months, six of those patients died without surgery. Three independent investigations documented the aberration resulting in the resignation of the program’s leader. So, at long last, the surgeon from Germany got the directorship, only to lose it several months later after three consecutive perioperative deaths due to poor donor selection and/or graft preservation. At this point the Minister of Health stepped in reinstating the vacationer and the race was on: the program *had* to produce in order to justify the game of musical chairs that was being played. Although organ donation was already declining, an unusually high number of transplants – 18 cases – was performed in 2012, awarding the program a 27.7% perioperative mortality for that year. After that it seems that prudence prevailed and the surgical output returned to the previous figures.



**Diagram II:** Survival in the second period of the program (2009- 2016) is substantially lower (10-15%) than in the first period (1996- 2008).



**Figure 1:** The perioperative mortality in the second period (2009-2016) is 15.5%, almost three times higher than in the first (5.4%).



**Figure 2:** Four transplants died during a 12-year follow-up (1996-2008), while 14 losses in the same group were recorded between 2009-2016.

So, in total, in the seven years 2009-2016, the program performed 71 heart transplants incurring 17 losses, 11 of them perioperatively (a 15.5% mortality), while six more patients died during the follow-up period. Early survival in this later period is shown in Diagram II. Even more painful was the loss, during the same period, of 14 “old guard” (1996-2008) patients, in some cases under obscure circumstances. For comparison, in that first 12-year period, only four patients were lost perioperatively (a 5.4% mortality), while another four died during follow-up.

Needless to say, none of these recent losses was ever investigated by any of three successive

administrations between 2011 and 2016. These developments and the comparison between the two periods of the program are shown in Diagram II and in Figures 1 and 2.

So, at this point and after a major reshuffling in 2016, the fourth since my departure in 2008, the program under new leadership “stumbles along the trail of the past, trying to reconstruct its scenes, to revive its echoes, and kindle with pale gleams the passion of former days”, to use a Churchillian quotation. The infrastructure is in place and all that is needed again is Vision, adherence to the International Guidelines and putting the hard-won Lessons to good use.

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## Απόηχος

*Δεν υπάρχει μεγαλύτερη προσβολή  
για άτομα με περιορισμένους ορίζοντες  
και αχαλίνωτη φιλοδοξία,  
από το να αποδειχθούν λανθασμένα  
στις προβλέψεις τους.  
Πλοίαρχος T. H.Dyer USN<sup>1</sup>*

Εφέτος συμπληρώνονται είκοσι πέντε χρόνια από την παράδοση του Ωνασείου Καρδιοχειρουργικού Κέντρου στο Ελληνικό Δημόσιο από το Κοινωφελές Ίδρυμα Αλέξανδρος Σ. Ωνάσης.

Πολλά, πάμπολλα τα γεγονότα αυτών των είκοσι πέντε ετών και αδύνατον να καταχωρηθούν σε ένα εκ προοιμίου βραχύ απολογισμό. Ίσως είναι ευκολότερο να επιλέξει κανείς με τη ματιά του ερασιτέχνη χρονικογράφου τις κρίσεις που διαμόρφωσαν το Κέντρο το οποίο γνωρίζουμε σήμερα. Είναι ανάλογες των πολέμων οι οποίοι καθόρισαν τα σύνορα των κρατών στην παγκόσμια ιστορία. Τηρουμένων, λοιπόν, των αναλογιών θα προσπαθήσω να αναφερθώ εν συντομία στις μείζονες κρίσεις, όπως τις ζήσαμε.

Η αρχική, αλλά με *σουρντίνα*, αφορούσε στην τραγική έλλειψη επικοινωνίας μεταξύ του αρχικού Δ.Σ. και των εκ της αλλοδαπής διευθυντών,

την οποία με εξαιρετική διορατικότητα και ευστοχία εντόπισε ο πρώτος Γενικός Διευθυντής, ο αείμνηστος Αντώνης Κονταράτος, ως «πρόβλημα διαφοράς κουλτούρας μεταξύ Ελλάδος και Αμερικής, που εκδηλώνεται στο επικοινωνιακό επίπεδο ως αδυναμία συνεννόησης». Επιπλέον, το Δ.Σ. υπό την ασφυκτική πίεση της τότε πολιτικής ηγεσίας προσπαθούσε να ξεκινήσει το Κέντρο πάση θυσία, ώστε να αποφευχθούν τυχόν επικρίσεις της αντιπολίτευσης για ολιγωρία ενόψει εκλογών. Φυσικά, η λειτουργία του Μεταμοσχευτικού Προγράμματος ήταν στην πρώτη γραμμή προτεραιότητας, χωρίς να αντιλαμβάνονται οι ενδιαφερόμενοι ότι τέτοια εγχειρήματα απαιτούν άριστα εδραιωμένες και στελεχωμένες νοσηλευτικές μονάδες. Αυτή η νοοτροπία με έθεσε σε απ' ευθείας αντιπαράθεση με τον Αντιπρόεδρο του Δ.Σ., καθηγητή Κ. Τούντα, στον οποίον, ενώπιον όλου

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1. Αξιοματικός του Πολεμικού Ναυτικού των Η.Π.Α. στον 2ο Παγκόσμιο Πόλεμο και φίλος του Πλωτάρχη Joe Rochefort, του αφανούς ήρωα της αποφασιστικής νίκης στη ναυμαχία της Midway, τον Ιούνιο του 1942. Ο δεύτερος, μετά το Pearl Harbor και ύστερα από εξάμηνες προσπάθειες, «έσπασε» τον ιαπωνικό κρυπτογραφικό κώδικα επιτρέποντας στον αμερικανικό στόλο να παγιδεύσει και να στείλει στον βυθό τα τέσσερα ιαπωνικά αεροπλανοφόρα. Λόγω ανταγωνισμού με την Υπηρεσία Κρυπτογράφησης στην Washington που είχε αποτύχει να προβλέψει την ιαπωνική επίθεση, ο Rochefort μετατέθηκε δυσμενώς και αργότερα αποστρατεύθηκε! Το Παράσημο Διακεκριμένων Υπηρεσιών του απονεμήθηκε δέκα χρόνια μετά θάνατον, χάρις στις προσπάθειες φίλων, μεταξύ των οποίων και ο T.H. Dyer.

του Συμβουλίου, είπα ξεκάθαρα: «Κύριε καθηγητά, δεν έχετε νοσοκομείο, έχετε ένα γιαπί, γιατί δεν έχετε ιατρικές και νοσηλευτικές υπηρεσίες.» Την απαισιοδοξία για την έλλειψη υποδομής συμμερίζονταν και οι άλλοι εκ της αλλοδαπής συνάδελφοι μου, έτσι το Δ.Σ. προσανατολίστηκε σε ένα άτυπο shopping καρδιοχειρουργών των Αθηνών, αν θα ήσαν πρόθυμοι να ξεκινήσουν. Αυτό είχε ως συνέπεια την παραίτηση του πρώτου εκλεγέντος, καθηγητή Κ. Αναγνωστόπουλου, τον Ιανουάριο του 1993. Ακολούθησε η ανάθεση καθηκόντων Συντονιστή Αναισθησιολογικού Τομέα στη Λίλα Παπαδημητρίου, η οποία οδήγησε σε παραίτηση, στις αρχές Ιουνίου του 1993, τον διασημότερο αναισθησιολόγο της εποχής εκείνης, Τάσο Τριανταφύλλου, άμεσο συνεργάτη του πρωτοπόρου Μεταμοσχεύσεων Πνεύμονος Joel Cooper. Ευτυχώς για το Κέντρο, είχε ήδη προσγειωθεί και εργαζόταν πυρετωδώς για την προετοιμασία της Μονάδας Εντατικής Θεραπείας, ο Διευθυντής Στέφανος Γερουλάνος. Έτσι, τον Ιούνιο του '93, ο συνάδελφος και φίλος Άλκης Μιχάλης ξεκίνησε με τόλμη την καρδιοχειρουργική δραστηριότητα του Κέντρου. Το φθινόπωρο, άρχισε εργαζόμενος ο αξιόπιστος και ευπρεπής καρδιοχειρουργός Διευθυντής Γεώργιος Παλατιανός. Το δίδαγμα από αυτή την περιπέτεια ήταν πως μόνο οι πραγματικά αποφασισμένοι στελέχωναν τότε το Κέντρο.

Μεταξύ 1993 και 1996 που επέστρεψα, έφθασα αρκετές φορές κοντά στην παραίτηση εξαιτίας της επιμονής του Δ.Σ. να διορίσει τους απολύτως απαραίτητους για τη δημιουργία μεταμοσχευτικού προγράμματος Συμβούλους Ειδικοτήτων, από τις πανεπιστημιακές κλινικές του Αρεταιείου (χειρουργούς) και του Ευαγγελισμού (παθολόγους). Δεν μπορούσαν ή δεν ήθελαν να αποδεχθούν ότι το Κέντρο χρειαζόταν δικούς του Συμβούλους, διαθέσιμους επί εικοσιτετραώρου βάσεως και όχι τον εκάστοτε εφημερεύοντα, όταν το επέτρεπαν τα άλλα του καθήκοντα, ώστε να επιληφθεί και του ασθενούς του Ωνάσειου.

Ήταν φανερό ότι το ιατρικό κατεστημένο του Δ.Σ. προσπαθούσε να έχει άμεσο λέγειν στις μεταμοσχεύσεις, το οποίο απέρριπτα διαρρήδη, παρά τις επανειλημμένες απειλές ότι θα κηρυχθεί έκπτωτη η εκλογή μου και θα προκηρυχθεί η θέση μου. Τελικώς, απεδείχθη ότι η ανάγκη δημιουργίας ενός

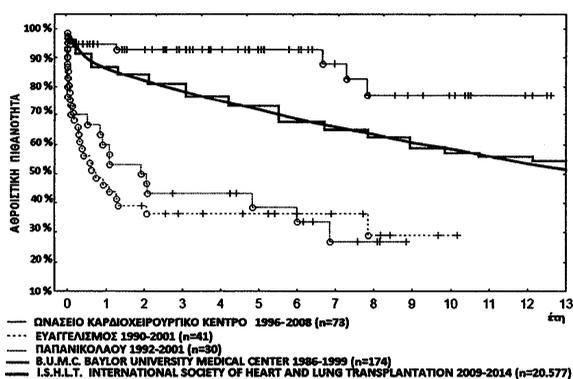
σοβαρού μεταμοσχευτικού προγράμματος υπερτερούσε των όποιων πολιτικοϊατρικών σκοπιμοτήτων. Μια παρ' ολίγον κρίση, στην οποία έχω ήδη αναφερθεί, για δήθεν απόρριψη δότου ενώ δεν υπήρχε καν λήπτης στη λίστα αναμονής, κατέρρευσε άδοξα και τα στόματα έκλεισαν οριστικά με την πρώτη και επιτυχή μεταμόσχευση καρδιάς του Κέντρου, τον Απρίλιο του 1995. Έτσι, παρά την επιθυμία του να καταληφθεί η θέση μου στο Ωνάσειο από άλλοτε μαθητή του, που έδινε μάλιστα και «ραντεβού τον Ιούνιο» σε ασθενείς του, ο Αντιπρόεδρος μου έστειλε σχετική συγχαρητήρια επιστολή, ευχόμενος «να συνεχιστεί και στο μέλλον αυτό το επιτυχές έργο».

Τα έτη 1996 και 1997 εσκίασε η οξύτατη, ακόμα και από εφημερίδων, αντιπαράθεση μεταξύ του Διευθυντή καρδιολόγου Δ. Κρεμαστινού και του υποδιευθυντή του, όταν ο πρώτος επέστρεψε στα καθήκοντα του μετά την υπουργία του και ο δεύτερος απαίτησε να είναι ο μόνος υπεύθυνος για τους προσωπικούς του ασθενείς. Το ζήτημα έλαβε διαστάσεις, δίχασε το ιατρικό προσωπικό και κόστισε στον γράφοντα τη στενή φιλία του με τον υποδιευθυντή. Ως Διευθυντής της Ιατρικής Υπηρεσίας δεν ήταν δυνατόν να υιοθετήσω τη δημιουργία ενός Doctors' Hospital, πετώντας ουσιαστικά στα σκουπίδια τον Εσωτερικό Κανονισμό Λειτουργίας του Κέντρου. Θλίβομαι ακόμα για τη διάλυση μιας φιλίας και παραβλέπω την ανταπόδοση του Δ. Κρεμαστινού προς τον γράφοντα, με την παραχώρηση της σκηνής της Επιτροπής Κοινωνικών Υποθέσεων της Βουλής για το ανέβασμα των θλιβερών εκείνων παραστάσεων που οργάνωσε — «γιατί είχε υποστεί μία σειρά από πιέσεις»— ο τότε Υπουργός Υγείας Α. Λοβέρδος, τον Μάρτιο του 2011.

Τα έτη 1996 έως 1998 καταναλώθηκαν στην προσπάθεια οργάνωσης του Μεταμοσχευτικού Προγράμματος το οποίο αντιμετώπιζε τον ανταγωνισμό εκείνων του «Ευαγγελισμού» και του «Παπανικολάου», για μοσχεύματα, καθώς και την έλλειψη οιασδήποτε παραπομπής ασθενών από άλλα νοσοκομεία, ιδίως από πανεπιστημιακές κλινικές. Ας μη λησμονείται ότι το «Ωνάσειο» είχε κατηγορηθεί ακόμα και από τηλεοράσεως, ως *ελιτίστικο* και απολάμβανε της γενικής αντιπάθειας. Εκ των ενόντων, λοιπόν, έγιναν οι λίγες εκείνες μεταμοσχεύσεις (σελ. 403) με τις οποίες το Πρό-

γραμμα κρατήθηκε στη ζωή μέχρι την τελική επικράτησή του το 2003, λόγω αυτοκαταργήσεως των δυο άλλων προγραμμάτων. Πιστεύω ότι εκτός από την αποχώρηση των αξιόλογων ιδρυτών τους, τα αποτελέσματα, όπως φαίνονται στο Διάγραμμα III, δεν ήταν ιδιαίτερα ενθαρρυντικά για τη συνέχιση της προσπάθειας από τους διαδόχους τους<sup>1</sup>.

Διάγραμμα III



Νέο εμπόδιο παρουσιάστηκε, ως μη όφειλε, με τη συγγραφή και ψήφιση του νόμου περί Μεταμοσχεύσεων και τη δημιουργία του Εθνικού Οργανισμού Μεταμοσχεύσεων (Ε.Ο.Μ.). Το έργο εκείνης της Επιτροπής, υπό τον σεβάσμιο καθηγητή Γ. Κουμάντο, θα παραμείνει στα χρονικά ως πρότυπο σώφρονος, ευσυνειδητής και λεπτομερειακής εργασίας. Ήταν επίσης και σύγχρονο, διότι έλαβε υπ' όψιν επί του προκειμένου τις Οδηγίες της Ευρωπαϊκής Ένωσης. Ο νόμος εκτός του ότι διευκρίνιζε τα της διαπίστωσης του εγκεφαλικού θανάτου που αποτελεί τον ακρογωνιαίο λίθο της δωρεάς οργάνων, εγκαθιστούσε και ένα αμερόληπτο σύστημα διαχείρισης και κατακύρωσης του μοσχεύματος στον δικαιούμενο λήπτη. Αυτό δημιούργησε νέες αντιδράσεις από το μεταμοσχευτικό κατεστημένο της εποχής, το οποίο οργάνωσε αξιοσημείωτη εκδήλωση στο ξενοδοχείο *Caravel* με panel καθηγητών και με συμμετοχή τού μακαριστού Χριστοδούλου, ο οποίος αγωνιούσε για «το τράβηγμα της πρίζας» από τον πιθανό δότη. Στην πράξη, αυτό σήμαινε την παράταση της μηχανικής υποστήριξης αναπνοής και κυκλοφορίας τού χωρίς νευρολογική

δραστηριότητα νοσηλευόμενου, ουσιαστικά δηλαδή αμφισβητούσε την ύπαρξη του εγκεφαλικού θανάτου και αντ' αυτού εννοούσε την παύση της καρδιακής λειτουργίας, οπότε το μόσχευμα είναι συνήθως ακατάλληλο για μεταμόσχευση. Οι αντιπαράθεσεις αυτές, όπως συνήθως συμβαίνει, διοχετεύθηκαν στον Τύπο και η κοινή γνώμη αντέδρασε κατά τον γνωστό τρόπο: με απόλυτη δυσπιστία προς το ιατρικό κατεστημένο, γεγονός που οδήγησε στην κατακόρυφη πτώση της δωρεάς οργάνων.

Έτσι, το 2001 ο δείκτης της δωρεάς έπεσε στους μόλις 3,6 δότες στο εκατομμύριο. Ήταν η παράπλευρη απώλεια της ιατρικής αντιπαράθεσης, ενώ και έμμεση συνέπεια για το Πρόγραμμα του «Ωνάσειου» υπήρξε η έκτοτε ανοιχτά εχθρική στάση μεταμοσχευτή καθηγητή. Το 2002, όταν προσκλήθηκε σε εκδήλωση στο «Ωνάσειο» Καρδιοχειρουργικό Κέντρο, με επιστολή του προς τον Γενικό Διευθυντή, καθηγητή Α. Μαΐλλη, διετύπωσε την άρνηση του ως εξής: «Ειλικρινά διερωτώμαι για ποιο Πρόγραμμα Μεταμοσχεύσεων του Ωνάσειου Καρδιοχειρουργικού Κέντρου μιλάτε; Γιατί αν εννοείτε την πραγματοποίηση δύο τριών μεταμοσχεύσεων ετησίως, ασφαλώς δεν πρόκειται περί Προγράμματος Μεταμοσχεύσεων.» Αυτά, σε ό,τι αφορά την ενθάρρυνση από το ιατρικό κατεστημένο!

Το επόμενο μείζον ζήτημα που έχει ήδη αναλυθεί διεξοδικά ήταν ο *εμφύλιος πόλεμος*, όπως τον αποκαλώ, με τον καθ' όλα αξιόλογο παιδοκαρδιοχειρουργό συνάδελφο μου. Διήρκεσε από το 2000 έως το 2007, οπότε και απεχώρησε από το Κέντρο. Παρά το γεγονός ότι διατηρήθηκε η ενότητα του Προγράμματος, θλίβομαι για την απώλεια συνεργασίας με τον επί βραχύ διάστημα συνεργάτη μου και καλύτερα εκπαιδευμένο καρδιοχειρουργό της χώρας μας. Εξακολουθώ να πιστεύω ότι το έλλειμμα αποφασιστικότητας των Διοικήσεων του «Ωνάσειου» επέτρεψε στην κρίση να λάβει ανεξέλεγκτες διαστάσεις, λόγω της εξ' υπαρχής λανθασμένης και αντίθετης προς τον Εσωτερικό Κανονισμό Λειτουργίας του Κέντρου απόφασης. Δίχασε το ιατρικό προσωπικό, κατανάλωσε εκα-

1. Αν και η πρώτη μεταμόσχευση καρδιάς στην Ελλάδα έγινε στο Θεραπευτήριο «Υγεία», τα πεπραγμένα του Προγράμματός του δεν περιλαμβάνονται στα στοιχεία του Υπουργείου Υγείας του 2001.

τοντάδες ωρών σε άσκοπες διαβουλεύσεις, αντιπαραθέσεις και συγγραφές υπομνημάτων, και τελικά οδήγησε και σε δικαστικές αναμετρήσεις. Το ζήτημα θα μπορούσε να είχε λυθεί οριστικά και τελεσίδικα με ορθή απόφαση του Δ.Σ. που θα σεβόταν τον Οργανισμό, θα προάσπιζε την ενότητα του Προγράμματος και θα χάριζε τον κότινο της διενέργειας παιδιατρικών μεταμοσχεύσεων στο Κέντρο. Το συμπέρασμα από αυτή την αναμέτρηση είναι ότι η αναποφασιστικότητα είναι χειρότερη και από τη λανθασμένη απόφαση.

Τα έτη 2004 έως 2009 σφράγισε η αντιπαράθεση με το Δ.Σ. του καθηγητή Ιωάννη Παπαδημητρίου για την εμμονή του να προκηρύξει όλες τις θέσεις διευθυντών, η οποία και πάλι έφερε αναστάτωση, άσκοπες αντιπαραθέσεις και αβεβαιότητα στο ιατρικό προσωπικό. Μέχρι τότε το Κέντρο όδευε ομαλά και παραγωγικά σε όλους τους τομείς και κατά τη σοφή λαϊκή αμερικανική ρήση *if it ain't broke, don't fix it!*. Ακόμη, έθεσε τις βάσεις για την έκτοτε συνεχώς ογκούμενη δυσμένεια προς το Πρόγραμμα Μεταμοσχεύσεων. Επιπλέον, καθιέρωσε και το ανύπαρκτο έως τότε «όριο ηλικίας», χωρίς πρόβλεψη για τη συνέχιση προσφοράς προς το Κέντρο γνώσεων, πείρας και ταλέντου των αποχωρούντων. Όπως ακριβώς γίνεται με τους συνταξιοδοτούμενους στο Δημόσιο!

Τα αποτελέσματα εκείνης της πρωτοβουλίας τα πλήρωσε, όπως απεδείχθη στο προηγούμενο κεφάλαιο, το Πρόγραμμα κατά την επόμενη επταετία και θλίβομαι για το ότι ακόμα και σήμερα δεν μπορώ να εκφράσω ούτε μία λέξη κατανόησης για την άσκοπη περιπέτεια στην οποία οδηγήθηκε. Αν μη τι άλλο, ο συγκεκριμένος Πρόεδρος θα μπορούσε να θέσει υπό τη σκέπη του το Πρόγραμμα του «Ωνασείου» λαμβάνοντας και τα σχετικά εύσημα. Ίσως δεν είχε πιστέψει στην ανάπτυξη και τελική επικράτηση ενός Προγράμματος Καρδιάς, σε αντίθεση με την προηγούμενή του απόπειρα δημιουργίας μεταμοσχευτικού προγράμματος ήπατος.

Θα αποτελούσε όμως αδικία η επίρριψη της αποκλειστικής ευθύνης για την απόφαση στον καθηγητή Ι. Παπαδημητρίου. Το Πρακτικό του Δ.Σ.

του Κέντρου, του Δεκεμβρίου 2006 (βλ. υποσημ. σελ. 336), αποδεικνύει τη συμμετοχή του Κοινοφελούς Ιδρύματος στη λήψη της ομόφωνης απόφασης, ενώ την ευθύνη γι' αυτή ανέλαβε με παρηυσία πέντε χρόνια αργότερα ο Πρόεδρος Αντώνης Παπαδημητρίου στην Επιτροπή Κοινωνικών Υποθέσεων της Βουλής, στις 29 Μαρτίου 2011 (βλ. σελ. 383), ως εξής: «Το Ίδρυμα Ωνάση είχε τότε εισηγηθεί και ψηφίσει την αποχώρηση του κ. Αλιβιζάτου λόγω ορίου ηλικίας, πράγμα με το οποίο ο κ. Αλιβιζάτος δεν συμφώνησε με το Ίδρυμα». Βέβαια, ξενίζει το γεγονός ότι μία τόσο σημαντική πρόταση περί «ορίου ηλικίας» – ουσιαστικά αλλαγής του Εσωτερικού Κανονισμού Λειτουργίας – έκαμε τότε ένα Αναπληρωματικό Μέλος και όχι ο παρών μόνιμος εκπρόσωπος του Κοινοφελούς Ιδρύματος Απόστολος Ζαμπέλας.

Η δήλωση, όπως διατυπώθηκε, αφήνει περιθώρια παρερμηνείας, ότι είχα συμμετοχή στη συζήτηση ή έστω ότι ενημερώθηκα για την επικείμενη απόφαση. Όπως έχω ήδη αναφέρει (βλ. σελ. 336), ουδείς ε γνώριζε γι' αυτήν μέχρι τον Δεκέμβριο του 2008, όταν μου ανακοινώθηκε ενώπιον όλου του Δ.Σ. ότι η υποψηφιότητά μου ήταν «άκυρη» λόγω της ύπαρξης «ορίου ηλικίας». Όσο για το σχετικό Πρακτικό του 2006, όπως ανέφερα, μόλις πρόσφατα εντοπίστηκε η ύπαρξή του (2017).

Ο Πρόεδρος Αντώνης Παπαδημητρίου μάλλον αναφερόταν σε μεταγενέστερη κατ' ιδίαν συνομιλία μας το 2009, όταν η αποχώρησή μου από το Πρόγραμμα και το Κέντρο είχε πλέον ολοκληρωθεί. Αφορούσε την προτροπή του για συνέχιση της συνεργασίας μου με τη Μονάδα Μεταμοσχεύσεων, ενώ όπως έχω εξιστορήσει, οι τέως συνεργάτες μου επανειλημμένα την είχαν αποκρούσει. Η συζήτηση έγινε σε απόλυτα φιλική ατμόσφαιρα και θυμάμαι χαρακτηριστικά τη φιλοπαίγμονα διάθεσή του όταν μου υπενθύμισε τη ρήση του Στρατηγού Charles de Gaulle, πως τα νεκροταφεία είναι γεμάτα από αναντικατάστατους! Βέβαια, οι μετέπειτα εξελίξεις απέδειξαν ότι ενδέχεται, για κάποιο χρονικό διάστημα, κάποιοι να αποδειχθούν παροδικά αναντικατάστατοι...

Η απόφαση αυτή του Δεκεμβρίου 2006 περι

1. Μην επιδιορθώνεις κάτι που δεν έχει σπάσει.

«ορίου ηλικίας» θα αποδεικνυόταν γεγονός καταλυτικής σημασίας για τη μετέπειτα πορεία του Κέντρου. Σηματοδότησε την εγκατάλειψη του ιδιωτικού χαρακτήρα που προβλέπει ο ιδρυτικός νόμος και την ουσιαστική προσχώρηση στο Δημόσιο. Αν και το σκηνικό είχε ουσιαστικά στηθεί αρκετά χρόνια ενωρίτερα με την αποδοχή από όλες τις Διοικήσεις της ανάληψης των χρονίων ελλειμμάτων του Κέντρου από την Πολιτεία, η εφαρμογή του δημοσιούπαλληλικού αυτού μέτρου αποδείχθηκε η Κερκόπορτα από την οποία εισχώρησε ο κρατικός παρεμβατισμός σε ίδρυμα που μέχρι τότε ίσχυαν η άμιλλα, η συνεχής προσπάθεια για βελτίωση της ποιότητας και προπαντός η αξιοκρατία. Τα αποτελέσματα της μοιραίας αυτής στροφής φάνηκαν λίγα χρόνια αργότερα με την αποπομπή Διοικητικών Συμβουλίων και με τις αλλαγές στην ηγεσία του Προγράμματος Μεταμοσχεύσεων, με πρωτοβουλία των εκάστοτε Υπουργών Υγείας. Ίσως σε αντιρρόπηση αυτών των κρατικών παρεμβάσεων το Κέντρο, από καιρού εις καιρόν, σηματοδοτεί την «αυτονομία» του κάνοντας προσλήψεις χωρίς προκήρυξη!!

Αυτές θεωρώ ως τις μείζονες κρίσεις της εικοσιπενταετίας. Κλείνοντας θέλω να αποτίσω φόρο τιμής σε τρεις ηγέτες, για τη γνωριμία των οποίων και για τη συνεργασία μαζί τους είμαι πραγματικά υπερήφανος. Αναφέρθηκα ήδη στον αείμνηστο Γ. Κουμάντο, ο οποίος δύο φορές βοήθησε ουσιαστικά το Πρόγραμμα Μεταμοσχεύσεων. Την πρώτη, όταν μου συνέστησε τον γνωστό νομικό και αυθεντία στο Διοικητικό Δίκαιο, Χρίστο Πολίτη, χάρις στο πόνημα του οποίου επί μία διετία «πάγωσε» η διάσπαση του Προγράμματος. Λίγο αργότερα, ως Αντιπρόεδρος του Ε.Ο.Μ., ματαίωσε την απόπειρα να ανακινηθεί το ζήτημα των παιδιατρικών μεταμοσχεύσεων και να συζητηθεί, εκτός τόπου και χρόνου, σχετικό έγγραφο του Δ.Σ. του «Ωνασείου» προς το Υπουργείο Υγείας. Το έγγραφο είχε περιέλθει ανεπισήμως στην κατοχή του Προέδρου του Οργανισμού, εφόσον δεν αναφερόταν καν ο Ε.Ο.Μ. στις κοινοποιήσεις. Ήρκεσε μια ματιά του σοφού Κουμάντου και μία μόνο φράση του: «Κύριε Πρόεδρε, πάμε να μπούμε σε χωράφια στα οποία δεν μας σπέρνουν», για να πάρει τέλος η απόπειρα επαναφοράς τού ζητήματος δια της πλαγίας οδού.

Για την ιστορία, συμπληρώνω ότι Πρόεδρος του Εθνικού Οργανισμού Μεταμοσχεύσεων ήταν ο συγγραφέας της επιστολής «περί δύο τριών μεταμοσχεύσεων ετησίως». Θυμάμαι, όμως, τον Γ. Κουμάντο και για μία άλλη στιχομυθία, εκείνη την εποχή. Διαφωνήσαμε, τρόπος του λέγειν, σχετικά με μία παράγραφο του νόμου και επειδή επέμενα για την ορθότητα της άποψής μου, ο μέγας Κουμάντος είπε: «Κύριε Αλιβιζάτε, θα το ελέγξω και σας υπόσχομαι να σας τηλεφωνήσω εντός της αύριον.» Όντως με κάλεσε λέγοντας το απίστευτο: «Λυπούμαι να ομολογήσω ότι εσείς είχατε δίκιο και εγώ άδικο! Ξέρετε, κύριε Αλιβιζάτε, είσθε επιτυχημένος καρδιοχειρουργός, όμως πιστεύω ότι εχάσατε το κάλεσμα της ζωής σας. Έπρεπε να είχατε γίνει νομικός!». Όποιος είχε γνωρίσει τον Γ. Κουμάντο αντιλαμβάνεται την αξία μιας τέτοιας φιλοφρόνησης...

Ο χρονολογικά δεύτερος, από τον χώρο της Ιατρικής αυτή τη φορά, ήταν ο καθηγητής Κώστας Στεφανής. Έχω αναφερθεί και προηγουμένως στην οξύνια και στη λιτότητα των εκφράσεών του, προϊόντων ασυνήθιστης πνευματικής συγκρότησης. Όμως, τον θαύμασα τον Μάρτιο του 2004, όταν ως Υπουργός Υγείας και δυο ημέρες πριν τη λήξη της θητείας του, είχε το θάρρος να διορθώσει προηγούμενη απόφαση που είχε λάβει το Δ.Σ. του Κέντρου, υπό την Προεδρία του, τον Νοέμβριο του 2001, βάσει της οποίας ουσιαστικά διεσπάτο το Πρόγραμμα σε δύο ανταγωνιστικές υποομάδες. *Εξέδωσε, λοιπόν, την Άδεια Σκοπιμότητας για το Ωνάσειο, με την οποία έθετε την Παιδιατρική Ομάδα Μεταμοσχεύσεων εντός του ευρύτερου πλαισίου του Μεταμοσχευτικού Προγράμματος του Κέντρου.* Ακόμη θυμάμαι το ενδιαφέρον και τη στοργή με την οποία μου ευχήθηκε «καλή επιτυχία», όταν τον κάλεσα για να τον ευχαριστήσω.

Ο τρίτος μεγάλος στην εικοσαετία της παραμονής μου στην Ελλάδα ήταν ο Πρόεδρος του Κοινοφελούς Ιδρύματος Στέλιος Παπαδημητρίου. Πάντα διεκήρυσσα ότι ο λόγος της επιστροφής μου στην Ελλάδα ήταν το «Ωνάσειο» και ακόμα ότι ως πραγματικό εργοδότη μου πάντα θεωρούσα το Κοινοφελές Ίδρυμα και όχι τους ερασιτέχνες προέδρους ή τους δημοσιούπαλλους apparatchiks του Δ.Σ. Για την ιστορία, σημειώνω ότι πριν αναλάβω, τον Μάρτιο του 1993,

σε επιστολή μου προς τον Γενικό Διευθυντή Α. Κονταράτο, έγραφα επί λέξει: «Είμαι διατεθειμένος να έλθω υπό την προϋπόθεση ότι το «Ωνάσειο» θα παραμείνει Νομικόν Πρόσωπον Ιδιωτικού Δικαίου και δεν θα περιέλθει υπό την εξουσία του λεγομένου Ε.Σ.Υ. Εις τοιαύτην περίπτωσιν ο γράφων θεωρεί το συμβόλαιόν του λελυμένο...». Αυτά, με τα καθαρευουσιάνικα εκείνης της εποχής. Όπως προσφώς έλεγε ο έχων τον ασυνήθιστα κοινόν νουν Πρόεδρος και καθηγητής Β. Γολεμάτης: «Το Ίδρυμα είναι η μητέρα και η τροφός του Καρδιοχειρουργικού Κέντρου.» Ίσως αυτά να έχουν εφαρμογή σήμερα περισσότερο παρά ποτέ.

Έτσι, αρέσκομαι να ανακαλώ την αδημονία, ίσως και το κάποιο δέος που όλοι νοιώθαμε όταν ερχόταν στην αίθουσα συγκεντρώσεων ο Στέλιος Παπαδημητρίου, ζωηρός, επιθετικός, αποπνέοντας *gravitas*, με ακριβοζυγισμένη εκφορά του λόγου. Αν και δεν υπήρξε φιλικός απέναντι μου στα πρώτα χρόνια της θητείας μου στο Κέντρο, λόγω της άκαμπτης, πιστεύω, στάσης μου στο θέμα των παιδιατρικών μεταμοσχεύσεων, το 2004 αντελήφθη τι διακυβεύετο και άρδην μετέβαλε στάση.

Είχα την ευκαιρία να τον αποχαιρετήσω λίγες εβδομάδες πριν φύγει, τον Νοέμβριο του 2005. Ήταν νοσηλευόμενος μετά από τη μείζονα και εργώδη επέμβαση που είχε υποστεί στην Αμερική και όλοι γνωρίζαμε ότι το τέλος δεν θα αργούσε.

Εκείνο το βράδυ τού κρατούσαν συντροφιά οι φίλοι και σύντροφοι του στο Συμβούλιο του Ίδρυματος, γι' αυτό και μετά τον σύντομο χαιρετισμό μου ετοιμάστηκα να αποχωρήσω. Ακόμη θυμάμαι την προσήνεια με την οποία είπε: «Καθίστε κύριε Αλιβιζάτε, εσείς είστε περισσότερο από συνεργάτης, είστε φίλος.» Και γυρίζοντας προς τους συνεργάτες του είπε: «Ξέρετε, ο κ. Αλιβιζάτος μου θυμίζει τον εαυτό μου, όταν ήμουν νέος, μαχητικός και επίμονος όπως αυτός.»

Αυτοί ήσαν οι τρεις αξιολογότεροι Έλληνες που ε γνώρισα μετά την επιστροφή μου, το 1996. Είχαν κάτι το κοινό, μια υπέρτατη αρετή: να αναγνωρίζουν και να επανορθώνουν το σφάλμα, γεγονός που απαιτεί ακεραιότητα, ικανότητα αυτοκριτικής και προπαντός αυτοπεποίθηση. Ήσαν το αντίπαλο δέος στους Λαιστρυγόνες και τους Κύκλωπας που με υποδέχθηκαν στην Ιθάκη του Προλόγου της Α' έκδοσης.

Γι' αυτό και όταν με ρωτούν: «Έχετε μετανιώσει που γυρίσατε στην Ελλάδα;» η απάντηση είναι πάντα ένα ηχηρό ΟΧΙ. Ακόμη και όταν συνδέουν την ερώτηση με τη συμπεριφορά άλλοτε συνεργατών μετά την αποχώρησή μου. Αντιθέτως, αισθάνομαι πραγματική ικανοποίηση έχοντας βιώσει στα δύσκολα χρόνια της Επταετίας, όπως και πριν, «χωρίς των δειλών τά παρακάλια και παράποννα». Όπως ακριβώς επιτάσσει ο Αλεξανδρινός...

*Anagnostopoulos Anne-Marie*

# A Letter to my Father

*Anne-Marie Anagnostopoulos MD*

**Dr. Constantine Efthymios Anagnostopoulos** is not just a world renowned heart surgeon, professor, and mentor, he is first and foremost a loving father. And after the loss of my mother at a young age, he was both a father and a mother to me until he met and married Madelaine and was able to bring together two amazing families and make them one. His strength to overcome life's challenges is remarkable.

From an early age he instilled in me a desire to learn and achieve and made my education a priority, no matter the personal sacrifice to him. For that, I am deeply grateful. My desire to become a physician emerged at an early age and I am convinced it is because of the pure joy that practicing medicine has brought to my father. He clearly was excited and passionate about his work every day and the way he could truly help another human being. It was clear that Medicine has provided important purpose to his life and that was an important example for me growing up. I also realized from an early age that the loyalty he had from his residents and fellows was unique. From *my* perspective, no matter what they had to go through, even putting on a Santa Claus costume to entertain the attending's young child on a cold Chicago night, he would support them in their careers. He would often tell me about all of the rising stars in his field that he had trained. Many-many times in my life, when people hear my name the first question is whether I am related to the heart surgeon and then they share a memorable story about my Dad. I am enormously proud in those moments.

As I have pursued my education and medical career, my father has always made my well-being a priority, no matter the distance or situation. While his roughly monthly visits over the past 20 years to Andover, Yale, Penn Medical School, Residency and Fellowship, and now to Boston where I live, are sometimes challenging, in the end I am always sad when he leaves and think about the next visit. Moreover, during my most trying times he has always dropped everything and been the rock that I needed. When Alexandra was going to be born extremely prematurely he arrived to my side from Athens unbelievably fast and I still have no idea how he persuaded a nurse to let him into my room in the middle of the night when he finally arrived. When he is set on something, there is no changing his mind. He has a stubbornness that is both a positive and challenging quality. But in the end, no one knows me better, is always willing to tell me the truth and ultimately be my most fierce advocate.

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Boston MA, USA*

I have now been married for 11 years and my husband Dr. Shaw Robert Natan, a cardiologist as well, still jokes that when he was first getting to know my father he had a hard time following his stories and how fast his mind would move from one topic to another. However now, years later, Shaw has a deep appreciation for the advice and guidance my father has given him as he has navigated his own career. I often hear them talking through cases from the hospital while sitting around the dinner table late into the evening. He still thinks his father-in-law would make a great subject on “This American Life” on NPR.

He is now also a loving and doting Pappou to my two children Alexandra and Theodore. I can tell he is waiting for them to be old enough to talk about the bigger topics in life that interest him - Medicine, Politics, Philosophy, Literature - and even argue with him.

He has always said to me that “creating new knowledge” was the ultimate goal in academics and I hope this volume shows that he has achieved that unique accomplishment - something only truly great minds achieve.

Now in the next phase of his life I wish him health and happiness so that he can continue to share with us his anecdotes, historical and biographical notes plus a book or two. Also may he continue to enjoy some open heart surgery with former colleagues and students, his love of real estate in the United States and Greece, long walks with Madelaine, cooking and paean singing.

I love you Dad.

# Μία επιστολή προς τον πατέρα μου

Ο Καθηγητής **Κωνσταντίνος Ευθυμίου Αναγνωστόπουλος** δεν είναι απλώς ένας παγκοσμίως γνωστός καρδιοχειρουργός, καθηγητής και μέντορας, είναι πρώτα και κύρια ένας αγαπημένος πατέρας. Και μετά από την απώλεια της μητέρας μου σε νεαρή ηλικία, ήταν πατέρας και μητέρα για μένα μέχρι που συναντήθηκε και παντρεύτηκε την Madelaine και ήταν ικανός να συγχωνέψει δύο εκπληκτικές οικογένειες και να τις κάνει μία. Η δύναμή του να ξεπεράσει τις προκλήσεις της ζωής είναι αξιοσημείωτη.

Από νεαρή ηλικία εμφύτευσε μέσα μου την επιθυμία να μάθω και να επιτύχω. Θεώρησε την εκπαίδευσή μου προτεραιότητα, ανεξάρτητα από την προσωπική θυσία γι' κείνον. Γι' αυτό, είμαι βαθιά ευγνώμων. Η επιθυμία μου να γίνω ιατρός εμφανίστηκε σε νεαρή ηλικία και είμαι πεπεισμένη ότι είναι λόγω της αγνής χαράς που η άσκηση της ιατρικής έχει φέρει στον πατέρα μου. Είναι σαφώς ενθουσιασμένος και φανατικός με το έργο του και ψάχνει κάθε μέρα τον τρόπο με τον οποίο μπορεί πραγματικά να βοηθήσει έναν άλλο άνθρωπο. Ήταν σαφές ότι η Ιατρική έχει δώσει σημαντικό σκοπό στη ζωή του και αυτό ήταν ένα σημαντικό παράδειγμα καθώς μεγάλωνα. Επίσης, συνειδητοποίησα από μικρή ηλικία, ότι η αφοσίωση που είχε από τους ειδικευόμενους και τους συναδέλφους του ήταν μοναδική. Από τη σκοπιά μου, ανεξάρτητα από το τι έπρεπε να υποστούν, ακόμα και να βάλουν ένα κοστούμι του Άγιου Βασίλη για να διασκεδάσουν τη μικρή του κόρη μια ψυχρή νύχτα στο Σικάγο, θα τους στήριζε στην καριέρα τους. Θα μου έλεγε συχνά για όλα τα ανερχόμενα αστέρια που είχε εκπαιδεύσει στον τομέα του. Πολλές φορές στη ζωή μου, όταν οι άνθρωποι ακούν το όνομά μου το πρώτο ερώτημα είναι αν συγγενεύω με τον καρδιοχειρουργό και στη συνέχεια μοιράζονται μια αξέχαστη ιστορία για τον μπαμπά μου. Αυτές οι στιγμές με κάνουν εξαιρετικά περήφανη.

Καθώς έχω επιδιώξει την εκπαίδευση και την ιατρική καριέρα μου, ο πατέρας μου ανέκαθεν έκανε την ευημερία μου προτεραιότητα, ανεξάρτητα από την απόσταση ή την κατάσταση. Ενώ οι μηνιαίες επισκέψεις του για τα τελευταία 26 χρόνια στο Λύκειο του Andover, Κολλέγιο του Yale, Ιατρική Σχολή στο U. Penn, Ειδικότητα και Υποειδικότητες και τώρα στη Βοστώνη όπου ζω, είναι μερικές φορές απαιτητικές, τελικά, πάντα λυπάμαι όταν φεύγει και περιμένω την επόμενη επίσκεψη. Επιπλέον, κατά τη διάρκεια των πιο δύσκολων στιγμών μου, παράτησε τα πάντα και έγινε ο βράχος που χρειαζόμουν. Όταν η Αλεξάνδρα ήταν να γεννηθεί, πολύ πρόωρα, ήρθε στο πλευρό μου, από την Αθήνα, απίστευτα γρήγορα και δεν έχω ακόμα ιδέα πώς έπεισε μια νοσοκόμα να τον αφήσει να μπει στο δωμάτιό μου στη μέση της νύχτας όταν τελικά έφτασε στη Βοστώνη. Όταν έχει αποφασίσει κάτι, δεν αλλάζει γνώμη.

Έχει ένα πείσμα που είναι τόσο θετικό όσο και προκλητικό. Αλλά τελικά, κανείς δεν με ξέρει καλύτερα, είναι πάντα πρόθυμος να μου πει την αλήθεια και τελικά να είναι ο πιο φανατικός υποστηρικτής μου.

Εδώ και 11 χρόνια είμαι παντρεμένη και ο σύζυγός μου, Καθηγητής Shaw Robert Natan, καρδιολόγος και αυτός, εξακολουθεί να αστειεύεται, λέγοντας πως, όταν πρωτογνώρισε τον πατέρα μου είχε δυσκολία να καταλάβει τις ιστορίες του και την ταχύτητα του μυαλού του όταν μετακινούνταν από το ένα θέμα στο άλλο. Ωστόσο, τώρα, χρόνια αργότερα, ο Shaw έχει βαθιά εκτίμηση για τις συμβουλές και την καθοδήγηση που μου έδωσε ο πατέρας του, καθώς έχει πλοηγηθεί στη δική του σταδιοδρομία. Συχνά τους ακούω να μιλάνε για περιπτώσεις από το νοσοκομείο ενώ κάθοντε στην τραπεζαρία αργά το βράδυ. Εξακολουθεί να πιστεύει ότι ο πατέρας μου θα αποτελούσε ένα σπουδαίο θέμα για το σήριαλ “This American Life” στο NPR.

Τώρα πιά, είναι επίσης ένας αγαπημένος και αφοσιωμένος «παππούκας» στα δύο παιδιά μου, την Αλεξάνδρα και το Θεόδωρο. Μπορώ να πω ότι περιμένει να μεγαλώσουν, ώστε να συζητήσουν για τα μεγαλύτερα θέματα της ζωής που τον ενδιαφέρουν την Ιατρική, την Πολιτική, τη Φιλοσοφία, τη Λογοτεχνία –και μάλιστα να διαφωνούν μαζί του.

Μου έλεγε πάντοτε ότι «η δημιουργία νέας γνώσης» ήταν ο απώτερος στόχος των ακαδημαϊκών και ελπίζω ότι αυτός ο τόμος να δείχνει ότι έχει επιτύχει αυτό το μοναδικό επίτευγμα –κάτι που μόνο πραγματικά μεγάλα πνεύματα επιτυγχάνουν.

Τώρα, στην επόμενη φάση της ζωής του, του εύχομαι υγεία και ευτυχία, ώστε να μπορέσει να συνεχίσει να μοιράζεται μαζί μας τα ανέκδοτα, τα ιστορικά και βιογραφικά του σημειώματα συν ένα βιβλίο ή δύο. Να μπορεί, επίσης, να συνεχίσει να απολαμβάνει, κάπου κάπου, μια χειρουργική επέμβαση ανοικτής καρδιάς με πρώην συναδέλφους του, την αγάπη του για τα κτηματομεσιτικά στις Ηνωμένες Πολιτείες και την Ελλάδα, μακρύς περιπάτους με την Madelaine, μαγείρεμα και άσματα παιάνων.

Σε αγαπάω μπαμπά.

Anagnostopoulos Anne-Marie - Perkins Archibald S.

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# Cooperating Oncogenic Events in Murine Mammary Tumorigenesis: Assessment of ErbB2, Mutant p53, and Mouse Mammary Tumor Virus

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We are investigating cooperating genetic events in the genesis of breast cancer, using the mouse as a model system. We have shown cooperativity between a mutant allele of *p53* (*p53-172H*) and overexpressed *ErbB2* in mammary tumorigenesis in transgenic mice. We are now performing additional crosses to further examine oncogene cooperativity with *ErbB2* and *p53-172H*. We attempted to test the dominant oncogenic potential of *p53-172H* in an *in vivo* setting by crossing the *p53-172H* transgene together with *ErbB2* onto either a *p53*<sup>-/-</sup> or a *p53*<sup>+/-</sup> background. We show that the *p53-172H* allele and the heterozygous *p53* genotype have an identical impact on the latency of *ErbB2*-induced mammary tumors; there was no evidence of additivity or synergy between *p53-172H* and the *p53*<sup>+/-</sup> genotype. On the *p53*<sup>-/-</sup> background, we obtained no mammary tumors due to the early onset of lymphomas and sarcomas, thus precluding assessment of the effect of the *p53-172H* transgene on mammary tumorigenesis in a *p53*-null background. Thus, in this *in vivo* model for breast cancer, we failed to find evidence that *p53-172H* can function as a dominant oncogenic allele, but rather found support for its being essentially equivalent to a null allele in its impact on *ErbB2*-induced mammary tumorigenesis. By comparative genome analysis, we showed that a common feature of tumors arising in *ErbB2*/mutant *p53* mice (*p53*-null allele with or without *p53-172H*) is a loss of chromosome 4, a feature of many epithelial tumors in mice and one that is consistent with a role for loss of INK4a/ARF in such tumors. We also attempted to accelerate *ErbB2*-induced mammary tumorigenesis with mouse mammary tumor virus (MMTV) proviral tagging mutagenesis, but we were surprised to find that mice with MMTV alone had the same

latency as mice with both MMTV and *ErbB2*, indicating no cooperativity between *ErbB2* and MMTV. This may have been due to the mixed C3H/HeN × FVB strain background used in this cross. © 2001 Academic Press

## INTRODUCTION

A central goal of current cancer research is the identification of the genes involved in tumorigenesis and the definition of the precise role that these genes play in tumor development. Analysis of human breast carcinomas has implicated a number of genes in the genesis of these tumors, including *ErbB2*, EGFR, *myc*, *HST* and *INT2* (Ali *et al.*, 1989), *p53* (Horak *et al.*, 1991), *src* (Rosen *et al.*, 1986), *Rb* (Lee *et al.*, 1988), BRCA1, and BRCA2. It has been suggested by a number of studies that the development of breast cancer in humans requires changes in more than one of these genes, which may in part explain the long latency associated with this disease (Horak *et al.*, 1991).

*ErbB2* encodes a receptor tyrosine kinase related to the receptor for epidermal growth factor (EGFR or ErbB) and is amplified in nearly 30% of human cancers, particularly intraductal carcinomas (Hynes and Stern, 1994; Slamon *et*

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*et al.*, 1989). Numerous studies suggest that this amplification leads to increased mitogenic signaling in the cell. The importance of this amplification is supported by the finding that 70% of transgenic mice that overexpress rat *ErbB2* in the mammary gland develop mammary carcinomas (Guy *et al.*, 1992). However, the latency of tumorigenesis is relatively long (over 200 days), suggesting that other oncogenic events are necessary. Analysis of these tumors revealed small in-frame deletions in the *ErbB2* transgene in 65% of the tumors analyzed (Siegel *et al.*, 1994). These deletions resided in the extracellular domain adjacent to the transmembrane domain and resulted in activation of *ErbB2* tyrosine kinase activity. These findings indicate that activation of *ErbB2* tyrosine kinase activity plays an important role in the development of these tumors. This is consistent with previous experiments, showing that mice carrying a mouse mammary tumor virus (MMTV)-driven rat *ErbB2* transgene with an activating mutation in the transmembrane domain develop multifocal mammary carcinomas with a significantly shorter latency (Muller *et al.*, 1988).

In 30% of human breast carcinomas, expression of *ERBB2* is associated with the presence of mutant *p53*, suggesting that activated tyrosine kinase receptors cooperate with mutant *p53* in the development of these tumors (Horak *et al.*, 1991). *p53* is a multifunctional protein that is involved in the regulation of growth of nearly all cell types within mammalian organisms (reviewed in Ko and Prives, 1996). The wild-type *p53* protein can suppress tumor cell growth (Hinds *et al.*, 1990) and likely functions as a regulatory protein in two capacities: as a key component of apoptosis pathways within the cell (Yonish-Rouach *et al.*, 1991) and as a checkpoint protein for controlling the G1 to S transition in the presence of genotoxic stress (Kuerbitz *et al.*, 1992). Structural domains of *p53* include an amino-terminal transcriptional activation domain, a central DNA-binding domain, and a carboxy-terminal domain important for oligomerization (reviewed in Ko and Prives, 1996). Genetic alterations at the *p53* locus are common in human cancers and are primarily either missense mutations or allele loss (Caron de Fromental and Soussi, 1992; Hollstein *et al.*, 1991; Nigro *et al.*, 1989). While the majority of human tumors with altered *p53* have one allele bearing a missense mutation and one null allele, occasionally tumors are found to have one mutated allele and one normal allele (Nigro *et al.*, 1989). These findings suggest a progression model in which the initial event is a missense mutation in one *p53* allele, leading to a proliferative advantage, and then loss of the other allele, which confers a further selective advantage.

*p53* point mutations are highly clustered into four regions that correspond to evolutionarily conserved domains of the

proteins that function in DNA binding. Some of the most commonly mutated amino acids are those that make direct contact with the DNA (Cho *et al.*, 1994). *p53* proteins bearing these mutations have been found to have altered DNA-binding and transactivation properties (Kern *et al.*, 1991, 1992). Some mutant proteins fail to activate normal target genes, such as p21, but can activate atypical targets, such as *MDR1* (Chin *et al.*, 1992). Thus, certain mutations in *p53* may lead to the acquisition of novel and dominant activities within the cell. It is evident from a number of studies that certain missense mutations in *p53* function as dominant negative alleles that encode proteins that lack transcriptional activation potential but retain the ability to oligomerize and thus can pull wild-type *p53* into nonfunctional complexes (Milner and Medcalf, 1991). An example of this is the 135V mutation, which can accelerate tumor development in heterozygous but not nullizygous *p53*-deficient mice (Harvey *et al.*, 1995). Other alleles, such as 143A, 175H, 248W, 248Q, 273H, and 281G act as dominant oncogenic alleles, since they can confer new malignant phenotypes upon gene transfer into cells that lack *p53* (Dittmer *et al.*, 1993; Hsiao *et al.*, 1994). These phenotypes include the ability to grow in soft agar and to form invasive tumors in nude mice. The molecular mechanisms that underlie the ability of mutant *p53* alleles to induce these changes are unknown.

*p53* alterations are common in human breast carcinomas (Davidoff *et al.*, 1991; Prosser *et al.*, 1990). Missense mutations have been identified at many of the hot-spot regions, including codons 175(R to H) and 248(R to Q). 175H represents approximately 8% of all *p53* mutations in human breast cancers. These alleles are dominantly oncogenic in cell culture and nude mouse tumorigenicity assays (Dittmer *et al.*, 1993; Hsiao *et al.*, 1994). To obtain a more accurate picture of the effect that the 175H allele has on mammary cell growth, we used transgenic mice in which the murine equivalent of this allele, *p53-172H*, was targeted to the mammary epithelium using the whey acidic protein (WAP) promoter. It was somewhat surprising to find that, despite high-level expression in the mammary gland, mice carrying the WAP-driven *p53-172H* were not abnormally susceptible to mammary carcinomas—only one mouse developed a mammary carcinoma and this was with a latency of 11 months (Li *et al.*, 1996). These data suggested that this allele is not dominantly oncogenic on its own in this setting and requires other cooperating events. Indeed, these mice were much more susceptible than nontransgenic control mice to mammary tumors induced by carcinogens that are known to activate Ha-Ras (Li *et al.*, 1997; Medina, 1974; Kumar, 1990),

suggesting that activated Ras is one molecule that can cooperate with *p53-172H* in this system. In addition, we demonstrated cooperativity between *ErbB2* and *p53-172H* in the development of mammary carcinomas (Li *et al.*, 1997). These bitransgenic mice constitute a model system that closely mimics the genetic changes in human breast cancers and that allows for further studies to uncover the mechanism of cooperativity between these two genes. In this study, we look at whether susceptibility to *ErbB2*-induced mammary tumorigenesis is influenced by additional genetic factors, including mouse mammary tumor virus (MMTV) and null alleles at the *p53* locus.

## MATERIALS AND METHODS

**Transgenic mice.** The *p53-172H* transgenic mice, in which the mutant *p53* transgene was preferentially over-expressed in the mammary epithelium by use of the whey acidic protein promoter, were created and characterized as described (Li *et al.*, 1996). *p53* knockout mice were obtained from Tyler Jacks (Jacks *et al.*, 1994). Unactivated *ErbB2* transgenic mice (line N#202), which contain the wild-type rat *ErbB2* gene driven by MMTV, have been described previously (Guy *et al.*, 1992). All three lines are on an FVB background. *p53/ErbB2* bitransgenic mice were generated by crossing female and male offspring of line 8512 *WAP-p53-172H* transgenic mice to offspring of line N#202 of *MMTV-ErbB2* transgenic mice. Mouse tail DNA from the offspring of this cross was isolated as described previously (Li *et al.*, 1997). The *WAP-172H* and/or *MMTV-ErbB2* transgenes and the *p53* knockout allele were identified by PCR as described (Jacks *et al.*, 1994; Li *et al.*, 1997). All mice for tumorigenesis studies were kept pregnant and/or lactating to maintain high-level expression of the *p53-172H* and *ErbB2* transgenes. C3H/HeO/J mice were obtained from The Jackson Laboratory. C3H/HeN mice were obtained from Clarence Reeders, NCI (Frederick, MD).

**Histologic analysis.** Mammary glands and mammary tumors were surgically removed, fixed in 10% neutral buffered formalin (ANATECH LTD, Battle Creek, MI) for 6 h, and placed in 70% ethanol until processed. These tissues were embedded in paraffin, and 5- $\mu$ m sections were placed on regular slides and stained with hematoxylin and eosin.

**Comparative genome hybridization.** For comparative genome hybridization (CGH), high-molecular-weight genomic DNA was prepared from mammary tumors as described (Gilbert *et al.*, 1993). CGH was performed as described:

Control (liver DNA) and tumor DNA were nick-translated by standard procedures incorporating digoxigenin-11-dUTP and biotin-16-dUTP (Boehringer Mannheim), respectively. Equal concentrations of both DNA's (approximately 500 ng) were coprecipitated in the presence of an excess (50  $\mu$ g) of unlabeled mouse Cot 1 DNA (GIBCO BRL). This mixture was then resuspended in 50% deionized formamide with 10% dextran sulphate in 2 $\times$  SSC. The genomic probe mixture was denatured at 88°C for 7 min and allowed to preanneal at 37°C for 2 h. Slides for CGH were pretreated with RNase A (0.1 mg/ml) (Boehringer Mannheim) and digested with pepsin (10  $\mu$ g/ml) to remove excess cytoplasm. Post-treatment included 1% formaldehyde incubation followed by denaturation in 70% formamide/2 $\times$  SSC at 88°C for 2 min and then dehydration in 70, 90, and 100% ethanol. Slides were allowed to air dry. The probe mixture was then added to the slide, covered with a 22  $\times$  22 mm<sup>2</sup> coverslip, and sealed with rubber cement. Slides were then incubated in a humidified chamber at 37°C for 3 to 4 nights.

**CGH detection.** Slides were washed in 50% formamide/2 $\times$  SSC at 45°C, 0.1 $\times$  SSC at 60°C, and 4 $\times$  SSC/Tween 20, 45°C. Detection of biotin-labeled DNA sequences was accomplished by incubation with avidin-FITC (Vector Laboratories, Inc., Burlingame, CA). Visualization of haptenized sequences with digoxigenin required a preliminary incubation with a mouse antibody against digoxigenin (Sigma) followed by successive incubations with polyclonal antibodies conjugated with TRITC. Slides were then counterstained with DAPI and embedded in an antifade, 1,4-phenylenediamine.

**Image acquisition.** Images were acquired using a cooled charge-coupled device camera CH250 (Photometrics, Tucson, AZ) mounted on a Leica DMRBE epifluorescence microscope. Three exposures were taken for each channel using specially designed filters (TR1, TR2, TR3; Chroma Technology, Brattleboro, VT). The CGH analysis was performed on a custom-designed software program based upon a similar human program (Du Manoir *et al.*, 1995; Weaver *et al.*, 1999).

## RESULTS AND DISCUSSION

**Assessing the genetic function of the *p53-172H* allele: dominant negative or dominant oncogenic.** We have shown previously that the *ErbB2* and *p53-172H* transgenes can cooperate to induce mammary tumors in mice. It is known that human p53-175H (equivalent to murine *p53-172H*) can cause immortalization of primary cells (Rovinski

and Benchimol, 1988), can cooperate with Ras in transforming primary cells (Eliyahu *et al.*, 1984; Hinds *et al.*, 1990), and can enhance the tumorigenic potential of cells lacking *p53* (Dittmer *et al.*, 1993). That these effects can be seen in the absence of endogenous *p53* argues that these alleles are not acting simply as dominant negative alleles, but also by exerting a dominant effect on cell growth. The nature of this effect is unknown.

We attempted to determine if the *172H p53* allele had the capacity to function in a dominant oncogenic manner in mice. One would predict that a dominant oncogenic allele of *p53* would accelerate tumorigenesis even in the absence of endogenous *p53*. We crossed the *p53-172H* allele with MMTV-*ErbB2* onto a *p53*<sup>-/-</sup> background to compare the latency of mammary tumorigenesis to that seen with *172H* and *ErbB2* on a *p53* wt (wild-type) background and *ErbB2* alone on a *p53*<sup>-/-</sup> background.

Table 1 shows the spectrum of tumors and latency of tumor development in *p53*<sup>-/-</sup> mice with no transgene (Group 9), the *ErbB2* transgene (Group 10), the *p53-172H* transgene (Group 11), or both transgenes. We found that the spectrum of tumors that arose in these mice included lymphomas and sarcomas but no mammary tumors, regardless of what other transgenes were present.

The results from the *p53*<sup>-/-</sup> mice (Groups 9,10,11,12; Table 1) were uninformative concerning the contribution of the *p53-172H* transgene to mammary tumorigenesis on a *p53*<sup>-/-</sup> background: the lymphoma and sarcoma phenotype precluded our ability to assess susceptibility to mammary tumors. To determine the tumorigenic potential of the mammary tissue of a *p53*<sup>-/-</sup>, *ErbB2*<sup>+</sup>, *p53-172H*<sup>+</sup> (Group 12) mouse over a longer period, we transplanted tissue from the mammary glands of one Group 12 mouse (No. 6475) at age 108 days into the cleared mammary fat pads of two syngeneic mice. The two recipient mice, which were caged with males to maintain a pregnant and/or lactating state, were allowed to age. Neither developed tumors at the site of transplant. One was sacrificed at 198 days following transplant; the

other at 288 days. Based on gross anatomic inspection, the transplant into each mouse was successful.

Thus, it appears from these data that either the *p53-172H* allele cannot act as a dominant oncogenic allele in the mammary glands of mice or that the strong lymphoma/sarcoma phenotype precludes our ability to discern a dominant oncogenic effect on mammary epithelial tumors.

*Mammary tumor latency and histopathology in transgenic and nontransgenic p53<sup>+/-</sup> mice.* We then examined the incidence and latency of mammary tumors in mice heterozygous for endogenous *p53*<sup>(+/-)</sup> or wild type for *p53* (*p53*<sup>(+/+)</sup>) bearing one, both, or neither of the two transgenes (Table 2, Fig. 1). As shown previously, the combination of *ErbB2* and *p53-172H* on a *p53*<sup>(+/+)</sup> background resulted in mammary tumor development with a shorter latency than that seen with *ErbB2* alone (Fig. 1A). However, when the same transgenes are placed on a *p53*<sup>(+/-)</sup> background, the *p53-172H* transgene has no effect on the latency of tumorigenesis (Fig. 1B, Table 2): tumors arose in *p53*<sup>(+/-)</sup>, *ErbB2*<sup>+</sup> mice (Group 6) with the same latency as in *p53*<sup>(+/-)</sup>, *ErbB2*<sup>+</sup>, *p53-172H*<sup>+</sup> mice (Group 8). The *p53*<sup>(+/-)</sup> genotype did shorten the latency of *ErbB2*-induced tumors relative to that seen on a *p53*<sup>(+/+)</sup> background (Group 6 versus Group 2; Table 2, Fig. 1C), but the effect of the *p53*<sup>(+/-)</sup> genotype appears indistinguishable from that observed with the *p53-172H* transgene (Group 4 versus Group 6; Fig. 1D). Thus, within our *in vivo* model of mammary tumorigenesis, in which tumors are induced with an overexpressed *ErbB2* transgene, the *p53*<sup>(+/-)</sup> genotype and the *p53-172H* transgene are both able to shorten latency, but do not, in combination, effect an additive decrease in latency. This provides genetic evidence that the *p53-172H* is not acting in a dominant oncogenic manner *in vivo*.

It is curious that *p53-172H*, which is thought to act in a dominant negative manner, does not cause a greater shortening of the latency of *ErbB2*-induced tumors than the *p53*<sup>(+/-)</sup> genotype (Group 4 versus Group 6; Fig. 1D, Table 2), with which presumably the remaining wt *p53* allele must be

TABLE 1  
FVB Cohorts with *p53*<sup>-/-</sup>

Group	Endogenous <i>p53</i>	<i>p53-172H</i>	<i>ErbB2</i>	No. of mice	% MT <sup>a</sup>	% sarcoma	% lymphoma	Latency (days)
9	-/-	-	-	14	0	57	50	98
10	-/-	-	+	10	0	60	60	93
11	-/-	+	-	12	0	75	58	100
12	-/-	+	+	4	0	50	25	97

<sup>a</sup>MT, mammary tumor.

TABLE 2

FVB Cohorts with  $p53^{+/+}$  and  $p53^{+/-}$ 

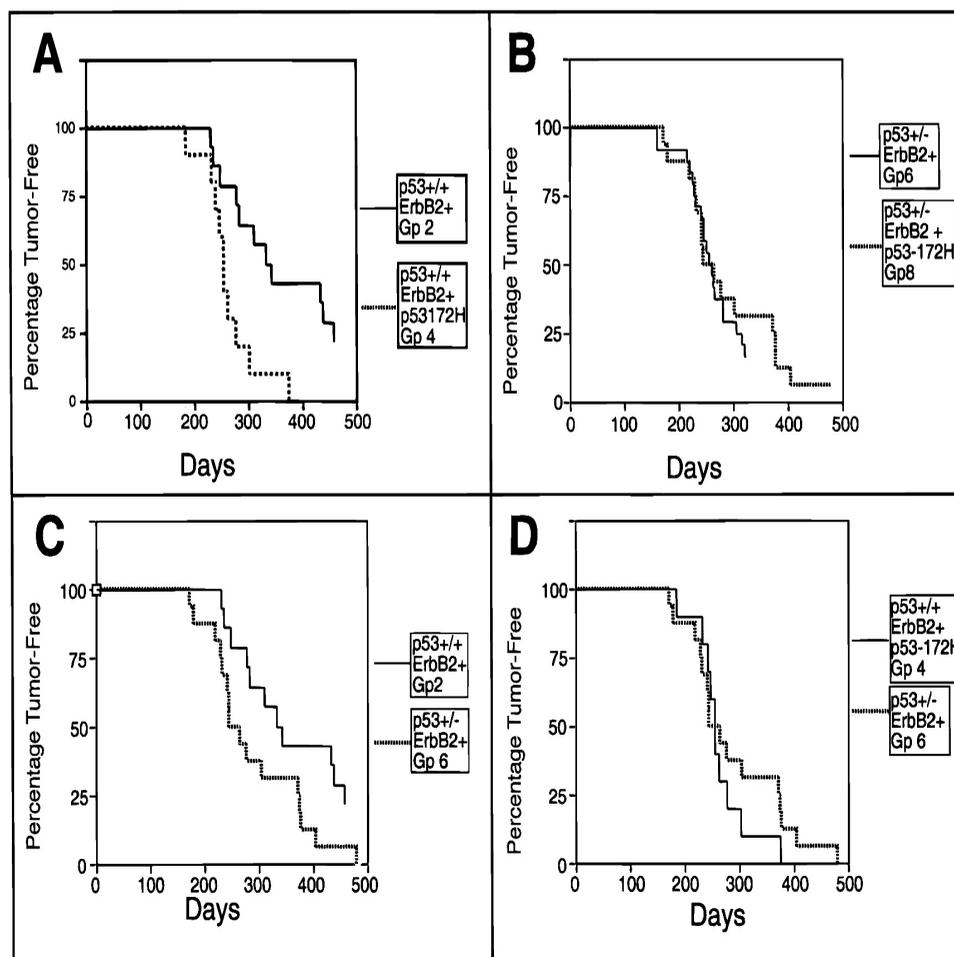
Group	Endogenous p53	p53-172H	ErbB2	No. of mice	% MT <sup>a</sup>	Latency (days)
2	+/+	-	+	14	79	321
4	+/+	+	+	10	100	251
5	+/-	-	-	10	70	338
6	+/-	-	+	16	100	256
7	+/-	+	-	11	55	341
8	+/-	+	+	21	100	251

<sup>a</sup> MT, mammary tumor.

mutated prior to tumorigenesis. This finding suggests two possibilities: one, that in  $p53^{+/-}$  mice, the loss of the remaining wt allele is not a rate-limiting step in tumor development. The other possibility is that  $p53-172H$  mice are essentially identical to  $p53^{+/-}$  mice in terms of level of wt  $p53$

function and that the steps required for tumor development (e.g., loss of the remaining  $p53$  allele) are essentially the same. We have not examined our tumors for loss of the remaining wt allele.

The data from the experiment suggests that in the setting



**FIG. 1.** Kaplan-Meier plots of tumor-free survival of FVB mice with the following genotypes and transgenes: (A)  $p53^{+/+}$ , *ErbB2* (Group 2);  $p53^{+/+}$ , *ErbB2*, *p53-172H* (Group 4). (B)  $p53^{+/-}$ , *ErbB2* (Group 6);  $p53^{+/-}$ , *ErbB2*, *p53-172H* (Group 8). (C)  $p53^{+/+}$ , *ErbB2* (Group 2);  $p53^{+/-}$ , *ErbB2* (Group 6). (D)  $p53^{+/+}$ , *ErbB2*, *p53-172H* (Group 4);  $p53^{+/-}$ , *ErbB2* (Group 6).

of a  $p53^{+/-}$  genotype, the  $p53-172H$  transgene does not have a significant effect on either the latency or the incidence of mammary tumors, with or without *ErbB2*.

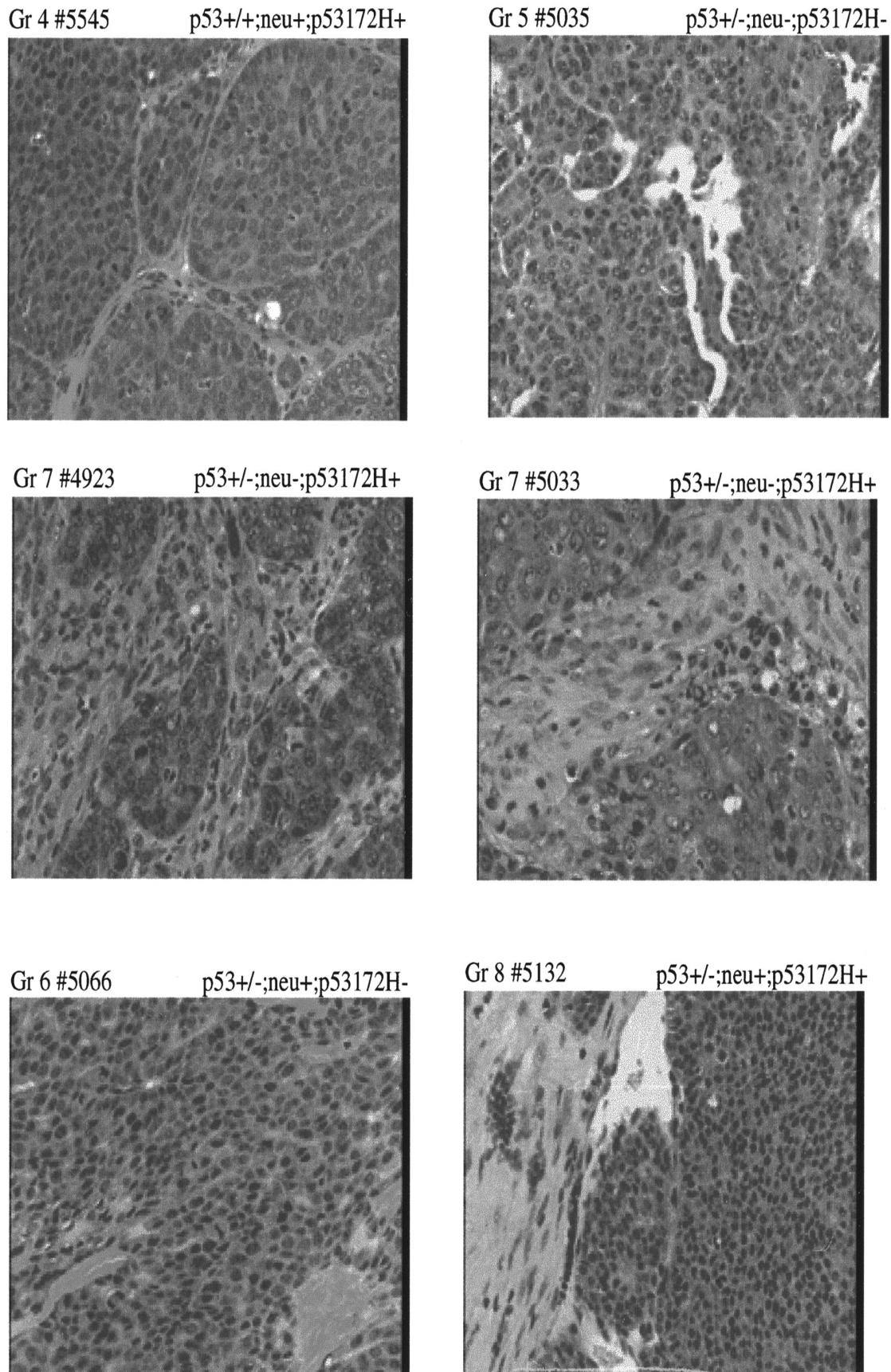
*Mammary tumors arise in  $p53^{+/-}$  mice lacking *ErbB2*.* One curious result is the development of mammary tumors in mice with the  $p53^{+/-}$  background without the *ErbB2* transgene. In previous experiments, we found that  $p53^{+/+}$  mice without *ErbB2* were not significantly susceptible to mammary tumors. This was true for nontransgenic animals as well as for those harboring the  $p53-172H$  transgene. Our current experiments show that both  $p53^{+/-}$  nontransgenic (Group 5) and  $p53^{+/-}$ ,  $p53-172H$  transgenic (Group 7) mice are susceptible to mammary tumors (Table 2, Fig. 2). This phenotype is clear with  $p53-172H^+$ ,  $p53^{+/-}$  mice: of the 10 mice that were allowed to age until either lesion development or age >1 year, 5 developed mammary adenocarcinomas of the mammary gland. One striking finding in these tumors, which had a median latency of over 300 days, was the presence of abundant fibrovascular stromata surrounding the islands of neoplastic epithelial cells (Fig. 2). This histologic feature has not been seen in any other tumors and appears to be specific for this particular genotype. The well-developed stroma seen in the  $p53^{+/-}$ ,  $172H^+$  tumors is reminiscent of that seen in human breast tumors, a feature that imparts a scirrhous quality to breast tumors. The etiology of this intense stromal reaction is unknown. One possibility is that in the absence of an *ErbB2* transgene driving the tumor process, tumorigenesis is instead dependent on mutational activation of other oncogenes. The identity of such an oncogene(s) is unknown.

*Comparative genome hybridization reveals recurrent loss of a region of mouse chromosome 4 harboring *pINK4a*.* In our bitransgenic model ( $p53-172H$  plus *ErbB2*), we do not observe the emergence of tumors with kinetics that indicate direct and immediate malignant transformation by coexpression of the two transgenes,  $p53-172H$  and *ErbB2*. Tumors arise after several pregnancies rather than after the first and are unifocal, suggesting the necessity for other tumorigenic events. This is distinct from the cell culture results in which  $p53-172H$  appears to have an immediate effect (Dittmer *et al.*, 1993). This discrepancy is likely due to several things, including the lower transforming potential of native *ErbB2* relative to the Ras oncogene used in cell culture, the presence of endogenous  $p53$  alleles in our transgenic mice, and other tumor control mechanisms that exist in the intact animal, such as tumor immunity, the inhibitory influence of surrounding tissue, and the requirement for tumor angiogenesis. Nonetheless, the  $p53-172H$  allele accelerates *ErbB2*-induced tumorigenesis, albeit by an unknown mechanism.

We postulated that additional oncogenic events in the form

of genetic lesions are required for tumor development in  $p53-172H$  transgenic mice. To address this, we used comparative genome hybridization to document large gains or losses of DNA in tumors arising in mice bearing *ErbB2* and/or  $p53-172H$ . In this technique, tumor DNA is fluorescently labeled and hybridized to a metaphase spread of normal mouse chromosomes in the presence of normal DNA labeled with a different fluor. Digital photomicroscopy and image analysis are performed to quantitate the relative intensities of the normal and tumor DNA hybridization to the metaphase chromosomes. In this way, regions of DNA overrepresented (amplified) or underrepresented (deleted) in the tumor DNA can be identified.

We analyzed the DNAs of five mammary carcinomas that arose in  $p53^{+/-}$  mice (Table 3): three from *ErbB2/p53-172H* bitransgenic mice and two from mice harboring *ErbB2* alone. The results showed that four of the five cases had loss of chromosome 4. This chromosome has been found to be lost in other tumors (Ritland *et al.*, 1997; Sargent *et al.*, 1999; Wu *et al.*, 1997), and it has been suggested that the selective loss of Chromosome 4 is due to the presence of the *INK4a/ARF* locus, which encodes two negative regulators of cell growth that are frequently lost during tumorigenesis: p16INK4a and p19ARF. *INK4a* acts to inhibit cyclin D-dependent kinases, thus preventing E2F activation and blocking transit from G1 to S. *ARF* binds to and thereby inhibits Mdm2, the ubiquitin ligase that targets  $p53$  for degradation. *ARF* can thereby induce a  $p53$ -dependent cell cycle arrest. In  $p53^+$  tumors, loss of *ARF* is thought to be an important mechanism by which the tumor cell effectively loses  $p53$  function: Mdm2, no longer inhibited by *ARF*, proceeds to reduce the pool of functional  $p53$ , which in turn leads to a loss of the apoptosis and cell cycle arrest response that occurs due to oncogene activation and hypoxia. Given that loss of *ARF* essentially results in loss of  $p53$  function, there would not appear to be any selective advantage offered by loss of *ARF* in the setting of  $p53$  loss. Indeed, analysis of human gliomas finds that  $p53$  loss and *ARF* loss are mutually exclusive: tumors show loss of one or the other, but apparently not both (Fulci *et al.*, 2000). Likewise, in *E $\mu$ -myc* transgenic mice, tumors exhibit loss of either *ARF* or  $p53$ , but not both (Eischen *et al.*, 1999). However, some tumors show an increase of Mdm2 in addition to loss of  $p53$ , suggesting that Mdm2 has other targets in addition to  $p53$ , the downregulation of which can contribute to tumorigenesis (Eischen *et al.*, 1999). Since *ARF* acts by inhibiting Mdm2, it is likely that loss of *ARF* would also increase the abundance of these other targets via an increase in Mdm2 function. Indeed, other suggested targets of Mdm2 action include E2F-1, RB, p300/CBP, and additional  $p53$  family



**FIG. 2.** Histology of tumors arising in FVB mice. Genotypes and mouse numbers are as designated. Note the significant stromal response in the tumors of Group 7 ( $p53^{+/-}$ ,  $p53-172H$ ).

TABLE 3  
Comparative Genome Hybridization Results

Chromosome no.	p53 <sup>+/-</sup> , ErbB2 <sup>+</sup>			p53 <sup>+/-</sup> , ErbB2, p53-172H	
	4968 <sup>a</sup>	5113 <sup>a</sup>	5184 <sup>a</sup>	4973 <sup>a</sup>	5050 <sup>a</sup>
1		Gain D-E1		Loss	
2				Gain	
3			Gain	Gain	
4	Loss		Loss	Loss	Loss
5	Loss G2-3		Loss	Gain	
6		Gain A; B1-G		Gain	Gain A2
7	Loss (at threshold)				Loss C
8	Loss of band A2				Loss
9					Partial loss
10				Loss B3-C2	Loss A-C3
11	Gain band A2			Gain × band B1	
12			Gain	Loss A-B1, C3-E	Loss A2-F
13					Loss A5 and D1
14		Gain band E	Gain	Gain	
16		Gain (C3-4)	Gain	Gain	Gain C1-2
17				Gain	Loss A2-3, D-E
18				Gain 1.5-2×	
19		Loss		Gain	
X	Gain band E-F2	Gain A6, C-D, F	Gain		

<sup>a</sup> Tumor/mouse number.

members (reviewed in Sherr and Weber, 2000). Thus, loss of ARF, resulting in increased Mdm2 function, may lead to downregulation of these other targets of Mdm2, contributing to tumorigenesis.

Loss of chromosome 4 obviously leads to hemizyosity of many other genes, the loss of which may promote tumor cell growth, such as *INK4b* and *p73*, both of which negatively regulate cell growth.

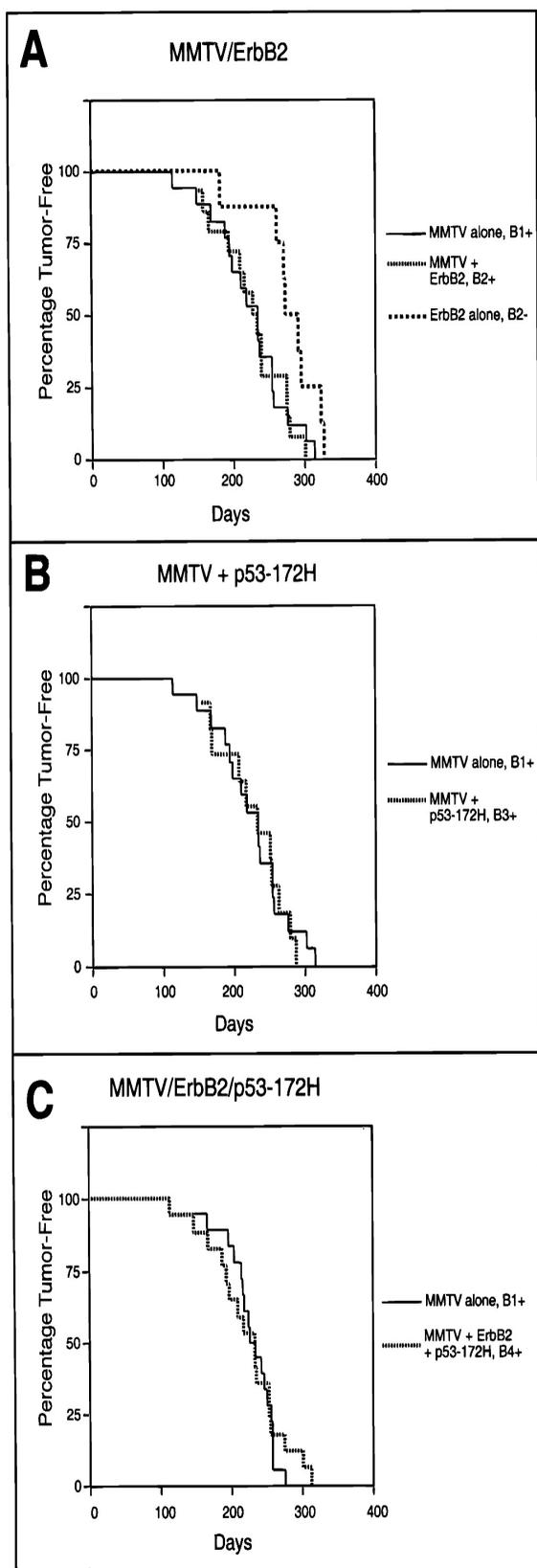
Bitransgenic tumor 4973 exhibited significant aneuploidy, with gains of chromosomes 2, 3, 5, 6, 14, 16, 17, 18, and 19, and losses of chromosomes 1 and 4. Tumor 5050, also bitransgenic, sustained losses of chromosomes 4, 8, and most of 12. The region of chromosome 12 lost included *Tgfb3*, a negative regulator of tumor cell growth. The identification of the particular gene the loss of which contributes substantially to tumorigenesis will require additional studies.

*Influence of ErbB2 in MMTV-induced mammary tumorigenesis.* *ErbB2* overexpression in the mammary glands of transgenic mice results in the development of mammary tumors with a latency of 200 to 280 days, depending on the strain of mouse (Guy *et al.*, 1992; Li *et al.*, 1997). This long latency suggests that other cooperating events are required for tumorigenesis. One approach to the identification of cooperating oncogenes is to use retroviral proviral tagging to

find cooperating oncogenes. Retroviruses can act as insertional mutagens in the somatic tissues of mice and can either activate genes through a promoter or enhancer insertion mechanism or can knock out gene function through insertional disruption. The inserted provirus provides a molecular tag by which one can molecularly clone the locus into which the virus has inserted. For mammary tumorigenesis, one can use mouse mammary tumor virus to achieve proviral insertional mutagenesis. This virus is transmitted horizontally through the milk from the dam to the pup in certain

TABLE 4  
Cohorts of FVB×C3H/HeN Mice

Group no.	mut p53	ErbB2	MMTV	Total no. mice	% with tumors	Median age
B1+	-	-	+	17	100	217
B1-	-	-	-	12	18	336
B2+	-	+	+	14	100	230
B2-	-	+	-	8	100	282
B3+	+	-	+	11	100	234
B4+	+	+	+	18	100	228



strains of mice, particularly in C3H/HeN mice (reviewed in Nusse, 1991).

We attempted to use MMTV to accelerate mammary tumorigenesis in *ErbB2* transgenic mice. We crossed hemizygous *ErbB2* transgenic male FVB mice with MMTV-positive C3H/HeN female mice. This cross generates FVB×C3H/HeN F1 hybrid mice, with or without the *ErbB2* transgene, all chronically infected with MMTV. In a companion cross, we generated similar FVB×C3H/HeN F1 hybrid mice that lacked MMTV by using as parents C3H/HeN males instead of females. The aging of these cohorts of mice resulted in the development of mammary tumors in all of the mice that had either MMTV or the *ErbB2* transgene (Table 4, Fig. 3A). *ErbB2* transgenic mice developed mammary tumors with a median latency of 282 days; the addition of MMTV shortened this latency to 230 days. However, MMTV alone induced tumors with a median latency of 217 days. Thus it appears that in this experiment, MMTV was the dominant force driving tumorigenesis, and the presence of the *ErbB2* transgene did not significantly accelerate tumorigenesis relative to this agent alone.

To examine possible cooperation between *p53-172H* and MMTV, we generated mice with either MMTV alone (Group B1+) or both MMTV and *p53-172H* (Group B3+) and determined their susceptibility to mammary tumorigenesis. As with the mice described above, we found no evidence of cooperativity between *p53-172H* with or without *ErbB2* and MMTV (Table 4, Fig. 3B).

We suspect that the failure to see cooperativity between MMTV and either *p53-172H* or *ErbB2* in these experiments is due to the mouse strain background: further crosses performed in our laboratory have successfully demonstrated cooperativity between MMTV and *p53-172H* when the strain background is a 2–5 generation backcross of the FVB×C3H/He F1 animals onto C3H/HeOuJ or C3H/HeN (Chatterjee *et al.*, in preparation). In two separate crosses, there was a statistically significant shortening of the latency to mammary tumorigenesis in mice harboring both MMTV and *p53-172H* relative to nontransgenic mice infected with MMTV. In the experiments described here, the mice were F1 hybrids between C3H/HeN mice, which are known to

**FIG. 3.** Kaplan–Meier plot of the tumor-free survival of FVB×C3H/N F1 mice with the following transgenes and/or viruses. (A) MMTV alone (B1 + group), MMTV plus *ErbB2* (B2 + group), and *ErbB2* alone (B2 – group). (B) MMTV alone (B1 + group), MMTV plus *p53-172H* (B3 + group). (C) MMTV alone (B1 + group), MMTV plus both transgenes, *p53-172H* and *ErbB2* (B4 + group).

be highly susceptible to MMTV-induced mammary tumorigenesis, and FVB, a strain whose sensitivity to MMTV has not been critically assessed. It may be that in the F1 there is a further heightening of susceptibility to MMTV-induced mammary tumors and that this overrides the influence of the *ErbB2* and *p53-172H* transgenes. Alternatively, there may be a significantly lower level of transgene expression in the F1 hybrid relative to that in the pure FVB background, thus mitigating the influence of the transgenes.

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Letter 2017*

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# A Little Letter for Dino Anagnostopoulos

*Anagnostopoulos MLLR.*

When I met Dino in 1981, he was already a very accomplished and productive cardiac surgeon. He had wasted no time launching his career. Fourteen months after high school, at the age of 18 years and 10 months, he entered medical school. At the age of 35, he published an extraordinary book “Acute Aortic Dissections” which continues to be read today by medical students. At 37, he had performed 1500 open heart operations in 13 years of clinical practice and research work. At 39 he is a Professor of Cardiac Surgery at the University of Chicago. He has ridden the wave of new complicated procedures that would save and/or improve people’s lives. Cardiac Surgery was no longer in its infancy.

In 1981, he was not prepared to relax and enjoy his success. He had already sketched in his mind what he wanted to do next: he wanted to give back to his native land which had provided him with an excellent education and life in spite of many wars. He realized, however, that first he needed to learn more about hospital administration.

Over the next few years, he started a new program of heart surgery at SUNY Stony Brook on Long Island. This experience gave him the tools he felt he needed to launch new programs in Greece.

For years he travelled every month between New York and Athens to start, monitor and improve programs in New York and Greece. In Greece alone, he was responsible for the development of three major programs and consulted at more than five others.

The family understood the importance and pride he took in his work. Although he was often gone for long hours, days and weeks, on his return he would share with us as much as we wanted to know of what had happened. His excitement was contagious. No surprise we have three children who are doctors.

Dinner conversations could be lively and long. From world events to daily events, Dino made sure we viewed all sides of the event and added any needed historic context. He was tough at playing devil’s advocate.

Travel became a focus: Greece, England, Netherlands, Germany, Italy, Denmark, France, Switzerland, Mexico, Belize, Caribbean, Puerto Rico, West Coast, Hawaii, Canada. We took everyone to as many places as we could.

Life is a journey, as Cavafy so beautifully expressed, and ours has certainly been that with Dino. We admire and respect this pioneering Renaissance man who brought an extraordinary dynamic to our lives.

*Anagnostopoulos Petros V.*

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# Surgical Management of Left Ventricular Outflow Tract Obstruction

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## ABSTRACT

**Background:** Left ventricular outflow tract obstruction (LVOTO) is caused by a spectrum of lesions. This study was performed to determine the outcomes of surgical management of LVOTO.

**Methods:** All patients who had surgery of the LVOT between 2002 and 2010 were retrospectively reviewed.

**Results:** There were 103 consecutive patients with median age 6.8 years (range 8 days to 62 years). Fourteen patients had simple subaortic membrane. Eighty-nine patients had complex LVOTO including fibromuscular obstruction (n = 53), tunnel obstruction (n = 22), hypertrophic cardiomyopathy/muscular obstruction (n = 15), and anomalies of the mitral subvalvar apparatus (n = 13). There were no early deaths. Mean LVOT gradient decreased from 33 mmHg (range 1 to 108 mmHg) to 6 mmHg (range 0 to 45 mmHg) (p < 0.001). Median follow-up was 3.8 years (range 0.9 to 8.5 years). There were three late deaths. Cumulative survival at one, three, and five years was 96% (95% CI 89% to 99%). All patients are in New York Heart Association classes I-II. Ten patients required reoperation (three for recurrent/residual LVOTO). Freedom from reoperation was 94%, 90%, and 78% at one, three, and five years (95% CI 86% to 98%, 80% to 95%, and 59% to 89%, respectively). No patient with complex LVOTO who had release of the fibrous trigones required reoperation [0% (0/26) vs. 16% (10/63) (p = 0.031)]. Factors associated with increased reoperation risk were interrupted aortic arch (OR 6.4, p = 0.22), atrioventricular septal defect (OR 15.4, p = 0.008), and higher mean LVOT gradient at discharge (OR 1.08, p = 0.023). Conclusions: Utilizing a multitude of operative strategies for surgery of the LVOT results in favorable early and midterm outcomes. Residual LVOTO and original cardiac diagnosis are associated with increased reoperation risk. Release of the fibrous trigones decreases reoperation risk in patients with complex LVOTO.

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## INTRODUCTION

Left ventricular outflow tract obstruction (LVOTO) continues to be a challenge and is caused by a wide array of morphologic lesions.<sup>1</sup> At the one end of the spectrum, there is discrete subaortic stenosis from a simple subaortic membrane.<sup>2-4</sup> The subaortic membrane can be complex with fibrous tissue extending toward the aortic valve leaflets, which become tethered and fail to open properly, thus exacerbating the LVOTO.<sup>3</sup> Hypertrophic obstructive cardiomyopathy (HOCM) is a primary genetic myocardial disease with variable clinical symptomatology, hemodynamic profile, and age at presentation. It can result in extreme septal hypertrophy and LVOTO, which is a strong predictor of heart failure and death.<sup>5</sup> LVOTO can also result from anomalies of the mitral subvalvular apparatus (AMSA) that, if untreated, can result in persistent obstruction. Fusion of the papillary muscles with the ventricular septum or the left ventricular free wall, abnormal false cords attaching to the septum and accessory papillary muscles can all tether the leaflets of the mitral valve and cause LVOTO.<sup>6</sup> LVOTO can also be caused by hypertrophy of the anterolateral muscle bundle of the left ventricle (muscle of Moutaert).<sup>7</sup> At the most complex end of the spectrum, there is the diffuse, tunnel-like form of LVOTO. Conventional transaortic resection fails to achieve satisfactory long-term results and tunnel LVOTO requires aggressive surgical approaches such as aorticoventriculoplasty (the Konno procedure) or aortic root replacement with pulmonary autograft and ventriculoplasty (the Ross-Konno procedure) for relief of subaortic obstruction.<sup>8-12</sup>

Although several studies have investigated the surgical management of the individual lesions, there is paucity of data examining the comprehensive surgical management of LVOTO. The purpose of this study was to review our experience with surgical management of the LVOT, including patient survival, risk of recurrence and reoperation, and factors affecting surgical outcomes.

## METHODS

### *Patients and data collection*

All patients who underwent surgical treatment for LVOTO between January of 2002 and March of 2010 were included in this study. Patients were identified using the Pediatric Cardiothoracic Surgery Database at the University of California, San Francisco (UCSF), CA, USA. The following data were retrieved from patient care-related medical records: basic demographic and diagnostic data, surgical history, echocardiographic data (preoperative, predischarge, and last clinic followup), intraoperative data, postoperative complications including need for pacemaker placement, follow-up data from the last clinic visit including New York Heart Association (NYHA) class, recurrence, and need for reoperation. The length of follow-up was calculated from the last documented clinic or hospital visit.

The study was approved and monitored by the UCSF Institutional Review Board and due to its retrospective nature, need for patient consent was waived.

### *Statistical analysis*

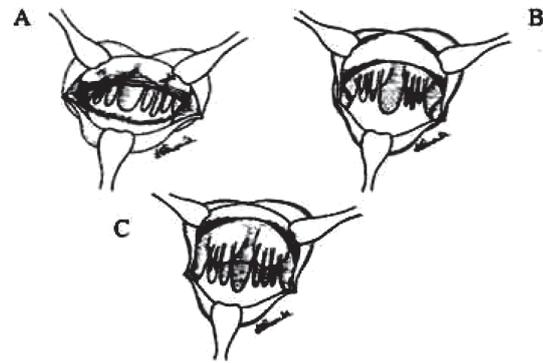
Data are expressed as frequencies, means with standard deviations, or medians with ranges. Counts and proportions were compared using the Chi-square tests. Non-normally distributed continuous variables were compared using the nonparametric Mann-Whitney tests.

Cumulative survival and freedom from recurrence and reoperation are reported using the Kaplan-Meier method. Univariate and multivariate logistic regression models were used to assess the effect of clinically significant covariates on death, reoperation, and recurrence/progression of LVOTO. Cox proportional hazards analysis was fitted with time to reoperation and proportional hazards regression analysis was performed to assess the effect of clinically significant covariates including: diagnosis of interrupted aortic arch, diagnosis of atrioventricular (AV) canal, surgical history of LVOT operation, bicuspid aortic valve, preoperative echocardiogram gradient, and discharge echocardiogram gradient. A p value of less than or equal to 0.05 was

considered significant. All analyses were performed using Stata 11 software package (Stata Corp, College Station, TX, USA).

### ***Surgical technique***

All operations were performed through a median sternotomy (Fig. 1). Cardiopulmonary bypass with intermittent cold blood antegrade cardioplegia was used. After cardioplegic arrest, the aortic valve was assessed. Fusion of the cusps at the commissures was sharply divided. In the patients where extension of the membrane to the aortic valve cusps was identified, the leaflets were thinned. The LVOT was next examined. The presence, consistency, and extension of the subaortic membrane toward the aortic valve cusps and the anterior mitral valve leaflet were noted. The membrane was engaged with a skin hook under the nadir of the right coronary cusp and a vertical incision was made toward the interventricular septum. Then, the membrane was excised toward the left fibrous trigone and mobilization of the left trigone was performed.<sup>1</sup> The anterior mitral valve leaflet was retracted anteriorly and to the right. A right angle clamp was passed behind the fibrous tissue connecting the lateral border of the anterior mitral valve leaflet and the muscular septum to assess the amount of fibrous deposition. A #11 blade was then used to make a perpendicular incision in this fibrous tissue. The depth of the incision was guided by the right angle clamp. It typically extended between 2 and 4 mm and continued until the anterior mitral valve leaflet/subaortic curtain separated from the muscular septum and dropped posteriorly. At that point, the lateral border of the leaflet was easily visualized and a distinct change occurred in the shape of the LVOT: before mobilization, the LVOT was restricted in the anteroposterior dimension, whereas after the restriction was relieved and the LVOT “popped” open. The depth of the incision in the area of the left fibrous trigone is important as the left anterior descending coronary artery is in close proximity and can be injured if one is too aggressive. The membrane was then bluntly removed from the anterior mitral valve leaflet. In the area of the right fibrous trigone, the remaining fibrous tissue between the subaortic curtain and the membranous septum was



**Figure 1.** View of the left ventricular outflow tract through the aortic valve. The aortic cusps are retracted. (A) There is a circumferential fibromuscular ring that is attached anteriorly to the muscular ventricular septum and posteriorly to the anterior leaflet of the mitral valve. Fibrous tissue deposits are seen in the left and right fibrous trigones that extend to the ventricular septum. The lateral borders of the anterior mitral valve leaflet are obscured by the fibrous tissue and the anteroposterior dimension of the left ventricular outflow tract is restricted. (B) The fibromuscular ridge is excised circumferentially. A left ventricular outflow tract myomectomy is performed lateral to the membranous septum. (C) Excess fibrous deposits on the left trigone are sharply and aggressively excised. The excess fibrous deposits along the right trigone are bluntly resected. This results in a drop of the anterior mitral leaflet away from the anterior muscular septum. The shape of the left ventricular outflow tract is restored and the lateral border of the anterior mitral valve leaflet is clearly seen through the aortic valve.

bluntly removed to complete the mobilization of the right fibrous trigone and to restore the right-sided hinge mechanism between the two structures. Aggressive removal of the fibrous tissue in the area of the right fibrous trigone can result in injury of the conduction tissue with heart block and/or perforation of the membranous septum and creation of an iatrogenic ventricular septal defect (VSD). Next, a myomectomy was performed if necessary. Two parallel incisions were made: one underneath the nadir of the right coronary cusp and one beneath the commissure between the right and left cusps. The depth of these incisions was guided by the preoperative transesophageal echocardiogram. A third incision 1 cm below the aortic valve was used to connect the previous two and a trough of muscle was removed. The myotomy was then extended toward the apex of the left ventricle to the base of the papillary mus-

cle. All areas of fusion between the papillary muscle and the interventricular septum were divided. The anterior mitral leaflet was inspected. All abnormal cords, attachments to the interventricular septum, and accessory valve tissue were removed. The cords that attach to the tip of the papillary muscles and to the leading edge of the valve leaflets were preserved to prevent mitral valve regurgitation.

When there was tunnel-like LVOTO or when the annulus was deemed inadequate, a standard complete root replacement Ross-Konno<sup>13</sup> or a modified Konno operation was performed.<sup>14</sup>

## RESULTS

Surgical repair of LVOTO was performed in 103 consecutive patients. The median age was 6.8 years (range 8 days to 62 years). The diagnostic characteristics of this patient cohort are shown in Table 1. There were 14 patients who had simple LVOTO from a discrete isolated subaortic membrane. Eighty-nine patients had complex LVOTO with complex fibromuscular obstruction (n = 53), tunnel obstruction with hypoplasia of the LVOT/aortic valve complex (n = 22), HOCM or muscular obstruction (n = 15), and accessory atrioventricular valve tissue with AMSA (n = 13). The preoperative median peak and mean gradients across the LVOT by echocardiogram were 60 mmHg (range 2 to 180 mmHg) and 33 mmHg (range 1 to 108 mmHg), respectively. Preoperative symptoms were present in 24 patients: 21 had dyspnea on exertion, syncopal episodes, or chronic fatigue with leg cramps, and three patients had history of arrhythmias. Nine patients had previous balloon valvuloplasty and one patient had alcohol ablation to relieve obstruction in the setting of HOCM. Although this was a very heterogeneous group of patients, the main hemodynamic criterion for surgical intervention was a mean LVOT gradient exceeding 30 mmHg. Surgical resection of LVOT pathology was performed in patients with lower gradients, when the patient needed an operation for a concomitant lesion (for example, aortic insufficiency or a VSD with subaortic membrane without significant hemodynamic gradient). Repeat sternotomies were performed in

**TABLE 1**  
**Primary Left Ventricular Outflow Tract Pathology and Associated Lesions**

<b>Left Ventricular Outflow Tract Obstruction Pathology</b>	<b>n</b>
Complex subaortic fibromuscular obstruction	53
Tunnel obstruction, hypoplasia of LVOT/aortic valve complex	22
Hypertrophic obstructive cardiomyopathy, muscular obstruction	15
Simple subaortic membrane	14
Accessory atrioventricular valve tissue, AMSA	13
<b>Associated lesions</b>	<b>n</b>
Ventricular septal defect	41
Interrupted aortic arch, aortic arch hypoplasia/ventricular septal defect	27
Aortic valve stenosis	25
Bicuspid aortic valve	24
Atrial septal defect	9
Double outlet right ventricle, tetralogy of Fallot	9
Atrioventricular canal defect	8
Transposition of the great arteries	7
Ascending aorta aneurysm	6
Other	14

LVOTO = left ventricular outflow tract obstruction; AMSA = anomalies of the mitral subvalvar apparatus. Note that some patients had more than one diagnosis and/or associated lesion.

45 patients: 29 patients had one, 12 patients had two, three patients had three, and one patient had four previous sternotomies. The complete surgical history of this cohort is depicted in Table 2.

### *Surgical interventions*

All operative procedures are outlined in Table 3.

Myomectomy was performed in 59 patients. Fiftythree patients had excision of a complex subaortic membrane, 26 patients had release of the fibrous trigones, 20 patients had repair or replacement of the aortic valve, and 17 patients had excision of the membrane from the anterior mitral valve leaflet. Fourteen patients had repair of abnormalities of the mitral subvalvar apparatus. Eleven patients had a Konno and 11 patients had a Ross-Konno operation. Seven patients had thinning of the aortic valve leaflets and seven patients had mitral valve repair or replacement.

### *Early results*

There were no early deaths. Two patients required temporary extracorporeal life support (ECLS) for postoperative low cardiac output syndrome. One patient required early reoperation for residual LVOTO and had a Konno procedure with aortic valve replace-

**TABLE 2**  
**Surgical and Interventional History**

Surgery	n
Subaortic resection	16
Aortic valve repair/replacement	12
Interrupted/hypoplastic aortic arch, ventricular septal defect repair	12
Ventricular septal defect repair	8
Atrioventricular septal defect repair	5
Tetralogy of Fallot repair, double outlet right ventricle repair	4
Pulmonary valve repair/replacement	4
Truncus arteriosus repair	3
Coarctation, ventricular septal defect repair	3
Atrial septal defect repair	2
Pulmonary artery band	2
Bidirectional cavopulmonary anastomosis	2
Rastelli	1
Fontan	1
Aortopulmonary shunt	1
Ross-Konno	1
Mitral valvuloplasty	1
LV-aorta tunnel	1
LV outflow tract aneurysm repair	1
<b>Intervention</b>	<b>n</b>
Balloon aortic valvuloplasty	9
Alcohol ablation for hypertrophic obstructive cardiomyopathy	1
<b>Previous LV outflow tract procedure</b>	<b>n</b>
One operation	15
Two operations	5
Three operations	1

LV = left ventricle.

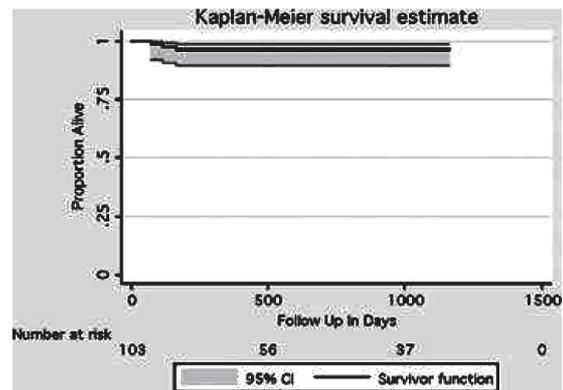
Note that some patients had more than one previous operation.

ment. Eight patients developed complete heart block and required pacemaker insertion (8%). Of these, three patients had release of the fibrous trigones (3/26 or 11.5%). At discharge, the median peak gradient across the LVOT by echocardiogram was 10 mmHg (range 1 to 75 mmHg) and the median mean gradient across the LVOT by echocardiogram was

**TABLE 3**  
**Surgical Procedures**

Surgical Procedure	n
Myomectomy	59
Complex subaortic membrane excision	53
Release of the fibrous trigones	26
Aortic valve repair/replacement	20
Membrane excision from the anterior mitral valve leaflet	17
Repair of abnormalities of the mitral subvalvar apparatus	14
Simple subaortic membrane excision	14
Konno operation	11
Ross-Konno operation	11
Aortic valve leaflet thinning	7
Mitral valve repair/replacement	7

Note that some patients had more than one operation.



**Figure 2.** Kaplan-Meier survival in all patients.

6 mmHg (range 0 to 45 mmHg) ( $p < 0.001$  and  $p < 0.001$  compared to the preoperative values, respectively).

### Late results

Survival information was available on all patients at a median duration of 46 months (range 11 to 109 months). There were three late deaths, all during the first year after surgery.

The first patient had myomectomy and truncal root replacement with an aortic homograft at four months of age and died of progressive heart failure four months later. The second patient had Ross-Konno operation and died suddenly at home three months later and no autopsy was performed. The last patient had atrioventricular septal defect repair with excision of accessory mitral valve tissue and died from low output syndrome after mitral valve replacement five months after the original repair. Overall cumulative survival at one, three, and five years was 96% (95% CI 89% to 99%). Kaplan-Meier survival is depicted in Figure 2. On univariate analysis, age, cardiac diagnosis of interrupted aortic arch or hypoplastic arch with VSD, complex LVOTO, release of the fibrous trigones, and discharge echocardiogram mean LVOT gradient were not associated with risk of death. In contrast to survival information, clinical follow-up was available on 86 out of 100 survivors at a median duration of 21 months (range 2 to 107 months). All patients are in NYHA class I or II. At follow-up, the median peak gradient across the LVOT by echocardiogram was 10 mmHg (range 1 to 84 mmHg) and the median mean gradient across the LVOT by echocar-

diagram gradient was 10 mmHg (range 1 to 47 mmHg) ( $p = 0.01$  and  $p = 0.01$  compared to the preoperative values, respectively).

#### Simple subaortic membrane group

The preoperative median peak and mean LVOT gradients in the simple group were 17 mmHg (range 4 to 69 mmHg) and 12 mmHg (range 5 to 37 mmHg), respectively. At discharge, the median peak and mean LVOT gradients decreased to 5 mmHg (range 1 to 30 mmHg) ( $p = 0.006$ ) and 2 mmHg (range 0 to 12 mmHg) ( $p = 0.005$ ). At follow-up, the median peak LVOT gradient was 7 mmHg (range 1 to 30 mmHg) and the median mean LVOT gradient was 1.5 mmHg (range 0 to 10 mmHg) ( $p = 0.01$  and  $p = 0.01$  compared to the preoperative values, respectively). All patients in this group are clinically well and no patient required reoperation or developed LVOTO recurrence.

#### Complex LVOTO group

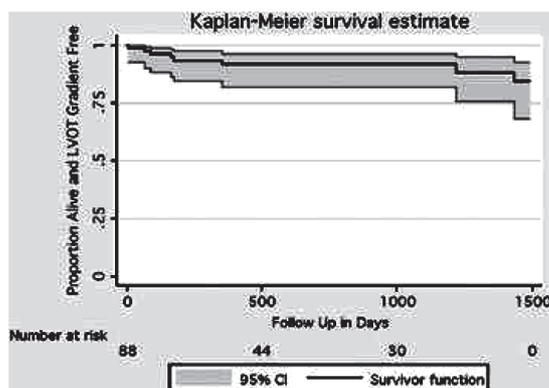
The median peak and mean preoperative LVOT gradients in the complex group were 65 mmHg (range 2 to 180 mmHg) and 35 mmHg (range 1 to 108 mmHg), respectively. At discharge, the median peak and mean LVOT gradients decreased to 12 mmHg (range 1 to 75 mmHg) ( $p < 0.001$ ) and 6 mmHg (range 1 to 45 mmHg) ( $p < 0.001$ ). At follow-up, the median peak LVOT gradient was 11 mmHg (range 1 to 84 mmHg) and the median mean LVOT gradient was 10 mmHg (range 1 to 47 mmHg) ( $p = 0.01$  and  $p = 0.01$  compared to the preoperative values, respectively).

At follow-up, six patients had evidence of persistent or recurrent LVOTO defined as echocardiographic mean LVOT gradient greater than 30 mmHg. Of these, one patient had mean LVOT gradient greater than 30 mmHg at the time of discharge from the hospital. Three patients had reoperations on the LVOT. For patients with complex LVOTO, the freedom from developing persistent or recurrent

**TABLE 4**  
Association of Preoperative and Perioperative Risk Factors with Recurrence/Progression of Left Ventricular Outflow Tract Obstruction in Patients in the Complex Group by Univariate Analysis

Risk Factor	Recurrence (%)	Odds Ratio	95% CI	p
Age	-	1.00	1.00 to 1.00	0.125
Diagnosis of interrupted aortic arch	3.6 vs. 19.0	8.58	0.95 to 77.2	<b>0.055</b>
Diagnosis of atrioventricular canal	7.1 vs. 14.3	5.10	0.52 to 50.0	0.162
Surgical history of LVOT operation	8.6 vs. 0	-	-	-
Bicuspid aortic valve	4.5 vs. 14.3	0.40	0.07 to 2.40	0.313
Preoperative echo mean gradient (mmHg)	-	1.00	0.97 to 1.04	0.853
Preoperative echo peak gradient (mmHg)	-	1.00	0.98 to 1.02	0.931
Discharge echo mean gradient (mmHg)	-	1.15	1.05 to 1.26	<b>0.002</b>
Discharge echo peak gradient (mmHg)	-	1.10	1.04 to 1.16	<b>0.001</b>
Ross/Ross-Konno procedure	9.5 vs. 0	-	-	-

CI = confidence intervals, LVOT = left ventricular outflow tract, echo = echocardiogram.

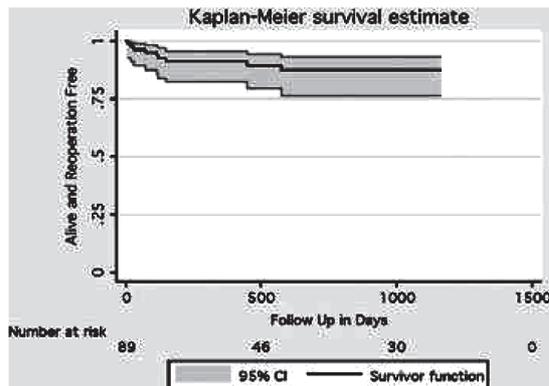


**Figure 3.** Kaplan-Meier recurrence-free survival in patients with complex left ventricular outflow tract obstruction.

**TABLE 5**  
Association of Preoperative and Perioperative Risk Factors with Recurrence/Progression of Left Ventricular Outflow Tract Obstruction in Patients in the Complex Group by Multivariate Analysis

Risk Factor	Odds Ratio	95% CI	p
Age	0.999	1.00 to 1.00	0.225
Diagnosis of interrupted aortic arch	4.134	0.34 to 50.50	0.266
Diagnosis of atrioventricular canal	17.959	0.50 to 641.92	0.113
Discharge echocardiogram mean gradient	1.236	1.07 to 1.43	<b>0.004</b>

CI = confidence intervals.



**Figure 4.** Kaplan-Meier reoperation-free survival in patients with complex left ventricular outflow tract obstruction.

LVOTO was 96% (95% CI 87%-99%), 96% (95% CI 87%-99%), and 88% (95% CI 70%-95%) at one, three, and five years (Fig. 3). On univariate analysis, factors associated with increased risk of developing progressive LVOTO at follow-up were cardiac diagnosis of interrupted aortic arch or hypoplastic arch with VSD (OR 8.58,  $p = 0.055$ ) and higher peak and mean LVOT gradients at discharge (OR 1.10,  $p = 0.001$  and OR 1.15,  $p = 0.002$ , respectively) (Table 4). By Cox proportional hazards multivariate regression analysis, higher discharge echocardiogram mean LVOT gradient was associated with recurrence of LVOTO (Table 5).

Ten patients had reoperation to address sequelae of the LVOT intervention in the aortic/mitral valve complex. Three patients had residual LVOTO that required Konno with aortic valve replacement or re-do complex SubAoM excision. Three patients had progressive aortic insufficiency that required Ross-Konno, Konno with aortic valve replacement, or

aortic valve replacement. Two patients had progressive mitral regurgitation that required mitral valve repair or replacement. Konno patch leak was repaired in two patients. Reoperation-free survival was 94% (95% CI 86% to 97%), 90% (95% CI 80% to 95%), and 78% (95% CI 59% to 89%) at one, three, and five years (Fig. 4). On univariate analysis, factors associated with an increased risk of reoperation were cardiac diagnosis of interrupted aortic arch/hypoplastic arch ( $p = 0.026$ ), cardiac diagnosis of atrioventricular septal defect ( $p = 0.015$ ), and higher mean LVOT gradient on discharge echocardiogram ( $p = 0.047$ ). Release of the fibrous trigones was associated with a decreased risk of reoperation ( $p = 0.031$ ). In contrast, age at operation, history of prior LVOT intervention, morphology of the aortic valve, and preoperative peak and mean LVOT gradients were not associated with the risk of reoperation (Table 6). By Cox proportional hazards multivariate regression analysis, factors associated with increased risk of reoperation were cardiac diagnosis of interrupted aortic arch/ hypoplastic arch (OR 6.4,  $p = 0.022$ ), cardiac diagnosis of atrioventricular septal defect (OR 15.4,  $p = 0.008$ ), and higher mean LVOT gradient on discharge echocardiogram (OR 1.08,  $p = 0.023$ ) (Table 7). Release of the fibrous trigones could not be entered in a multivariate model as no patient who had release of the fibrous trigones required reoperation.

The patients in the complex LVOTO group who had release of the fibrous trigones were further analyzed. The age, diagnosis of interrupted or hypoplastic aortic arch with VSD, and history of LVOT operation were not significantly different in the group

**TABLE 6**  
**Association of Preoperative and Perioperative Risk Factors with Reoperation in Patients with Complex Left Ventricular Outflow Tract Obstruction by Univariate Analysis**

Risk Factor	Reoperation (%)	Odds Ratio	95% CI	p
Age	-	1.00	1.00 to 1.00	0.222
Diagnosis of interrupted aortic arch	6.3 vs. 24.0	4.74	1.21 to 18.57	<b>0.026</b>
Diagnosis of atrioventricular canal	8.5 vs. 42.9	8.04	1.49 to 43.35	<b>0.015</b>
Surgical history of LVOT operation	9.6 vs. 18.8	2.18	0.50 to 9.53	0.302
Bicuspid aortic valve	11.8 vs. 8.3	1.47	0.27 to 7.87	0.655
Preoperative echo mean gradient (mmHg)	-	0.99	0.97 to 1.02	0.724
Preoperative echo peak gradient (mmHg)	-	1.00	0.98 to 1.01	0.763
Discharge echo mean gradient (mmHg)	-	1.06	1.00 to 1.13	<b>0.047</b>
Discharge echo peak gradient (mmHg)	-	1.03	0.99 to 1.07	0.105
Ross/Ross-Konno procedure	9.0 vs. 27.2	2.58	0.75 to 9.05	0.139

CI = confidence intervals, LVOT = left ventricular outflow tract, echo = echocardiogram.

that had release of the fibrous trigones compared to the group that did not have release of the fibrous trigones. The incidence of bicuspid aortic valve was higher in patients who had release of the fibrous trigones (12/26 vs. 12/63,  $p = 0.022$ ). The preoperative peak and mean LVOT gradients were higher in the patients who had release of the fibrous trigones compared to the patients who did not have release of the fibrous trigones [86 mmHg (range 24 to 140 mmHg) vs. 56 mmHg (range 2 to 180 mmHg),  $p = 0.010$  and 48 mmHg (range 12 to 90 mmHg) vs. 30 mmHg (range 1 to 108 mmHg),  $p = 0.026$ ]. At discharge, the peak and mean LVOT gradients were similar between the two groups [18 mmHg (range 1 to 73 mmHg) vs. 10 mmHg (range 1 to 75 mmHg),  $p = 0.09$  and 9 mmHg (range 1 to 38 mmHg) vs. 5 mmHg (range 1 to 45 mmHg),  $p = 0.15$ , respectively]. At follow-up, there was no difference in the peak and mean LVOT gradients between the two groups [16 mmHg (range 4 to 60 mmHg) vs. 10 mmHg (range 1 to 84 mmHg),  $p = 0.40$  and 10 mmHg (range 2 to 31 mmHg) vs. 8 mmHg (range 1 to 47 mmHg),  $p = 0.26$ , respectively].

#### *Patients older than 20 years*

At the time of surgery 14 patients (14%) were older than 20 years. Of these, eight patients had history of a prior heart surgery for a congenital heart lesion and four patients had history of previous operation for LVOTO. No patients older than 20 years had simple LVOTO from a discrete isolated subaortic membrane. Eight patients had complex LVOTO with complex fibromuscular obstruction, four patients had tunnel obstruction with hypoplasia of the LVOT/aortic valve complex, and two patients had HOCM. The median peak and mean preoperative LVOT gradients in the patients older than 20 years were 85 mmHg (range 4 to 180 mmHg) and 53 mmHg (range 2 to 85 mmHg), respectively. Myomectomy was performed in ten patients, eight patients had resection of a subaortic membrane, four patients had a Konno operation, and three patients had release of the fibrous trigones. There were no early and late deaths in this group of patients. Three patients developed heart block and required a pacemaker. At discharge, the median peak and mean LVOT gradients decreased to 24 mmHg (range 2 to

**TABLE 7**  
**Association of Preoperative and Perioperative Risk Factors with LVOT Reoperation in Patients with Complex LVOTO by Multivariate Analysis**

Risk Factor	Odds Ratio	95% CI	p
Diagnosis of interrupted aortic arch	6.420	1.32 to 31.33	<b>0.022</b>
Diagnosis of atrioventricular canal	15.390	2.04 to 115.97	<b>0.008</b>
Discharge echocardiogram mean gradient	1.085	1.01 to 1.16	<b>0.023</b>

LVOTO = left ventricular outflow tract obstruction, CI = confidence intervals.

45 mmHg) ( $p < 0.001$ ) and 12 mmHg (range 1 to 22 mmHg) ( $p = 0.002$ ). At follow-up, all patients are in NYHA class I and no patient developed recurrence of LVOTO. The median follow-up peak LVOT gradient in patients older than 20 years of age was 11 mmHg (range 4 to 46 mmHg) and the median follow-up mean LVOT gradient was 6 mmHg (range 2 to 20 mmHg) ( $p = 0.006$  and  $p = 0.006$  compared to the preoperative values, respectively).

## DISCUSSION

In this series, 103 patients had a variety of operations to relieve LVOTO either as an isolated procedure or part of a procedure to address coexistent lesions. There were no early deaths and the cumulative one-, three-, and five-year survival was 96%. Patients with a simple, isolated subaortic membrane resection had uncomplicated durable relief of the LVOTO. In the complex subset of LVOTO, ten patients required reoperations to address the sequelae of the surgery on the aortic-mitral complex and eight patients required pacemaker placement. Cardiac diagnosis of interrupted or hypoplastic aortic arch was a risk factor for recurrence/progression of LVOTO and LVOT reoperation. Diagnosis of atrioventricular septal defect was associated with the need for reoperation. Higher mean LVOT gradient on discharge echocardiogram was a risk factor for recurrence and reoperation in patients with complex LVOTO, suggesting risk of progressive obstruction, except in patients who had release of the fibrous

trigones. No patient in the complex LVOTO group who had release of the fibrous trigones required reoperation. Patients who had release of fibrous trigones during the LVOT procedure experienced similar relief of the LVOTO when compared to the patients who did not have release of the fibrous trigones, even though the former group had higher incidence of bicuspid aortic valve and more severe degree of LVOTO as measured by preoperative echocardiogram peak and mean LVOT gradients.

Left ventricular outflow tract obstruction is caused by a spectrum of different diseases. The most frequent cause of LVOTO is stenosis from a discrete subaortic membrane. There are two anatomic types of subaortic membrane. In the simple form, a distinct membranous or fibromuscular ridge exists in the LVOT. This lesion is usually associated with other lesions (most often a VSD) and LVOTO is relieved effectively by simple excision of the membrane. In the more complex form, the fibromuscular ridge extends toward the aortic valve cusps. Fibrous tissue coats the aortic valve cusps, limits the opening, and exacerbates the LVOTO by adding a component of valvar aortic stenosis. The continued scarring deforms the cusps, leads to failure of coaptation, and results in aortic insufficiency.<sup>3</sup> It is unclear whether simple and complex subaortic membranes are acquired or congenital lesions. Subaortic membrane is seldom seen in neonates and infants and has not been reported antenatally.<sup>15</sup> The disease is progressive, but the rate of progression is quite variable.<sup>2,3,16</sup> This makes not only the timing but also the extent of surgical repair quite controversial. Repair of subaortic stenosis can be accomplished with minimal perioperative morbidity and mortality. Recurrence of the subaortic obstruction, however, occurs in up to 27% of the patients.<sup>1,3,4,15-17</sup> Residual postoperative gradient and inability to fully relieve the LVOTO during the initial operation was associated with higher risk of recurrence and need for reoperation in this and other series.<sup>2,4,15,17</sup> Even after successful and complete relief of the LVOT gradient, aortic valve regurgitation can appear, persist, or progress.<sup>4,15,17,18</sup> The risk of recurrence and the risk of development of progressive aortic regurgitation correlated with the severity of preoperative LVOTO in some studies<sup>3,4,16</sup> but not in others.<sup>15,17</sup> In

this series, the severity of the preoperative LVOT gradient as measured by the mean and peak gradient was not associated with reoperation or with the development of persistent or recurrent LVOTO at follow-up. Many have advocated early surgical repair in order to prevent the development of high LVOT gradient.<sup>3,4</sup> The variable results of this aggressive treatment strategy have generated skepticism and early intervention is not universally accepted. Karamlou et al. followed 313 children-who were diagnosed with subaortic stenosis. The freedom from initial subaortic membrane resection was 40% at 16 years from diagnosis. They concluded that subaortic resection should be delayed until the mean gradient across the LVOT exceeds 30 mmHg because most patients with lesser gradients have quiescent disease without progression of LVOTO or the degree of aortic insufficiency.<sup>2</sup> The same criteria for intervention and the diagnosis of persistent or recurrent LVOT postoperative gradient were used in this series. At the same time, excision of subaortic membranes was pursued in patients with lesser mean gradients if the patient required an operation to correct a coexisting lesion (i.e., repair of VSD). Such surgical intervention may alter the local flow hemodynamics across the LVOT and may accelerate the progression of LVOTO even in patients in whom the morphology and size of the subaortic membrane alone would have predicted a more quiescent disease.

The extent of surgery for subaortic-membrane is also controversial. Parry et al. pursued an aggressive surgical approach that included peeling the entire subaortic membrane of the muscle and the undersurface of the aortic valve cusps with an aggressive myomectomy down the length of the interventricular septum in order to remove all pathological tissues and to restore the normal LVOT hemodynamics.<sup>3</sup> There was no recurrence of LVOTO following this aggressive surgical resection, but the trade-off was AV block in 14% of the patients. The routine use of a myomectomy as well as the need for an aggressive surgical resection has been questioned.<sup>16</sup> Hirata et al. used myomectomy selectively and reported that simple enucleation offers relief of LVOTO without increasing the risk of recurrence in patients undergoing primary operation for discrete

subaortic stenosis. In contrast, for the patients who had a previous cardiac operation, myomectomy resulted in significant reduction in the risk of recurrence.<sup>19</sup> In centers where myomectomy is used selectively, need for myomectomy is a surrogate for more complex LVOT disease and this may explain observed trends toward higher risk of recurrence.<sup>16</sup> In this series, myomectomy was used selectively, but resection of the membrane alone was reserved only for the simplest forms of the lesion, usually associated with a VSD. The incidence of postoperative heart block requiring pacemaker insertion was 8%.

Yacoub et al. analyzed the functional anatomy of the LVOT and the pathophysiologic features of subaortic stenosis.<sup>1</sup> They stressed the importance of the left and right fibrous trigones that fix the anterior mitral valve leaflet to the muscular and membranous septum. The fibrous trigones act as hinge mechanisms allowing the subaortic curtain and the anterior mitral valve leaflet to move forward and backward during the different phases of the cardiac cycle. In subaortic obstruction, fibrous tissue fills the space between the mitral valve and the subaortic curtain posteriorly and the septum anteriorly. The hinge mechanism fails and there is narrowing of the LVOT in the anteroposterior dimension. Optimal relief of the LVOTO cannot be achieved without mobilization and release of the fibrous trigones. This is accomplished by removing scar tissue between the anterior mitral leaflet and the septum. On the left, there is close proximity to the left main coronary artery. On the right, the bundle of His is also close and deep incisions can result in heart block.<sup>1</sup>

Successful resection results in springing open of the LVOT in the anteroposterior dimension. Mobilization of the fibrous trigones is a key intraoperative maneuver in the management of complex subaortic membrane. None of the patients with complex LVOTO who had mobilization of the fibrous trigones needed reoperation despite higher severity of preoperative LVOTO. At discharge, the patients who had mobilization of the fibrous trigones had similar mean LVOT gradients when compared to the patients who did not have mobilization of the fibrous trigones even though the former group had more severe degree of LVOTO. At follow-up, patients who had mobilization of the fibrous trigones had a median follow-up LVOT gradient of 10 mmHg.

Another less common cause of LVOTO is the anomalous insertion of mitral valve cords or papillary muscle to the ventricular septum.<sup>6,20,21</sup> Simple excision, mobilization of the papillary muscle of the septum, and mitral valve replacement are the main surgical options. This pathology has been associated with HOCM in the literature. In this series, though, of the 13 patients who required AMSA repair, only two had HOCM. Anomalies of the mitral subvalvar apparatus can be present without HOCM. In summary, LVOTO is caused by a variety of pathologies and a multitude of operative strategies is required to address LVOTO with favorable early and midterm outcomes. Residual LVOT gradient and original cardiac diagnosis are associated with increased reoperation risk. Release of the fibrous trigones decreases the risk of reoperation in patients with complex LVOTO.

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# Ethics in the Era of e-Commerce: the EU Approach

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## ABSTRACT

E-commerce of goods and services has a two-way relationship with ethics. E-commerce, due to the digital environment it operates, may put in danger the compliance with ethical rules of that state or another state in case it is transborder. On the other hand ethics may restrict, even prohibit e-commerce. This paper defines ethics in a global environment and sets the issues pending in global e-commerce. It launches the analysis on the EU case law in the era before e-commerce in order to reply to the question if the Internal Market Freedoms respect ethics. It proceeds to the EU legislation and case law that could be used in e-commerce problems putting the emphasis on the role of professional bodies in the EU level, medicinal products, medical devices and cosmetics, as well commercial communications of members of liberal professions and the confidentiality privilege. The paper concludes that the EU supports both ethical principles and e-commerce. The rules in e-commerce and brick-and-mortar business in the EU are fundamentally the same, but should be restricted to e.g. the first supply according to the principle of the proportionality. The Court has also recognized the different ways to compliance since the digital environment has interactive features which could help in respecting ethics as well as increase e-commerce.

## 1. The role of ethics in e-commerce

### 1.1. What does the term “ethics” mean?

The term “ethics” refers to a system of moral values and principles which allow a person to distinguish between right and wrong. Ethics “govern a person’s behavior of the conduction of an activity” and are generally defined as “rules or code of professional conduct” which correspond “to the chosen values” (e.g., trust). While codes of business ethics and codes of conduct for employees try to regulate the behavior of business

nationally or worldwide, members of liberal professions use the codes of professional conduct as an obligatory set of professional ethics principles governing the professional pursuit of their activity in relation to customers and colleagues. The nature of a code of conduct and issues addressed differ widely between the EU and the US. Codes in the US tend to be more compliance-oriented and are even legalistic, because the laws in the US tend to leave more business matters to the private sector. Codes in the EU tend to be more focused on social responsibility.

In Europe, ethics are usually imposed by law or by professional bodies and associations on their members. In case of their infringement, the professional bodies may impose disciplinary sanctions, even expulsion from the profession, while the courts may order civil or criminal actions if the infringement is serious. The European codes of conduct include professional ethics, such as the principles of independence, impartiality and protection of the interests of the customers, professional secrecy, professional qualifications and partnership rules, commercial communications, remuneration and sanctions mechanism.

### 1.2. Ethics and e-commerce

The importance of “establishing ethical conduct in the global village” is significant. Commercial transactions or service provision are based on *trust*, which is difficult to establish across national frontiers, with people who are acquainted only via phone, email or the internet, in states with different customs and ways of doing business. Studies pin point ethical factors such as assurance of *e-consumer privacy and security* (against e.g. dissemination of consumer habits), guaranteeing e-vendor accountability, accurate product description, the first factor having the greatest effect on consumers’ willingness to engage in e-commerce. In addition, the speed of technological change and of development of new commercial practices on the internet may exceed the speed of ethical development on the internet and thus establish the phenomenon of the “ethical lag”.

Consequently, the first question is “whether there is an *ethical lag* in the Internet”, and if there is such lag who is going to decide about the new ethics on the internet: The state or the professional bodies / associations? Does the EU support self-regulation of professions and industries in order to solve ethical dilemmas by promoting consumer and investor confidence instead of enacting rigid and technologically obsolete legislation or allowing the slow and expensive procedure of litigation?

The second question is “whether there are *special* moral rules in a digital environment or whether e-commerce should simply use the *same* ethical rules employed in brick-and-mortar busi-

ness”. The answer given so far is that “ethical principles and rules in e-commerce and brick-and-mortar business are *fundamentally the same*, but have *different manifestations*, due in part to the very nature of e-commerce”: its speed, its pervasiveness and its scope.

And the last question is what happens in case that ethics of one state are infringed because of e-commerce activities emanating from another state which there are no such ethics? LICRA, an activist anti-racist organization, discovered 800 Nazi-related items for sale on yahoo.com, including a box of Zyklon-B, the poison gas used at Auschwitz, identified as a “museum quality replica”. LICRA filed an action against the Yahoo! Inc., a US company, and its French subsidiary claiming infringement of the French Criminal Code which included a specific prohibition on exhibition and sale of Nazi emblems and memorabilia. The French court ordered Yahoo Inc and Yahoo France to take all necessary measures to “dissuade and render impossible” any access by persons in France via Yahoo.com to Nazi related content on servers located in the US. Yahoo Inc. continued the litigation in US where the order from France should have been enforced invoking *free speech* rights. The District Court issued its Order in favor of Yahoo but the judgment was reversed by the 9 Circuit Court of Appeal in favor of LICRA. The Yahoo case revealed a business ethics lack and rose pressure on business to assume responsibility for social consequences of commercial activities *beyond the simple respect of legal constraints*. Which is the policy of the European Union towards the solution of such problems?

## 2. The EU law on ethics in the era of e-commerce

### 2.1. The era before e-commerce: restrictive measures justified by ethics in the EU

#### 2.1.1. Introduction

The Treaty of Rome establishing the EEC (EEC-1958) as well as the Treaty on the Functioning of the European Union (TFEU - 2009) have provided for the free movement of goods,

persons, services and capital between member states as well as protection of free competition. Member states may restrict these freedoms if the restriction is justified on certain grounds stated by the Treaty under the condition that the measures are proportionate to the aim they pursue. For the free movement of goods the Treaty has provided the exception of protection of public morality, which can be invoked by a member state according to its own scale of values. The Court of Justice of the European Communities (CJEC) now Court of Justice of the European Union (CJEU) has expanded the Treaty exceptions in case of non-discriminatory measures to “imperative requirements justified by the general interest”. Since the 1970ies, the EU law has expressly considered ethics as a possible justification of national measures restricting the freedom of establishment and the free provision of services in the internal market. In the words of the Advocate General Leger: “the application of professional rules to lawyers – in particular, rules relating to organisation, qualifications, professional ethics, supervision and liability - pursue an *objective in the public interest*. The Court considers that the application of such professional rules ensures that the ultimate consumers of legal services are provided with the *necessary guarantees in relation to integrity and experience and contributes to the sound administration of justice*”.

## 2.2. Ethics and freedom of establishment

A vivid example of the way professional rules apply is the case 71/76. Thieffry was a Belgian lawyer who had applied to be admitted for the training stage in the Paris Bar, after having already assisted in the chambers of a French lawyer. He submitted the academic recognition by a French University of his Belgian doctorate in law as an *equivalent* to a French degree in law and his “certificat d’aptitude a la profession d’avocat”, after he had sat and passed that examination. The Bar Council refused his application on the ground that *he lacked a degree in French law*. The Court ruled that this *prima facie* non-discriminatory national professional rule (French degree) was an obstacle to the freedom of establishment (Art. 49

TFEU). It could however be *justified by the general good* related to the organization and qualifications of the profession, *professional ethics and the supervision and liability* of the member of the Bar. In addition, the Court recognized that “freedom of establishment, *subject to observance of professional rules* justified by the general good, is one of the objectives of the Treaty”. Finally the Court recognized the normative power of the “*practices of the professional bodies*” as equivalent with state legislation, for ensuring the freedom of establishment.

In the case C-3 09/99, the Court examined the prohibition of multidisciplinary partnerships between lawyers and accountants. In 1994, Mr. Wouters, a member of the Amsterdam Bar, informed the Supervisory Board of the Rotterdam Bar of his intention to enroll in the Rotterdam Bar and to practice under the name of “Arthur Andersen & Co., advocaten en belastingadviseurs” (lawyers and tax consultants). However, the Board found that members of that company were in professional partnership with the members of “Arthur Andersen & Co. Accountants”. The Board refused the application of Mr. Wouters and justified the prohibition of merging lawyers and accountants together on the “*independence and duty of loyalty of lawyers*” as well as on the “*observance of lawyers’ professional secrecy*”. The Court considered that rules emanating from associations or organisations, which are *designed to regulate, collectively*, self-employment and the provision of services may create obstacles that could neutralize the freedoms guaranteed by Articles 49 and 56 TFEU. Therefore such prohibitions could be incompatible with the Treaty even though the professional associations were not governed by public law and possessed legal autonomy while the professional rules they adopted were not public in nature. However, the Court declared that such prohibition could reasonably be justified as necessary for the *proper practice* of the legal profession in order to ensure integrity and experience for the ultimate consumers of legal services and the sound administration of justice. Such guarantees are the duties of the lawyer *to act for his/her clients in complete independence and in their sole interest*, to avoid all risk

of conflict of interest and to observe strict professional secrecy.

In the case of C-55/94, another professional rule was infringed: the use of a *professional title* by a lawyer of another member state, without registering in the Bar. Mr. Gebhard, a German lawyer, was accused by the Milan Bar Council of pursuing a professional activity in Italy on a permanent basis in chambers set up by himself whilst using the Italian professional title “awocato”, without being registered in the Milan Bar. During the disciplinary proceedings, Mr. Gebhard invoked, inter alia, Directive 77/249/EEC to facilitate lawyers in the exercise of the freedom of services. For the pursuit of *all other activities* except representation before the court, the lawyer remains subject to the conditions and rules of professional conduct of the Member State of *origin*, (here Germany) without prejudice to respect for the rules which govern the profession in the host Member State (Italy), especially those concerning the *incompatibility of the exercise* of other activities, *professional secrecy*, etc. The Court ruled that membership of a professional body may be a prerequisite of taking up and pursuing particular activities but it cannot itself be a constitutive element of establishment. The Court gave a broad interpretation of Art. 49 TFEU, so that a provider of services may also use a chamber set up by himself to facilitate his activities.

### 2.3. *Freedom to provide services in another member state*

Article 56 TFEU requires not only the elimination of all discrimination against providers of services established in another Member State, where he lawfully provides similar services, but also the *abolition of any restriction*, even if it applies without distinction to national providers of services and to those of other Member States, which is liable to *prohibit, impede or render less advantageous his activities*. However, the Court rules that service providers, especially in the case of regulated professional activities, may be subject to the rules of the host Member State *where the application of those rules is justified in the general interest*.

In the case 33/74, Van Binsbergen had entrusted his defence to Mr. Kortmann, a Dutch lawyer who had changed his residence from Netherlands to Belgium during the proceedings, thus infringing the Dutch Code of Lawyers that required that the lawyer must reside or be established in Netherlands in order to have the capacity to act before the Dutch courts. The CJEU enshrined the direct effect of the Treaty rule on the free provision of services and consequently, the national provisions must in principle be abolished. However, the Court confirmed the *lawfulness of “specific requirements* imposed on the person providing the service ... where they have as *their purpose the application of professional rules justified by the general good* - in particular rules relating to organisation, qualifications, professional ethics, supervision and liability - which are binding upon any person established in the State in which the service is provided”. The Court ruled that art. 56 TFEU cannot be used “for the *purpose of avoiding the professional rules of conduct* which would be’ applicable to [a service provider] if he were established within that State”. However, compliance to professional rules of the *host* member state may restrict the freedom to provide services and such restriction could be justified pursuant to one of the exceptions provided for in the Treaties and in the case-law of the Court if the professional rule was proportional to this aim. In particular, it must be confirmed a) whether those rules constitute a restriction within the meaning of Article 56 TFEU, and, if so, a) whether they pursue an objective in the public interest, b) are appropriate to ensuring that it is attained, and c) do not go beyond what is necessary for attaining it.

In the recent case C-475/11, Dr. Konstantinides, a Greek doctor established in Athens since 1981, visited Germany, throughout 2006 to 2010, for one or two days a month on average, in order to perform highly specialized andrological surgical operations. The operations took place in the out-patient surgery department of a private medical centre, which arranged appointments and provided in-house post-operative care. The Association of Doctors of the Land of Hesse received a complaint by a patient operated in 2007 disputing the amount of the bill sent to him by Dr.

Konstantinides. After investigation, the Association opened a disciplinary proceeding for infringement of the Regulation on doctors' fees accusing him that he had applied an excessive fee to the provision of his service. Dr. Konstantinides claimed that the service he provided is not included in the so-called list of fees and that he applied to the operation the fee code which was closest to the operation performed. The Advocate General clearly stated that the *risk of the imposition of a disciplinary penalty* (e.g. 50.000 Euros) or a declaration of unfitness for the profession just because a professional charged a higher fee within the scope of the discretion allowed by the professional association rules clearly creates for that professional a situation of legal uncertainty which is likely to limit or render less attractive his activity and thus constitutes a restriction of the freedom to provide services. The Court emphasized that rules of a Member State do not constitute a restriction within the meaning of the FEU Treaty solely by virtue of the fact that other Member States *apply less strict, or economically more favourable*, rules to providers of similar services established in their territory. Therefore the mere fact that doctors established in Member States other than Germany have to submit, for calculating their fees for services provided in that Land, to the rules applicable in that Land *does not amount by itself to a restriction*. However, in case that the national court found an absence of any flexibility of the calculating system, its application would be liable to have a deterrent effect on doctors from other Member States and constitute a restriction within the meaning of the Treaty.

During the 1970ies the EEC has tried to harmonize the conditions of establishment and rendering services of many professions. For doctors, member states had to set up information centres in order to enable the doctors from other member states to obtain information on the professional ethics of the host member state. They also included exchange of information on the good character and good repute of the professional in question. They exempted the doctor rendering services in another member state from membership of a professional body, but expressly required that

he will subject to the rules of conduct of a professional or administrative nature which apply in the host member state. For lawyers, art. 4 of the Directive 77/249/EEC provided that in pursuing activities relating to *representation*, the lawyer must observe the rules of professional conduct of the *host* Member State, without prejudice to his obligations in the Member State of his origin (Article 4(2)). As far as the pursuit of *all other activities* is concerned, the lawyer remains subject to the conditions and rules of professional conduct of the Member State of *origin*, without prejudice to respect for the rules which govern the profession in the host Member State, especially those concerning the *incompatibility of the exercise* of the activities of a lawyer with the exercise of other activities in that State, *professional secrecy, relations with other lawyers*, the prohibition on the same lawyer acting for parties with mutually conflicting interests, and secrecy.

#### 2.1.4. Conclusion

These were just some examples of the case law on ethics in brick and mortar cases. How will this case law fit in the e-commerce, taking into account the specific horizontal legislation which has emerged since then?

### 3. The Era of E-commerce and ethics

#### 3.1. EU legislation on e-commerce and ethics

##### 3.1.1. Ethics and the Directive 2000/31/EC on certain legal aspects of e-commerce

The Directive 2000/31/EC has approximated certain national provisions on information society services relating to the establishment of service providers, the provision of services by professionals, their commercial communications, their electronic contracts, the liability of intermediaries, *codes of conduct, court actions and out-of-court dispute settlement and cooperation between Member States*. The Directive 2000/31/EC provides for mandatory pre-contractual information rights for on-line transactions. In addition to the usual requirements, a member of a regulated profession should provide the e-consumer the following obligatory information before an electronic transac-

tion is concluded: any *professional body* or similar institution with which the service provider is registered, the *professional title* and the Member State where it has been granted and the reference to the applicable *professional rules* in the Member State of establishment and the means to access them. The service provider is also required, except when otherwise agreed by parties who are *not consumers*, to indicate “*any relevant codes of conduct to which he subscribes and information on how those codes can be consulted electronically*”. The use of commercial communications provided by a member of a regulated profession is “permitted *subject to compliance with the professional rules* regarding, in particular, the *independence, dignity and honour of the profession, professional secrecy and fairness towards clients and other members of the profession*”. In this regard, professional associations and bodies will be encouraged by member states and the Commission to establish codes of conduct at *EU level* “in order to determine the *types of information that can be given for the purposes of commercial communication* in conformity” with the above rules. These codes of conduct should be taken in due account by the Commission when drawing up proposals for Community initiatives for the proper functioning of the Internal Market, acting “*in close cooperation with the relevant professional associations and bodies*”. Indeed, codes of conduct at EU level are considered to be the *best means* of determining the rules on professional ethics applicable to commercial communications in order to remove barriers to cross-border e-services of members of the regulated professions. The Directive 2000/3 I/EC strongly encourages the “drawing-up” or the adaptation of “codes of conduct” at EU level, “by trade, professional and consumer, associations or organisations, will to contribute to the proper implementation of the Directive is encouraged by the member States and the European Commission. This however should not impair neither the autonomy of professional bodies and associations nor the voluntary nature of such codes and the possibility for interested parties of deciding freely whether to adhere to such codes.

In addition, art. 16 sets voluntary rules of cooperation between professional associations, con-

sumer associations, the member states and the Commission, putting the latter into the center of cooperation: Member States and the Commission shall encourage the voluntary *transmission of draft codes of conduct* at national or EU level to the Commission and their accessibility in the *EU languages* by electronic means as well as the involvement of *consumer associations* in the drafting and implementation of such codes affecting their interests. Finally, trade, professional and consumer associations or organisations, should be encouraged to communicate to the Commission and the member states their *assessment of the application of their codes of conduct and their impact upon practices, habits or customs relating to electronic commerce*.

### 3.1.2. *Ethics and the Directive 2006/123/EC on Services in the Internal Market*

The Directive 2006/123/EC on services in the Internal Market constitutes a balanced mix of measures that involve targeted harmonization, administrative cooperation, freedom to provide services and the encouragement of the development of *codes of conduct* on certain issues in order to ensure a high level of protection of general interest objectives, especially protection of consumers and quality of services. Therefore it provides for the following rules that involve ethics:

1. All procedures and formalities relating to access to a service activity and its exercise may be easily completed, at a distance and by electronic means, through the “point of single contact” and with the relevant competent authorities.

2. As in the e-commerce Directive, information must be provided from a member of regulated professions for “any professional body or similar institution with which the provider is registered, the professional title and the Member State in which that title has been granted” in order to ensure the quality of service provided.

3. At the recipient’s request, no matter if he is consumer or not, providers must supply the following *additional information* before the conclusion of the contract or the provision of the service: i) the exact price, otherwise the method for calculating the price or a sufficiently detailed es-

imate; ii) a reference to the *professional rules* applicable in the Member State of establishment and how to access them; iii) information on their *multidisciplinary activities* and partnerships which are directly linked to their service as well as on the measures taken to avoid *conflicts of interest*; (iv) *any codes of conduct to which the provider is subject and the address at which these codes may be consulted by electronic means, specifying the language version available*; v) information on recourse to a non-judicial means of dispute settlement by a professional body.

4. Ensure the freedom to provide services: free access to and free exercise of a service activity will not be subject to compliance with any requirements which do not respect the principles of: (a) non-discrimination; (b) necessity: the requirement must be justified for reasons of public policy, public security, public health or the protection of the environment; and c) proportionality: the requirement must be suitable for attaining the objective pursued, and must not go beyond what is necessary to attain that objective.

5. Codes of conduct should be drawn up by professional bodies, organisations and associations at EU level, in order to promote the quality of services and *facilitate the provision of services or the establishment of a provider* in another Member State. These codes of conduct should: a) comply with EU law, especially competition law; b) be compatible with legally binding rules governing professional ethics and conduct in the Member States; c) take into account the specific nature of each profession; d) include appropriate rules for *commercial communications* relating to the regulated professions and *rules of professional ethics* and conduct of the regulated professions which aim, in particular, at ensuring independence, impartiality and professional secrecy as well as the conditions to which the activities of estate agents are subject; d) set minimum standards of conduct and are complementary to Member States' legal requirements and e) are accessible at a distance, *by electronic means*. Member States: a) are not precluded from taking more stringent measures in law (national professional bodies may also provide for greater protection in their national

codes of conduct); b) should take *accompanying measures* to encourage professional bodies, organisations and associations to *implement* at national level the codes of conduct adopted at EU level. As the European Commission announced in 2007 there were at least 172 professional organisations representing different service sectors who have replied in a public consultation. Among these associations a percentage of 35% replied that they possess a European Code of Conduct, while there were also *European* professional associations especially for the regulated professions e.g. for lawyers, architects, engineers and veterinarians. Only 10% of the respondents have been assigned a regulatory power by the State.

6. *Information on the good repute* of providers maybe exchanged between the authorities of different member states, namely, on disciplinary or administrative actions or criminal sanctions if a final decision has been taken against the provider, which are directly relevant to the provider's competence or professional reliability. Decisions concerning insolvency or bankruptcy involving fraud should specify whether a particular decision is final or whether an appeal has been lodged. The member states must inform the provider and must respect the rules on personal data and the rights of the persons found guilty.

7. Commercial communications: All total prohibitions which, in a general way and for a given profession, forbid one or more forms of commercial communication, such as a ban on all advertising in one or more given media, will be removed. As regards the content and methods of commercial communication, it is necessary to encourage professionals to draw up codes of conduct at EU level. Until then, commercial communications by the regulated professions must comply with professional rules on the independence, dignity and integrity of the profession, as well as on professional secrecy, in a manner consistent with the specific nature of each profession. They shall be non-discriminatory, justified by an overriding reason relating to the public interest and proportionate.

8. Multidisciplinary activities: Member States should not impose obligations to providers to exer-

cise a specific activity *exclusively or restrict* the exercise jointly or in partnership of different activities. However, such exclusivity requirements may be imposed to members of the regulated professions, in so far as is justified in order to guarantee compliance with the rules governing *professional ethics and conduct*, which vary according to the specific nature of each profession, and is necessary in order to ensure their *independence and impartiality*. In case that member states authorize the above professionals to proceed to multidisciplinary activities, they should take such measures so that: (i) conflicts of interest and incompatibilities between certain activities are prevented; (ii) the independence and impartiality required for certain activities is secured; and (iii) the rules governing professional ethics and conduct for different activities are compatible with one another, especially as regards matters of professional secrecy.

9. Member states and the Commission will encourage with accompanying measures: Providers on a voluntary basis to *ensure the quality of their service using certification* or assessment of their activities by independent or accredited bodies and drawing up their own *quality charter* or participating in quality charters or labels drawn up by professional bodies at EU level; b) Professional bodies, as well as *chambers of commerce and craft associations and consumer associations*, to cooperate at EU level in order to promote the quality of service provision and facilitate the assessment of the competence of a provider and c) The development of voluntary European standards with the aim of facilitating compatibility between services supplied by providers in different Member States, information to the recipient and the quality of services provided.

### 3.1.3. Codes of conduct as self regulation

Self-regulation is very important in the Internet in order to support an ethical e-commerce environment. It is said that the Internet has the power to spotlight issues of ethical concern and “get [them] swiftly resolved because of both the actual or perceived exposure to and reaction from the public or market”. Certain professions such as accountants, lawyers, doctors, pharmacists and

real estate agents established EU codes of conduct almost a decade ago. These codes laid down professional rules in particular related to the *independence, dignity and integrity* of the profession. Technological progress in combination with the increasing use of the Internet by regulated professions may require that these codes be updated”. The Directive 2005/36/EC lists professional associations or organizations in its Annex and defines as their purpose “... *to promote and maintain a high standard in the professional field concerned*. To that end they are recognised in a *special form by a Member State and award evidence of formal qualifications* to their members, ensure that their members *respect the rules of professional conduct* which they prescribe, and *confer on them the right to use a title or designatory letters or to benefit from a status corresponding to those formal qualifications*”.

The Council of Bars and Law Societies of Europe (CCBE) has adopted the Code of Conduct of European Lawyers (1988) and the Charter of Core principles of the Legal profession (2006). Very important is the role of the Code of Conduct adopted by the Federation of European Accountants (FEE) and its use in reference to the commercial communications of accountants. The FEE Council has approved a Code of Conduct which applies to *on-line advertising* but not to the actual provision of services, whether provided physically or *electronically*. The FEE Code of Conduct serves as a model code for use by each FEE member body and is available in electronic format. The Principles of European Medical Ethics were adopted by the International Conference of Medical Professional Associations as early as January 1987 while their Appendix on February 1995. The Conference recommended that the medical professional associations in each EU member state ensure that their national requirements, conform with the principles set out in this text, and to take all useful measures to ensure that the legislation in their country allows the efficient implementation of these principles. In June 2011, *the European Charter of Medical Ethics* was adopted in Kos. The Charter relates to the duties and rights of doctors regarding their patients and society, and in their professional rela-

tionships while the *Deontological Guidelines* are still being drafted. Another European Code of Professional Conduct is adopted for Homeopathic doctors. In 2013 the European Federation of Pharmaceutical Industries and Associations (EFPIA) has adopted the EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations. The Architects' Council of Europe (ACE) has adopted the European Deontological Code For Providers of Architectural Services, revised in March 2009.

In Greece, the Code of professional rules for distance sales has been approved in 2005 by the General Assembly of "the Greek Union of Businesses of distance sales and direct marketing (EPAM) since EPAM members believe that the promotion of public acceptance of distance sales requires that all firms in Greece comply to minimum rules of conduct.

#### 3.1.4. Conclusion

The E-Commerce Directive has paved the way to respecting ethics on the internet, while the Services Directive has built upon the *acquis* of the E-Commerce directive, since some of its provisions correspond to the older ones but are clearer and bolder (e.g. additional information and commercial communications). In fact, the Services Directive expanded and elaborated the *acquis* in order to create a model of co-regulation with self-regulating professional bodies at EU level, at the same time respecting the self-regulation of professional bodies to adopt amongst themselves and for themselves common guidelines at European level.

### 3.2. Case law on medicinal products, medical devices and cosmetics concerning ethics on the internet

#### 3.2.1. Case law on the internet sale of medicinal products

The Case C-322/01 is a significant example, taking into consideration that the German legislation in 2000 prohibited internet sales of medicinal products for human use by pharmacies established in another Member State. The dispute concerned the complaint filed in a Frankfurt Court

by Deutscher Apotheker Verband, the German pharmacists' association, against DocMorris, formed as a limited company in the Netherlands and directed by a pharmacist authorized in the Netherlands. DocMorris sold medicinal products either via a traditional pharmacy in the Netherlands or on internet in Germany, which were both covered by a licence issued by the Dutch authorities and were subject to control in the Netherlands, where the company was established.

The EU Court of Justice found that the prohibition of selling medicines through mail order is a measure having an effect equivalent to a quantitative restriction contrary to art. 34 TFEU since the prohibition has a *greater impact on pharmacies established outside Germany* and could impede access to the market for products from other Member States e.g. the Netherlands, more than it impedes access for domestic products. However, the Court ruled that the German prohibition for the sales of *prescription medicines* via the Internet could be justified in order to ensure that a pharmacist could: a) check in an *effective and responsible way of the authenticity of doctors' prescription* and b) confirm that the medicine is handed over either to the *customer himself*, or to a person to whom its collection has been entrusted by the customer. Therefore the Court concluded that the German prohibition on the sale of medicinal products by mail order is compatible with EU law only when it applies to *prescription* medicines but incompatible if it applies to non-prescription medicines.

In conclusion, the CJEU allowed the Internet sale of medicinal products authorized at the EU level or in the member state of destination if they do not require a doctor's prescription in that member state and are sold by a traditional pharmacy. The importance of the judgment was significant since it covered an issue sensitive for all member states, their social security systems and their public health. In three weeks after the publication of the judgment, Germany had modified its legislation abolishing the prohibition of "Versandhandel" and allowing the internet sale of all Pharmaceuticals, even prescription ones, to pharmacies on certain conditions, e.g. that drugs are received by

the consumer in person.

The case of DocMorris NV, however, had a follow-up. In 2006, the German Ministry granted DocMorris, this Dutch company, a licence to operate a branch pharmacy in Saarbriicken (Germany), subject to the condition to recruit a pharmacist who would be entrusted with managing the pharmacy in question personally and on his own responsibility. However, the Apothekerkammer des Saarlandes and other professional bodies brought actions before the German Administrative Court, for the annulment of this decision, on the ground that the right to own and operate a pharmacy is restricted to pharmacists alone and not to companies ('the rule excluding non-pharmacists'). The Ministry, supported by DocMorris, submitted that this rule was invalid because it had as a result that a company lawfully operating a pharmacy in a Member State did not have *access* to the German pharmacy market and such a restriction was not necessary for achieving the legitimate objective of protection of public health. The CJEU rejected their argument and upheld the German "rule excluding non-pharmacists", since the EU law recognized such discretion to the Member states. It based its judgment on ethics and in particular on the fact that pharmacists *enjoy genuine professional independence which safeguards the reliability and the good quality of medicines offered to the public*, and that they operate "not with a purely economic objective but also from a professional viewpoint".

The CJEU characterized ethics as a "*moderating factor*" in the pursuit of profit by stating: "His private interest connected with the making of a profit is thus *tempered* by his training, by his professional experience and by the responsibility which he owes, given that any breach of the rules of law or professional conduct undermines not only the value of his investment but also his own professional existence". Since non-pharmacists by definition lack the above qualifications and consequently do not provide the same safeguards as pharmacists, a Member State may take the view, that, the operation of a pharmacy by a non-pharmacist may represent a risk to public health, in particular to the reliability and quality of the sup-

ply of medicinal products at retail level, because the pursuit of profit in the course of such operation does not involve the abovementioned moderating factors.

### 3.2.2. *E-commerce of medicines and ethics today*

At least two million people in Great Britain and two million people in Germany receive professional advice and service in European mail order pharmacies every day. In Germany, more than 1,800 on-site pharmacies have a mail order permit. The US market is thriving thanks to the US Patient Protection and Affordable Care Act while the global telemedicine market is expected to grow from \$9.8 billion in 2010 to \$11.6 billion in 2011, and to \$27.3 billion in 2016, a compound annual growth rate (CAGR) of 18.6% over the next five years.

E-commerce is very convenient, even vital especially for older people, who are no longer mobile or live in rural areas. The internet pharmacies mail prescription medicinal products only with a *valid, original prescription*. Compliance with this requirement is guaranteed both by technological verification processes and visual checks of the original prescription undertaken by pharmacists. The original prescription must be submitted to the mail order pharmacy. If there is any doubt regarding the authenticity of the prescription, the doctor named on the document will be contacted, as will the relevant authorities, e.g. the Federal Criminal Office (BKA). Besides, the *patient records are maintained*, therefore any medication dispensed to a patient can therefore be documented at any time.

However, the pharmaceutical industry is «under worldwide attack from brandjackers using the Internet to illegally use protected trademarks and other intellectual property («cybersquatting or cyberpiracy») to market counterfeit drugs». The International Chamber of Commerce (ICC) Commercial Crime Services reported that the Internet is "k-wash with fake Pharmaceuticals" and warned against purchasing pharmaceuticals through unregulated markets. In 2008 eight million counterfeited pills produced by gangs based in China,

who copied of the world's best selling pharmaceuticals, were purchased in Britain. Mail order pharmacies however do not allow cyberpiracy. Their association claims that a mail order pharmacy is a proper pharmacy with a shipping licence, "not an anonymous web address". It is subject to the *same strict rules* as any local pharmacy.

### 3.2.3. *E-commerce of medical devices and cosmetics*

#### 3.2.3.1. *The Case of Ker-Optika — can lenses be sold via the internet?*

In the case C-208/09, the CJEU examined the Hungarian provision that reserved the sale of contact lenses to shops specialized in medical devices with the use of qualified staff. Ker-Optika, which sold contact lenses via its Internet site challenged this prohibition. The EU Court of Justice, after referring to its DocMorris judgment, held that member states should not restrict the sale of contact lenses to only physical outlets that specialize in medical devices. In particular, the EU Court ruled:

1. The national rules that regulated how medical devices are supplied to the end user (e.g., only after a prior examination for fitting) fall outside the scope of the e-commerce directive 2000/31/E but inside the field of application of free movement rules of the Treaty.

2. Selling contact lenses is separate from obtaining *medical advice* which requires the physical examination of a patient and on which the sale may be dependent".

3. The prohibition on selling contact lenses by mail order deprives traders from other Member States of a particularly effective means of selling those products and thus significantly impedes access of those traders to the market of the Member State concerned. Therefore the national legislation does not affect in the same manner the Hungarian traders and traders from other Member States and constitutes an obstacle to free movement.

4. Given the risks to public health, a Member State may impose a requirement that contact lenses are to be supplied by qualified staff who

should alert the customer to those risks, carry out an examination and recommend or advise against wearing contact lenses, determine the most appropriate type of lenses, check their positioning on the eyes and provide information on their correct use and care.

5. The above mentioned national requirements amount to selling certain medical devices only from brick-and-mortar shops with qualified personnel and are unjustified since the customer is normally required to be *physically present* to have his eyes examined by an optician at the sales outlet only when contact lenses *are first supplied*. At the time of *subsequent supplies*, there is, as a general rule, no need to provide the customer with such services. It is "sufficient that the customer advise the seller of the type of lenses which was provided when lenses were first supplied". In addition, supplementary information and advice can be given to the customer by means of the *interactive features of the website* of the Internet sales provider: e.g., through a qualified optician whose task is to give to the customer, at a distance, individualized information and advice on the use and care of the contact lenses. Therefore the national legislation is incompatible with the general EU Treaty rules on the free movement of goods.

This judgment demonstrates that that even in cases concerning devices for which initial clinical/fitting advice would be prudent, EU member states are not allowed to completely ban Internet sales of the devices. Moreover, requirements may be fulfilled also in the electronic environment through individualized information.

#### 3.2.3.2. *Sale of cosmetics via the internet*

In the case C-439/09, Pierre Fabre Dermo-Cosmetique had selective distribution agreements with a group of companies in which there was a contractual clause requiring sales of cosmetics and personal care products to be made in a *physical space with the presence of a qualified pharmacist* during all opening hours. In 2006, the Competition Authority opened an ex officio investigation of practices in the distribution sector for cosmetics and personal care products and asked

the cosmetics companies to amend their selective distribution contracts in order to enable the members of their networks to sell their products via the internet, subject to certain conditions. Pierre Fabre Dermo-Cosmetique did not accept this arrangement, explaining that cosmetics require the physical presence of a qualified pharmacist in order that the customer may in all circumstances, request and obtain the *personalised advice* of a specialist, based on the *direct observation* of the customer's skin, hair and scalp as well as that the ban on internet sales avoids the risks of *counterfeiting* and of free-riding between authorised pharmacies. The Authority rejected the argument invoking the DocMorris judgment.

The CJEU ruled that such a ban on the use of the internet for sales of cosmetics amounts to a restriction by object infringing Art. 101 para. 1 TFEU, and could be exempted only after examination from the referring French court if the conditions in paragraph 3 of that article were met. The Court stated that, "in the light of the freedoms of movement, it has not accepted arguments relating to the *need to provide individual advice* to the customer and to ensure his protection against the incorrect use of products, in the context of non-prescription medicines and contact lenses, to justify a ban on internet sales". Such ban could neither be exempted by the block exemption provided for in Art. 2 of Commission Regulation (EC) No 2790/1999 on exemption categories of vertical agreements. The reason was that the block exemption does not apply to a contractual clause of a selective distribution contract, "prohibiting de facto the internet as a method of marketing, which at the very least has as its object the restriction of *passive sales to end users* wishing to purchase online and located outside the physical trading area of the relevant member of the selective distribution system".

### 3.4. Case law on commercial communications and ethics

Advertising "plays a decisive role in enabling a company to establish itself in a new Member State and develop its business there", since it "thus enables consumers to break with their habits and,

consequently, promotes competition." Members of liberal professions are subject to heterogeneous professional rules, thereby impeding even more the ability of the professionals concerned to enter the market in another Member State.

In the case C1 19/09, Societe fiduciaire nationale d'expertise comptable had applied to the French Conseil d'Etat for the annulment of a Decree on the grounds that the general and absolute prohibition on any canvassing is contrary to Art. 24 of Directive 2006/123/EC and seriously undermines the implementation of that directive. According to the CJEU, the Directive aimed at eliminating total bans to one or more *forms* of commercial communication, such as advertising, direct marketing or sponsorship, that is to say, not only traditional advertising but also *other forms of advertising* and communications of information intended to obtain new clients. However, the concept of commercial communication does not encompass: a) information *enabling direct access to the activity* of the undertaking, organisation or person, such as a *domain name or an e-mail address*, and b) communications relating to the goods, services or image of the undertaking, or person, *compiled in an independent manner, particularly when provided for no financial consideration*. Then the Court defined canvassing as a *form* of communication of information intended to seek new clients, *involving personal contact between the provider and a potential client, in order to offer the latter services*, like direct marketing. Consequently, canvassing constitutes a *form of commercial communication* within the meaning of the Directive 2006/123/EC. Since the national prohibition was *total as it was of very broad conception*, it covered *all means* of communication enabling the carrying out of that form of commercial communication. Therefore, it did fall within the scope of Article 24(1) and was incompatible with the Directive 2006/123/EC. Though the French Government invoked the overriding reason of independence of the profession, the Court rejected the argument by ruling that since the total ban comes within the scope of Article 24(1) of Directive 2006/123, it "cannot be justified under Article 24(2) of Directive 2006/

123, even if it is non-discriminatory, based on an overriding reason relating to the public interest and proportionate”. Thus the Court did not examine the question whether the total prohibition on any canvassing for the regulated profession of qualified accountants provided in the French Code of conduct constituted a professional rule which aimed to protect the independence of the profession of qualified accountancy. This question had been dealt by the Advocate General in his Opinion on the case.

In the case of Kostas Kostnantides, a doctor who provided cross-border medical services in Germany, risked a disciplinary penalty as a result of advertising on the internet under the wording “European Institute” or “German Institute”. The CJEU left the solution to the national court to decide whether its settled case law on freedom to provide services (Art. 56 TFEU) could be applied on the facts of the case. However, the Advocate General pointed out that the disputed measure did not concern a *total* ban on advertising or a prohibition on a particular type of advertising. It was a measure which precluded medical professionals from *effecting forms of advertising which are contrary to the image of the profession* or professional ethics. It was, therefore, *a condition relating to content which is applicable to forms of advertising a regulated professional activity*. He also emphasized that the restriction *did not refer to the professional rules but rather to their application* in a case, in which a doctor risked a serious disciplinary penalty as a result of advertising his activities in another member state.

### 3.5. Case law on confidentiality

It is of the essence of a lawyer’s function that the lawyer should be told by his or her client things which the client would not tell to others, and that the lawyer should be the recipient of other information on a basis of confidence. The lawyer’s obligation of confidentiality serves the interest of the administration of justice as well as the interest of the client. Confidentiality is therefore entitled to special protection by the State. A lawyer shall respect the confidentiality of all information that becomes known to him/her in the course

of his or her professional activity.

In the case of C-550/07, Akzo Nobel Chemicals Ltd and Akcros Chemicals Ltd, appealed against the judgment of the Court of First Instance (CFI which is now the General Court of the EU) in so far as it rejected the claim of legal professional privilege for correspondence with Akzo’s in-house lawyer. The appeal concerned exclusively two e-mails exchanged between the Director General of Akcros and Mr. S., a member of the Netherlands Bar, who was employed in the legal department of Akzo on a *permanent basis*, as the coordinator for competition law. Despite the objections on legal privilege submitted by the applicants, the two emails were copied and placed with the rest of the file by the Commission officials, when investigations were carried out at the applicants’ premises in the United Kingdom, aimed at seeking evidence of possible anti-competitive practices.

It is important to emphasize that both in the procedures before the CFI and the CJEU, there was the intervention of European, American and international professional organizations, e.g. the Conseil des barreaux europeens, the Algemene Raad van de Nederlandse Orde van Advocaten, the European Company Lawyers Association, the American Corporate Counsel Association (ACCA) - European Chapter and the International Bar Association all asking for the judgment of the CFI to be set in so far as the CFI “held that the communications between Akcros and the member of the legal department of Akzo were not subject to legal professional privilege”. According to previous case law, the confidentiality of written communications between lawyers and clients should be protected at EU level. However, the Court stated that that protection was subject to two cumulative conditions: a) the exchange with the lawyers must be connected to the client’s rights of defense and, b) the exchange must emanate from independent lawyers, who are not bound to the client by a relationship of employment. This condition is “based on a conception of *the lawyer’s role as collaborating in the administration of justice and as being required to provide, in full independence and in the overriding interests of*

that cause, such legal assistance as the client needs. The counterpart to that protection lies in the rules of professional ethics and discipline which are laid down and enforced in the general interest. Such a conception reflects the legal traditions common to the Member States and is also to be found in the legal order of the EU”.

Therefore, the Court dismissed the appeal and ruled that the professional privilege does not cover exchanges of emails within a company or group with in-house lawyers so that such exchange is protected only if the lawyer is not an employee of the enterprise.

In that case, the Court gave also other insightful clarifications on the *concept of the independence of lawyers* which is determined not only positively, by reference to professional ethical obligations, but also negatively, by the absence of an employment relationship. The Court emphasized the consequences of the lower *degree of independence* of an in-house lawyer and a lawyer working in an external law firm: An in-house lawyer, despite his enrolment with a Bar or Law Society and the professional ethical obligations to which he is subject, “does not enjoy the same degree of independence from his employer as a lawyer working in an external law firm does in relation to his client” and therefore “is less able to deal effectively with any conflicts between his professional obligations and the aims of his client” due to the *close ties between the lawyer and his employer*. Though the “rules of professional organisation may strengthen the position of an in-house lawyer within the company”, but that “they are not able to ensure a degree of independence comparable to that of an external lawyer”. Therefore “an in-house lawyer cannot, whatever guarantees he has in the exercise of his profession, be treated in the same way as an external lawyer, because he occupies the position of an employee which, by its very nature, does not allow him to ignore the commercial strategies pursued by his employer, and thereby *affects his ability to exercise professional independence*”.

The result recognized by the CJEU was that the in-house lawyer does not enjoy a level of professional independence comparable to that of an

external lawyer both from the in-house lawyer’s economic dependence and the close ties with his employer. A large number of Member States still exclude correspondence with in-house lawyers from protection under legal professional privilege, while a considerable number of Member States do not allow in-house lawyers to be admitted to a Bar or Law Society and, accordingly, do not recognise them as having the same status as lawyers established in private practice. Therefore no predominant trend towards protection under legal professional privilege of communications within a company or group with in-house lawyers may be discerned in the legal systems of the 27 Member States of the EU.

otherwise the use of national rules or legal concepts would adversely affect the unity of EU law.

In addition, the CJEU invoked the fact that a large number of Member States still exclude correspondence with in-house lawyers from protection under legal professional privilege, while a considerable number of Member States do not allow in-house lawyers to be admitted to a Bar or Law Society and, accordingly, do not recognise them as having the same status as lawyers established in private practice. Therefore no predominant trend towards protection under legal professional privilege of communications within a company or group with in-house lawyers may be discerned in the legal systems of the 27 Member States of the EU.

## Conclusions

In the EU legislation and case law, ethics are usually defined as professional rules regarding “the independence, dignity and honour of the profession, professional secrecy and fairness towards clients and other member of the profession” including impartiality. Lawyers e.g. have the duties to *act for clients in complete independence and in their sole interest*, to avoid all risk of conflict of interest and to observe strict professional secrecy.

Their importance have been recognized in EU law since the 70ies as an imperative requirement of the general interest justifying national restric-

tive measures in the Internal Market. Sectoral directives for liberal professions have also shown great respect for ethics both of the member state of origin and the host member state. In the digital era, e-commerce of goods and services is very important for their access in all Member States. This access however is rendered impossible or difficult because of national professional rules on ethics. However, the significance of ethics is even greater since ethics may be fundamental to the protection of consumers, public health, the good organization of the liberal professions and the good administration of justice. The Court uses the principle of proportionality to counterbalance the strictness of ethics especially in case of physical presence and examination. This principle allows e-vendors or e-providers to *comply to professional ethics with electronic or other means* even in case of medicinal products and medical devices (DocMorris, Ker optika etc.). This principle also may restrict the application of ethics for a limited number of sales.

The EU legislation on e-commerce and services shows also great respect to ethics. In order to facilitate e-commerce, the EU legislation opts for self-regulation asks the cooperation of the professional bodies in an overall system of co-regulation. The case law presented on e-commerce demonstrates that despite all the efforts to regulate e-commerce and the respect of the EU legislator to ethics, there exist many lacunae (ethical lags) that today are being solved by the Treaty rules on fundamental freedoms, thus making the CJEU the final arbiter.

We can therefore conclude that though ethical principles in e-commerce and brick-and-mortar business in the EU are fundamentally the same, ethics in the digital environment should be restricted to e.g. the first supply according to the principle of the proportionality. The Court has also recognized the different ways to compliance since the digital environment has interactive features which could help in respecting ethics as well as increase e-commerce. So the rules may be the same but their necessity or the means to achieve them may be different in the e-commerce. In order to solve the ethical lags and improve access

in e-commerce and transborder activities, the best method, opted by the EU, is self-regulation of professional bodies with codes of conduct, compatible with the EU law and easily accessible by electronic means. This why the Services Directive 2006/123/EC emphasizes again, as did the E-Commerce Directive 2000/31 the need of drawing up codes of conduct at the EU level and their implementation by national professional associations.



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# A Cross-Cultural Investigation of College Student Alcohol Consumption: A Classification Tree Analysis

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## ABSTRACT

In this cross-cultural study, the authors attempted to identify high-risk subgroups for alcohol consumption among college students. American and Greek students ( $N = 132$ ) answered questions about alcohol consumption, religious beliefs, attitudes toward drinking, advertisement influences, parental monitoring, and drinking consequences. Heavy drinkers in the American group were younger and less religious than were infrequent drinkers. In the Greek group, heavy drinkers tended to deny the negative results of drinking alcohol and use a permissive attitude to justify it, whereas infrequent drinkers were more likely to be monitored by their parents. These results suggest that parental monitoring and an emphasis on informing students about the negative effects of alcohol on their health and social and academic lives may be effective methods of reducing alcohol consumption. Classification tree analysis revealed that student attitudes toward drinking were important in the classification of American and Greek drinkers, indicating that this is a powerful predictor of alcohol consumption regardless of ethnic background.

**Keywords:** alcohol consumption, classification tree analysis, college students, crosscultural study

**H**EAVERY STUDENT DRINKING on American college campuses is a problem despite strict laws governing the purchase and consumption of alcohol by people under the age of 21 and an increase in preventive efforts by university officials to curtail student drinking. However, the prob-

lem of drinking by adolescents and young adults in other countries appears to be less severe (Delk & Meilman, 1996; Leavy & Alexander, 1992; Medianos, Gefou-Madianou, & Stefanis, 1994). Nevertheless, the lack of excess student drinking in these countries often coexists with less rigid

regulation of alcohol. For example, Medianos et al. found that although there are no restrictive measures for obtaining alcoholic beverages in Greece, drinking is not a serious problem among young adults there.

In Scotland, where alcohol use appears to be part of the culture and is readily accepted without restrictions, Scottish students are less likely to report drinking problems than are their American counterparts (Leavy & Alexander, 1992). In addition, results of cross-cultural studies of Scottish and American students (Delk & Meilman, 1996) have suggested that drinking is handled in a more controlled, safe, and responsible way by Scottish than by American college students. Cronin and Ballenger (1991) found that American students in Germany reported a higher frequency and amount of drinking and higher rates of negative consequences compared with their German peers.

In American and international studies, risk factors that have been associated with alcohol consumption among college students include parental and student attitudes toward alcohol (Ary, Tildesley, Hops, & Andrews, 1993; Teichman & Kefir, 2000; Yu, 1998) and parental control and monitoring (Barnes, 1984; Barnes & Farrell, 1992). Yu found that perceived parental attitudes significantly influence alcohol use among underage drinkers, whereas perceived peer attitudes appear to be effective across all legal and underage samples. Barnes and Farrell found that the highest levels of parental monitoring were associated with the lowest instances of drinking, illicit drug use, deviance, and school misconduct.

Other factors, such as religious beliefs (Engs, Hanson, Gliksman, & Smythe, 1990; Galen & Rogers, 2004), gender (Berkowitz & Perkins, 1987), parental drinking (VanVoorst & Quirk, 2003), beliefs concerning drinking consequences, and exposure to alcohol-related advertisements (Saffer, 2002) have not been explored systematically and collectively to uncover the role they play in drinking among adolescents. Nevertheless, researchers studying these variables individually have revealed that significant differences exist in religious beliefs and alcohol consumption between cultures. For example, Engs et al. found that American Ro-

man Catholic and mainstream Protestant students consume more alcohol and have more alcohol-related abuse problems than do Canadian students in the same religious groups. Other researchers have also found that religious beliefs (Galen & Rogers) and parental alcohol use (Van Voorst & Quirk) can positively influence alcohol consumption. Alcohol advertising has also been found to increase consumption among college students (Saffer), and other researchers (Berkowitz & Perkins) found that American men generally drink more frequently than do American women.

Because these findings indicate the complexity of risk factors for alcohol use and because alcohol consumption among college students remains less problematic in countries outside the United States, cross-cultural research is of critical importance, as it may suggest solutions for ameliorating this problem. To date, the primary goal of alcohol consumption research in cross-cultural studies among young adults has been the identification of differences in specific risk factors, alcohol consumption patterns, and perceptions. However, little is known about the interactive nature of risk factors and their ability to define subgroups of individuals who are at risk for excessive alcohol consumption.

One method that could identify segments of a population that are most likely to engage in alcohol use or abuse and could uncover constellations or interactions of multiple factors previously found to have an impact on alcohol consumption is classification and regression trees (CART; Breiman, Friedman, Olshen, & Stone, 1984). Data-driven approaches such as CART may provide important information in the distinctions of heavy drinking versus light or infrequent drinking among young individuals. CART analysis can partition populations or samples into subgroups of individuals with similar characteristics. This methodology has increasingly been applied to health-related fields and clinical settings (Bachur & Harper, 2001; Kitsantas, Hollander, & Li, 2006; Kitsantas, Moore, & Sly, 2007).

In the present study, we used classification trees to explore (a) factor interactions or con-

stellations that identify and distinguish infrequent, light, and heavy drinkers and (b) how American college students differ from Greek students given the same set of risk factors. These factors include demographics, parental drinking, attitudes toward drinking, parental monitoring, advertisement influences, and drinking consequences. On the basis of previous research findings (e.g., Berkowitz & Perkins, 1987; Galen & Rogers, 2004; Saffer, 2002), we hypothesized that religion, age, and alcohol advertising would be important in the classification of American students, whereas parental monitoring and attitudes toward alcohol would play a significant role in identifying high-risk subgroups among Greek students. We also used traditional statistical methodology such as the chi-square tests, analyses of variance (ANOVAs), and *t* tests to describe differences in alcohol consumption and risk factors between and within these ethnic groups.

## Method

### *Participants and Procedure*

Participants were 132 college students (66 American, 66 Greek; 86 men, 46 women). Most (96%) were full-time students, and 3.8% were part-time. The ages of the students were 18 to 19 years (3%), 20 to 21 years (81.1%), 22 to 23 years (12.1%), 24 to 25 years (1.5%), and older than 25 years (2.3%). The religious preferences of the students were 29.5% Catholic, 51.5% Greek Orthodox, 3% Jewish, 12.1% Protestant, and 3.9% other. We recruited the American students from an introductory educational psychology course consisting of two sections. We randomly selected these sections from six required sections offered in educational psychology. The response rate was 75% from the first section and 93% from the second section. The Greek students were similarly enrolled in a psychology class at a major university in Greece; their response rate was 87%. Both universities are public, large, and representative of the typical college populations in both countries. We asked all students to read and sign an informed consent form and gave them extra credit for their participation.

The protocol for this study was approved by the institutional review boards at both universities.

### *Measures*

We used a questionnaire developed specifically for this study to survey students about demographic characteristics, alcohol consumption, perceptions of parental drinking, attitudes toward drinking, perceived parental monitoring, advertisement influences, and beliefs about drinking consequences. All measures were developed by a panel consisting of four experts in the fields of health education and health psychology. Content validity was established by asking two experts to examine the contents of the instrument and indicate separately the degree to which it measured predetermined objectives. Disagreements between the experts were resolved by a third expert in the field. We also conducted extensive pilot tests regarding the wording of the items with 20 college students and revised the items.

*Demographics.* We collected data about students' gender, age, and religion. Two questions asked about religious beliefs; one asked about religious preference and the other asked about the extent to which participants were religious.

*Alcohol consumption.* We used this measure to assess students' consumption of alcoholic beverages. It consisted of two multiple-choice questions. In the first question, participants rated how frequently they drink on a scale ranging from 1 (doesn't drink) to 5 (more than 3 times per week). The second question asked participants how many drinks they consumed the last time they drank. In this question, one drink was defined as a 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of liquor by itself or with a mixer. We asked participants about their parents' frequency of alcohol consumption using the same survey format.

We used these variables to construct the dependent variable, which consisted of three classes: infrequent, light, and heavy drinkers. To create this variable, we found natural breaking points in a matrix cross-referencing the number of times the participants drank in the past year, month, or week and the number of drinks they consumed. Infrequent drinkers were those who did not drink or drank 1 to 2

times per year. We defined light drinkers as people consuming alcohol 1 to 2 times per month, with the number of drinks per sitting ranging from 1 to 9, and heavy drinkers drank 1 to 3 times or more per week with 1 to 9 drinks per sitting. The correlation between frequency of drinking and how many drinks the respondents consumed the last time they drank was high ( $r = .90$ ), providing evidence of consistency for this measure.

*Attitudes toward drinking.* In this part of the survey, we gathered information about student attitudes toward drinking. Students selected one of three statements that best represented their attitude toward alcohol. An example statement is "Drinking is never a good thing to do." The interitem reliability was .91 according to Cronbach's alpha.

*Perceived parental monitoring.* This measure assessing student perceptions of parental monitoring consisted of five yes-or-no questions. A sample item is "My parents try to limit or control with whom I can socialize." We created a composite variable to reflect these questions, with scores ranging from 0 to 1. Cronbach's alpha reliability score was .78.

*Advertisement influence.* This measure consisted of two questions. Using a Likert scale from 1 (strongly agree) to 5 (strongly disagree), participants rated whether advertisements influence people to drink alcohol. A sample item is "Drinking of alcohol in movies and TV shows strongly influences people to drink." The reliability coefficient for this scale was .89.

*Drinking consequences.* This measure gathered information about students' beliefs regarding drinking consequences. Participants responded to three questions using a Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree). A sample item is "Student drinking often interferes with academic performance." We created a composite variable from these questions that measured student beliefs about drinking consequences, with total scores ranging from 1 to 5. The reliability coefficient for this measure was .91.

### **Statistical Analysis**

We calculated descriptive statistics for both groups. We used a chi-square test to assess differences be-

tween American and Greek students for categorical variables and one-way ANOVAs or t tests on continuous variables. We built classification trees using CART software (version 5.0; Salford Systems, 2005) for each group to identify high-risk subgroups for alcohol consumption.

Classification tree analysis, which was formalized by Breiman et al. (1984), is a nonparametric technique that makes no distributional assumptions and is not affected by outliers, collinearities, heteroskedasticity, or distributional error structures. It can be used to classify data that involve both continuous and categorical variables. The first step in tree construction consists of partitioning the entire data set into binary subsets on the basis of a selected variable split. The best possible variable split is selected to maximize homogeneity in the subsamples. This partitioning process involves criteria that can maximize subsample homogeneity, including the Gini index, twoing, or entropy (Breiman et al.). Initially, large and highly accurate trees with zero misclassification rates are built. Then a pruning procedure is integrated into the algorithm to reduce tree size, thereby making it interpretable. The predictive accuracy of the pruned tree is assessed via test-sample estimation (large samples) or cross-validation (samples with fewer than 3,600 cases).

In the current study, we used the Gini index in the splitting process and cross-validation, because of the small sample size, to evaluate the predictive performance of each tree model or classifier. Using these criteria, we built two classification trees: one for the American sample and one for the Greek sample. The outcome variable consisted of infrequent, light, and heavy drinkers, and the independent variables included gender, age, religiosity, parental drinking, student attitudes toward drinking, parental monitoring, alcohol advertisement influences, and beliefs about drinking consequences. Furthermore, because of the small sample size, we used bootstrap aggregation (Breiman, 1996) to evaluate the stability of the models. This analysis revealed no instability issues, as the results obtained were similar across all replications.

## Results

### Exploratory Analyses

Tables 1 and 2 provide information about all variables grouped by participant nationality and alcohol consumption status. The number of infrequent drinkers was significantly higher in the Greek sample ( $n = 26$ , or 39.4% of the sample) than in the American sample ( $n = 10$ , or 15.2% of the sample), whereas the number of heavy drinkers was higher among Americans ( $n = 37$ , or 56.1%) compared with their Greek counterparts ( $n = 24$ , or 36.4%),  $\chi^2(2, N = 132) = 10.2, p < .001$ . The  $t$  tests for continuous variables revealed significant differences between infrequent American and Greek drinkers in their reports of drinking consequences and parental monitoring. Greek students who drank infrequently reported significantly higher levels of parental monitoring behaviors,  $t(34) = -2.78, p < .001$ , than did their American counterparts. The Greek students were also more likely to agree that drinking can affect academic performance, physical health, and social well-being,  $t(34) = 2.73, p < .01$ . However, Greek students who we classified as heavier drinkers were less likely to agree with these drinking consequences than were American heavy drinkers,  $t(59) = -2.88, p < .001$ .

Chi-square analyses for categorical variables yielded differences between Greek and American students on the basis of their alcohol consumption status. First, there were more infrequent male and female drinkers in the Greek sample than in the American sample,  $\chi^2(1, N = 36) = 4.86, p < .01$ . There were more American than Greek men classified as light drinkers, whereas there were fewer American than Greek light female drinkers,  $\chi^2(1, N = 35) = 5.02, p < .01$ .

Furthermore, there were no significant age and attitude differences between the two samples on the basis of their alcohol-consumption status. In relation to religious beliefs, American heavy drinkers were less likely to be religious,  $\chi^2(1, N = 60) = 21.5, p < .001$ , than were their Greek counterparts, who expressed being religious regardless of alcohol status. We also found significant differences in parental drinking, with American parents drinking more frequently among American heavy drinkers than Greek parents did among Greek heavy drinkers,  $\chi^2(1, N = 61) = 32.1, p < .001$ . However, parental drinking was infrequent among Americans classified as light drinkers,  $\chi^2(1, N = 35) = 3.83, p < .05$ .

Separate examination of differences in alcohol consumption status within samples revealed

**TABLE 1. Demographic Characteristics of Participants, by Alcohol Consumption Status and Nationality**

Variable	American students						Greek students					
	Infrequent drinkers <sup>a</sup>		Light drinkers <sup>b</sup>		Heavy drinkers <sup>c</sup>		Infrequent drinkers <sup>d</sup>		Light drinkers <sup>e</sup>		Heavy drinkers <sup>f</sup>	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Gender												
Male	9	17.6	17	33.3	25	49.0	13	37.1	9	25.7	13	37.1
Female	1	6.7	2	13.3	12	80.0	13	41.9	7	22.6	11	35.5
Age												
≤ 21 years	10	18.2	12	21.8	33	60.0	22	39.3	14	25.0	20	35.7
> 21 years	0	0.0	7	63.6	4	36.4	4	40.0	2	20.0	4	40.0
Religion												
Religious	10	22.7	19	43.2	15	34.1	26	39.4	16	24.2	24	36.4
Not religious	0	0.0	0	0.0	21	100	0	0.0	0	0.0	0	0.0
Parental Drinking												
Infrequent	5	29.4	8	47.1	4	23.5	16	33.3	12	25.0	20	41.7
Frequent	5	10.2	11	22.4	33	67.3	10	55.6	4	22.2	4	22.2
Attitudes												
“Drinking is never a good thing to do”	3	15.8	5	26.3	11	57.9	8	72.7	3	27.3	0	0.0
“Being drunk occasionally is okay” or “Drinking is alright, but a person should not get ‘smashed’”	7	15.0	14	29.7	26	55.3	18	33.0	13	23.6	24	43.4

<sup>a</sup> $n = 10$ . <sup>b</sup> $n = 19$ . <sup>c</sup> $n = 37$ . <sup>d</sup> $n = 26$ . <sup>e</sup> $n = 16$ . <sup>f</sup> $n = 24$ .

**TABLE 2. Means and Standard Deviations of Participant Responses to Questions About Parental Monitoring, Advertising Influences, and Drinking Consequences**

Variable	American students						Greek students					
	Infrequent drinkers <sup>a</sup>		Light drinkers <sup>b</sup>		Heavy drinkers <sup>c</sup>		Infrequent drinkers <sup>d</sup>		Light drinkers <sup>e</sup>		Heavy drinkers <sup>f</sup>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Parental monitoring <sup>g</sup>	0.57	0.20	0.59	0.18	0.58	0.19	0.76	0.18	0.68	0.23	0.83	0.92
Advertising influences <sup>h</sup>	4.20	0.58	3.63	0.89	3.78	0.85	4.09	1.07	3.68	0.91	3.37	1.11
Drinking consequences <sup>h</sup>	1.77	0.56	1.98	0.77	2.03	0.74	1.24	0.49	2.06	0.86	2.63	0.91

<sup>a</sup>*n* = 10. <sup>b</sup>*n* = 19. <sup>c</sup>*n* = 37. <sup>d</sup>*n* = 26. <sup>e</sup>*n* = 16. <sup>f</sup>*n* = 24. <sup>g</sup>Scores ranged from 0 to 1. <sup>h</sup>Scores ranged from 1 to 5.

that American heavy drinkers were more likely to be younger than 21 years old, whereas light drinkers were more likely to be older than 21 years,  $\chi^2(2, N = 66) = 8.48, p < .01$ . Infrequent and light drinkers in the American sample were more likely to be religious, and heavy drinkers considered themselves unreligious,  $\chi^2(2, N = 65) = 25.0, p < .01$ . We did not find significant differences in gender and student attitudes in the American sample across the three levels of alcohol consumption. However, the number of American parents consuming alcohol frequently was significantly higher among the heavy student drinkers compared with students in the other categories,  $\chi^2(2, N = 66) = 10.1, p < .01$ .

The only significant differences across the three levels of alcohol consumption within the Greek sample were in their attitudes, with heavy drinkers agreeing that being drunk occasionally is okay if it does not interfere with responsibilities,  $\chi^2(4, N = 66) = 11.4, p < .01$ . Furthermore, in the Greek sample, overall infrequent drinkers were more likely to agree that drinking influences well-being and academic performance,  $F(2, 65) = 21.4, p < .001$ , compared with light (Bonferroni 95% CI [-1.41, -0.23]) and heavy Greek drinkers (Bonferroni 95% CI [-1.92, -0.86]). We did not find significant differences for influences of alcohol advertisements or parental monitoring in Americans or Greeks across the three alcohol consumption levels.

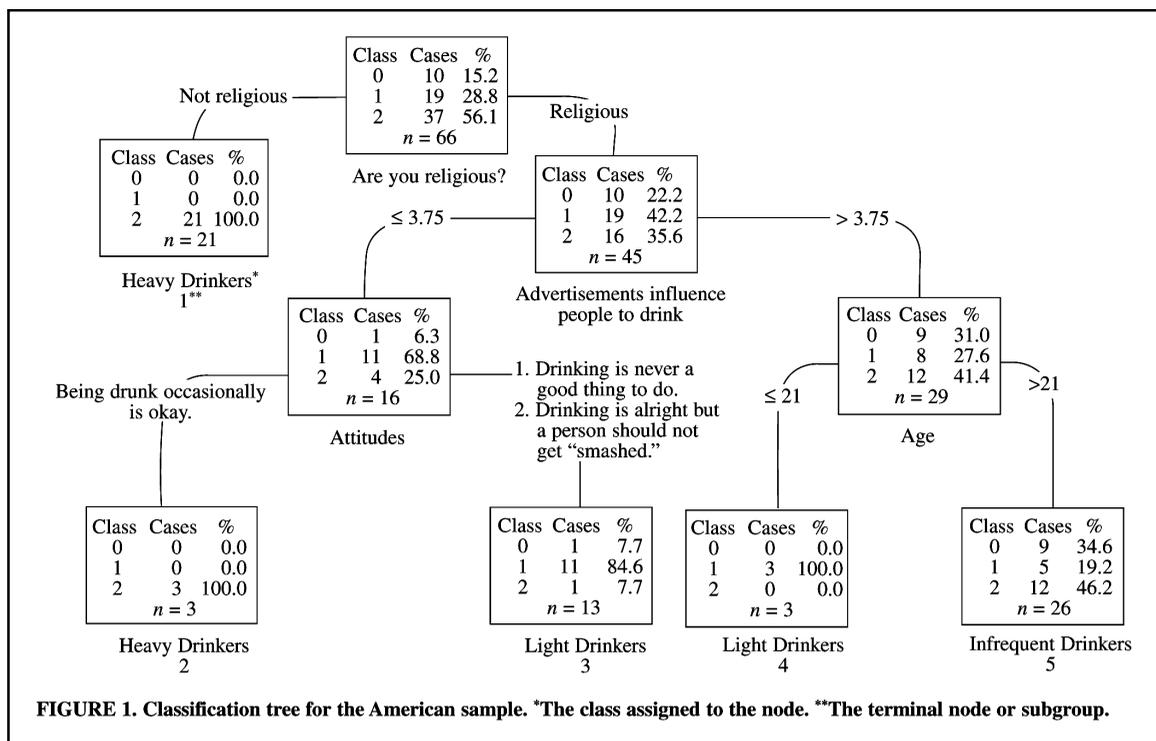
### Classification Tree Analyses

We constructed two classification models. The tree classifier for American students (*n* = 66) is shown in Figure 1. This model consists of five terminal nodes or subgroups; each node contains

the number of cases, associated percentage, and classes. For example, for this model, the root node (the node that contains the entire sample) contains 10 individuals who were classified as infrequent drinkers (class 0), 19 light drinkers (class 1) and 37 heavy drinkers (class 2).

We found the primary split on religion. The subgroup of adolescents who identified themselves as nonreligious was classified directly as heavy drinkers (subgroup 1, 100%). Alcohol advertisement influences further divided those who expressed religious beliefs. If they had a score less than or equal to 3.75 (closer to no opinion or agreeing that ads influence people to drink) and agreed that being drunk occasionally is okay, they were classified as heavy drinkers (subgroup 2, 100%). However, if they believed that drinking is never a good thing to do or drinking is alright, but a person should not get “smashed,” they were characterized as light drinkers (subgroup 3, 84.6%). Light drinkers were also likely to have an advertisement score greater than 3.75 (close to disagreeing that ads influence people to drink) and be 21 years old or younger (subgroup 4, 100%). Infrequent drinkers within the American sample were identified as religious and being older than 21 years old (subgroup 5, 34.6%).

The tree model for the Greek student sample is shown in Figure 2. The tree consists of five terminal nodes, and it classified 26 individuals as infrequent drinkers, 16 as light drinkers, and 24 as heavy drinkers. The classifier initially split on beliefs about drinking consequences. Students with a score less than or equal to 1.83 (agreeing that drinking has consequences) were further di-



vided by parental monitoring. Individuals with a parental monitoring score greater than 0.70 (parents monitor their behaviors) were classified as infrequent drinkers (subgroup 2, 84.2%). Infrequent and light drinkers were also likely to have a parental monitoring score less than or equal to 0.70 (parents do not monitor their behaviors as much; subgroup 1).

Students with a score greater than 1.83 (disagreeing that drinking has consequences or having no opinion) and expressing attitudes such as “Drinking is never a good thing to do” were more likely to be classified as light drinkers (subgroup 3, 100%). Light drinkers were also classified as those who reported that being drunk occasionally is okay or that drinking is alright, but a person should not get “smashed” and that their parents drank infrequently (subgroup 4, 50%). However, if their parents consumed alcohol frequently, they were classified as heavy drinkers (subgroup 5, 77.3%).

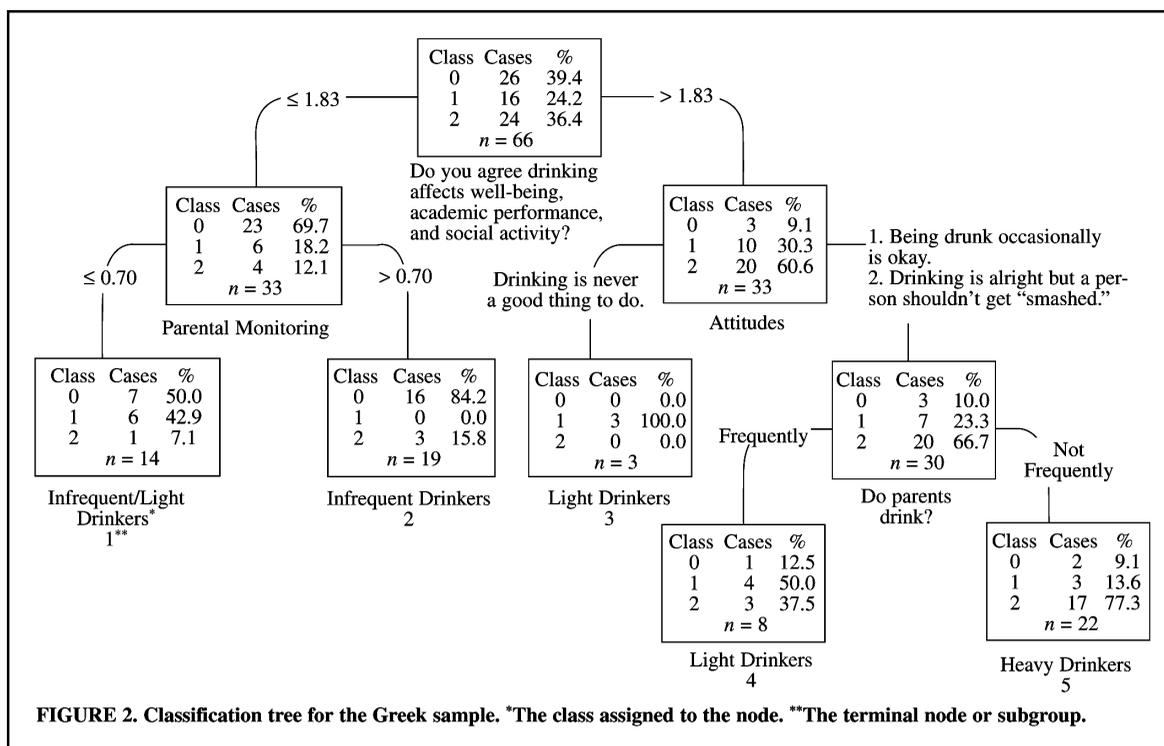
## Discussion

In this study, we explored the interactions of risk factors in identifying high-risk subgroups for al-

cohol consumption among American and Greek college students. Overall, the findings suggest that heavy drinking among college students constitutes a more serious problem in the United States than in Greece, with American students drinking more often than their Greek counterparts. This is true in spite of U.S. laws against consumption of alcohol by minors and strong university regulations against underage drinking.

Classification tree analyses revealed that the student attitudes toward drinking variable was present in the classification of both American and Greek drinkers; thus, this is a powerful predictor of alcohol consumption regardless of ethnic background. However, certain risk factors and their interactions or combinations led to the development of different high-risk subgroups across the samples.

In particular, the extent to which participants were religious played an important role in the classification of American college students. Researchers have found that individual religious beliefs influence alcohol consumption through several mechanisms (Galen & Rogers, 2004). These mechanisms have been associated with various faiths and parental upbringing. In the present study, nonreligious American students were classified by



CART directly as heavy drinkers. This constitutes the most robust finding in this study, indicating a straightforward association between heavy drinking and lack of religiosity. Religion seems to act as a buffer against heavy drinking. That no other variables contributed to their classification may indicate that a set of factors other than those we examined may influence or explain alcohol consumption among American heavy drinkers. Although previous researchers (Galen & Rogers) have investigated the association between specific religious groups (e.g., Catholics, Protestants) and alcohol consumption, little is known about the degree of religious activity or practice and alcohol among college students.

Social influences, such as beliefs about the influence of alcohol advertising, affected alcohol consumption among American students who characterized themselves as religious. Thus, it may be useful to investigate the role of alcohol advertising in drinking on the basis of religious beliefs. Previous researchers have demonstrated the effect of alcohol advertising on knowledge, attitudes, and intention to drink (Grube & Wallace, 1994) through cultural myths and symbols (Parker, 1998). Although the purpose of this study was not to exam-

ine the effects of advertising on alcohol consumption, it is clear that attitudes toward drinking and age were important in the context of alcohol advertising. This finding indicates that age and attitudes may further explain the effects of alcohol advertising and its influences on alcohol consumption among young people.

Furthermore, the interplay of these variables led to the classification of light drinkers who agreed that alcohol advertisements influence people to drink and whose attitudes toward drinking were more responsible (e.g., “Drinking is alright, but a person should not get smashed”) and inhibitive (e.g., “Drinking is never a good thing to do”) than those of heavier drinkers who indicated that being drunk occasionally is okay. Infrequent American drinkers were profiled as older students who believed that alcohol advertising does not influence drinking, whereas students 21 years old or younger were more likely to be light drinkers given the same beliefs about alcohol advertising.

Although a number of variables were similar between the Greek and American classifiers, different combinations of these variables and high-risk subgroups emerged for the Greek sample. Heavy drinking among the Greek students was as-

sociated with the interplay of several variables: They disagreed that drinking has consequences, and although their parents did not drink frequently, they believed that being drunk occasionally is okay or drinking is alright. These results suggest that heavy drinkers in the Greek sample are in a state of denial regarding the effects of alcohol, and they may use the culturally sanctioned permissive attitude toward alcohol to justify their behavior. One unexpected result was that Greek college students whose parents drank frequently were likely to be light drinkers. It seems that exposure to frequent parental drinking acts as a protective factor, whereas strong parental monitoring leads to the classification of light and infrequent drinkers who disagreed with drinking consequences. This result suggests that permissive attitudes can be used as either a regulator of drinking behavior or a justification of heavy drinking. Less cultural variability existed in the group of light drinkers.

Overall, the findings suggest that the permissive attitudes toward drinking in college students who live in Greece may act as a buffer against problematic student drinking. When less of a taboo surrounds drinking, it may become less attractive to students, or perhaps students are socialized into drinking in a less dangerous way by Greek parents. Greek students may have been taught at a young age to drink responsibly and respect social norms for alcohol use. Another factor that may explain the less problematic student drinking in Greece is the amount of parental monitoring. Many more college students live at home with their parents in Greece than in the United States. When students live at home, Greek parents can show concern for where they go, who they associate with, and what they do.

There are several limitations associated with this study. First, its small sample size limits the external validity of the results. Also, the small number of variables we examined may have limited the study in exploring further relationships of factors that distinguish heavy, light, and infrequent drinking. Self-report measures such as those used in this study can introduce bias. In addition, because we examined only two college samples, it is difficult to generalize these findings to the

entire Greek and American college populations.

As a nonprobability sample, it may not be representative of the populations. Despite these limitations, this study provides evidence of the different combinations of factors that influence drinking behavior across two cultural groups. On the basis of the high-risk subgroups generated from the tree classifiers, future researchers should investigate the interactions between external factors such as sociocultural factors (e.g., alcohol advertising) and internal factors (e.g., attitudes, religiosity). It would be interesting to examine (a) the effect of alcohol advertisements on drinking on the basis of religious beliefs and (b) age and attitudes toward alcohol, as they may explain the effects of alcohol advertising and its influences on alcohol consumption among young people. It is also important to investigate the correlates of religiosity and how it acts as a buffer against heavy drinking, especially among American college students.

Our findings have implications for preventing the onset of alcoholism during college. Strict laws, rules, and regulations to combat this problem on American campuses do not seem to reduce or eliminate alcohol use among college students. However, parental monitoring and an emphasis on informing students about the negative effects of alcohol on their health and social and academic lives may be effective methods of reducing drinking among college students. Finally, developing workshops about responsible drinking for parents and their children as early as in high school could help them drink responsibly during college.

#### AUTHOR NOTES

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# Postoperative and Long-Term Outcome of Patients with Chronic Obstructive Pulmonary Disease Undergoing Coronary Artery Bypass Grafting

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**Background.** Chronic obstructive pulmonary disease (COPD) has been conventionally associated with increased operative mortality and morbidity after coronary artery bypass grafting. Some studies, however, challenge this association. Moreover, the effect of COPD on long-term survival after coronary artery bypass grafting has not been adequately assessed. Thus, in this clinical setting, both early and late outcome require further examination.

**Methods.** We studied 3,760 consecutive patients who underwent isolated coronary artery bypass grafting between 1992 and 2002. The propensity for COPD was determined by logistic regression analysis, and each patient with COPD was matched with 3 patients without COPD. Matched groups were compared for early outcome and

long-term survival (mean follow-up, 7.6 years). Long-term survival data were obtained from the National Death Index.

**Results.** There were 550 patients (14.6%) with COPD. Multivariate analysis showed that patients with COPD were older and sicker. However, propensity-matched groups did not differ in terms of hospital mortality or major morbidity, although COPD was associated with a slightly longer hospital stay. In contrast, COPD patients had increased long-term mortality, with a hazard ratio of 1.28 (95% confidence intervals, 1.11 to 1.47;  $p$  0.001). Freedom from all-cause mortality at 7 years after CABG was 65% and 72% in matched patients with and without COPD, respectively ( $p$  0.008). In patients with COPD, the hazard estimate was consistently increased up to 9 years postoperatively.

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**Conclusions.** Chronic obstructive pulmonary disease, although not an independent predictor of increased early mortality and morbidity in this series, is a continuing detrimental risk factor for long-term survival.

As smoking is etiologically related to both pulmonary and atherosclerotic disease, not surprisingly chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients undergoing coronary artery bypass grafting (CABG), and its incidence ranges from 6% to 27% [1–8]. Chronic obstructive pulmonary disease is conventionally associated with increased hospital mortality after CABG [9–12]. Accordingly, most well-established risk stratification models, such as The Society for Thoracic Surgeons score and EuroSCORE include COPD among independent predictors of operative mortality [6, 13]. Several studies have additionally demonstrated an association of COPD with post-CABG morbidity, such as prolonged length of stay (LOS) and pulmonary complications [3, 6, 14, 15]. Yet, other studies have failed to document a negative effect of COPD on early postoperative outcome [2, 16, 17], hence making further investigation on this issue necessary.

Regarding the impact of COPD on long-term survival after CABG, literature is sparse. Leavitt and colleagues [4] have published the largest relevant study to date, documenting a significantly reduced long-term survival for COPD patients after a mean follow-up of approximately 4 years after CABG. Most other data are derived from few studies with relatively small number of patients or short follow-up or studies not specifically dealing with COPD as a factor of long-term survival [1, 2, 7, 8, 14, 18].

The purpose of this study is to fully define the outcome of CABG in patients with COPD. Therefore, we studied 3,760 consecutive isolated CABG patients from a large single-center database and compared early outcome between propensity-matched groups with and without COPD. Additionally, we used long-term follow-up survival data (mean follow-up, 7.6 years) to determine whether, in our experience, COPD influences similarly hospital and long-term mortality.

## Patients and Methods

### *Patient Population and Data Collection*

The present study was approved by the institutional review board. The need for informed consent was waived because the data used in this study had already been collected for clinical purposes. Furthermore, the present study did not interfere with the treatment of patients, and the database was organized in a way that makes the identification of an individual patient impossible. A total of 3,760 consecutive patients, who underwent isolated CABG at St. Luke's/Roosevelt Hospital Center of Columbia University, from January 1992 to March 2002, were included in this analysis. Data were prospectively collected as part of routine clinical practice and entered into the New York State adult cardiac surgery report for the variables shown in Table 1. Risk stratification was performed according to EuroSCORE [13]. Patients who required chronic (3 months) bronchodilator therapy to avoid disability from obstructive airway disease, had a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 75% of the predicted value or less than 1.25 L, or had room air partial pressure of oxygen less than 60 mm Hg or partial pressure of carbon dioxide greater than 50 mm Hg were considered COPD patients.

### *Data Analysis*

Long-term patient mortality data were obtained from the United States Social Security Death Index database (<http://ssdi.genealogy.rootsweb.com>). The sensitivity of the National Death Index to identify deaths depends on the combination of available identifiers [19]. We used social security number alone as it was available for most patients (99.1%), it allowed avoiding use of patients' names, and reportedly has the best accuracy with a sensitivity of 97% and a specificity of 99% [19]. Patients without social security number (n 34) were censored at the time of discharge from the hospital. The index was queried in March 2006, and patients not found were assumed to be alive at that date.

### Statistics

Numerical variables were presented as mean standard deviation. Parametric variables were compared using independent Student's t test. Non-parametric variables, such as LOS, angina class, number of distal anastomoses, and EuroSCORE, were compared using Mann-Whitney U test. Discrete variables were summarized by percentages and compared using  $\chi^2$  test or Fisher's exact test, as appropriate.

The propensity for COPD was determined using logistic regression analysis. The backward stepwise method was used for model selection starting from all preoperative variables with a probability value of less than 0.05 in univariate analysis. The C statistic was calculated to assess the discriminatory ability of the model. The model was used to calculate a propensity score that represented the probability of a patient to have COPD. Each patient with COPD was then matched to 3 patients without COPD using propensity scores identical to within 1%. Matched groups were compared for early outcome, as well as for long-term survival with the Kaplan-Meier method. Survival curves were compared with the log-rank test.

Finally, the impact of COPD on long-term mortality was analyzed by Cox regression analysis. Cox proportional hazard models were selected with the backward stepwise method starting from all variables with a probability value of less than 0.05 in univariate analysis. Models were then confirmed using forward stepwise selection. The COPD parameter was forced to remain in each multivariate model, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. All analyses were performed in SPSS 15.0 (SPSS, Inc, Chicago, IL) and all probability values are two-tailed. Hazard function curves for the propensity-matched groups were constructed using STATA/SE 9.1 (StataCorp LP, College Station, TX).

## Results

### *Patient and Disease Characteristics:*

#### *Early and Late Outcome*

Patients' mean age was  $64.1 \pm 10.4$  years; 30.9% (n 1,162) were women and 34.0% (n = 1,277)

had diabetes. During the 28,575 person-years of follow-up (mean follow-up,  $7.6 \pm 4.1$  years), 1,265 deaths (33.6%) were recorded. There were 550 patients (14.6%) with COPD, and their comparison with patients without COPD is shown in Table 1. Chronic obstructive pulmonary disease patients were slightly older, more likely of black race, and clearly had more comorbidities and higher EuroSCORE. Although the two groups had the same number of distal anastomoses overall, bilateral internal thoracic artery (BITA) grafting was performed less regularly in COPD patients (48.4% versus 56.5%;  $p < 0.001$ ). Postoperatively, COPD patients had an unadjusted higher hospital mortality (4.2% versus 2.6%;  $p = 0.048$ ), longer LOS (13.6 versus 10.5 days;  $p < 0.001$ ), more gastrointestinal complications (2.5% versus 1.1%;  $p = 0.014$ ), and a higher respiratory failure rate (7.1% versus 3.8%;  $p = 0.001$ ), defined as pulmonary insufficiency requiring intubation and mechanical ventilation for a period of 72 hours or more, at any time during postoperative stay. Freedom from all-cause mortality in patients with COPD at 1, 7, and 14 years after surgery was  $88.7\% \pm 1.4\%$ ,  $62.0\% \pm 2.2\%$  and  $40.5\% \pm 2.8\%$ , respectively, compared with  $94.0\% \pm 0.4\%$ ,  $76.8\% \pm 0.8\%$ , and  $56.6\% \pm 1.5\%$  for unmatched patients without COPD ( $p < 0.001$ ; Fig 1).

### *Multivariate Logistic*

#### *Regression Analysis and Matched Groups*

Table 2 shows the independent predictors for COPD as determined by multivariate logistic regression analysis. The discriminatory ability of the logistic model as measured by C statistic was 0.72 (95% CI, 0.70 to 0.74), and the Lemeshow-Hosmer goodness-of-fit test was not statistically significant ( $p = 0.896$ ), indicating good discriminative power and acceptable calibration of the model, respectively. From 550 patients with COPD, 453 (82.4%) were appropriately matched with 1,359 patients without COPD. Propensity-matched COPD patients had higher EuroSCORE as expected because COPD is a risk factor, which scores in the EuroSCORE algorithm. There was no difference in other preoperative risk factors, hospital mortality, and major postoperative com-

Table 1. Preoperative, Intraoperative, and Postoperative Variables in Coronary Artery Bypass Grafting Patients With and Without Chronic Obstructive Pulmonary Disease Before and After Propensity Matching

Variable	Unmatched Groups			Matched Groups		
	CABG With COPD (n = 550)	CABG Without COPD (n = 3,210)	p Value	CABG With COPD (n = 453)	CABG Without COPD (n = 1,359)	p Value
<b>Preoperative variables</b>						
EuroSCORE, mean ± SD	8.2 ± 3.6	6.0 ± 3.4	<0.001	7.8 ± 3.5	6.9 ± 3.6	<0.001
Age (y), mean ± SD	65.2 ± 9.6	64.0 ± 10.5	0.012	64.8 ± 9.6	64.7 ± 10.6	0.922
Female sex, n (%)	161 (29.3)	1,001 (31.2)	0.370	131 (28.9)	434 (31.9)	0.230
<b>Race</b>						
White, n (%)	335 (60.9)	2,125 (66.2)	0.016	275 (60.7)	836 (61.5)	0.759
Black, n (%)	119 (21.6)	531 (16.5)	0.004	97 (21.4)	276 (20.3)	0.615
Other, n (%)	96 (17.5)	554 (17.3)	0.911	81 (17.9)	247 (18.2)	0.888
<b>Vessels involved</b>						
1-vessel disease, n (%)	31 (5.6)	174 (5.4)	0.837	28 (6.2)	64 (4.7)	0.217
2-vessel disease, n (%)	121 (22.0)	715 (22.3)	0.886	111 (24.5)	301 (22.2)	0.300
3-vessel disease, n (%)	398 (72.4)	2,321 (72.3)	0.977	314 (69.3)	994 (73.1)	0.115
Unstable angina, n (%)	423 (76.9)	2,147 (66.9)	<0.001	341 (75.3)	999 (73.5)	0.458
Previous MI, n (%)	343 (62.4)	1,509 (47.0)	<0.001	265 (58.5)	788 (58.0)	0.847
Transmural MI (most recent), n (%)	244 (44.4)	1,034 (32.2)	<0.001	182 (40.2)	525 (38.6)	0.559
More previous MI, n (%)	144 (26.2)	517 (16.1)	<0.001	98 (21.6)	310 (22.8)	0.603
Previous cardiac operation, n (%)	34 (6.2)	231 (7.2)	0.390	26 (5.7)	91 (6.7)	0.473
CCS angina class, mean ± SD	3.7 ± 0.5	3.6 ± 0.6	<0.001	3.7 ± 0.5	3.7 ± 0.6	0.408
<b>Urgency operation</b>						
Emergent, n (%)	53 (9.6)	245 (7.6)	0.108	41 (9.1)	115 (8.5)	0.699
Urgent, n (%)	378 (68.7)	1,948 (60.7)	<0.001	310 (68.4)	921 (67.8)	0.794
Elective, n (%)	119 (21.6)	1,017 (31.7)	<0.001	102 (22.5)	323 (23.7)	0.586
Hemodynamic instability, n (%)	20 (3.6)	69 (2.1)	0.047	13 (2.9)	43 (3.2)	0.876
Shock, n (%)	2 (0.4)	13 (0.4)	0.999	1 (0.2)	7 (0.5)	0.688
<b>Ejection fraction categories</b>						
Ejection fraction > 0.50, n (%)	92 (16.7)	960 (29.9)	<0.001	83 (18.3)	287 (21.1)	0.201
Ejection fraction 0.30–0.50, n (%)	331 (60.2)	1,798 (56.0)	0.068	285 (62.9)	793 (58.4)	0.087
Ejection fraction < 0.30, n (%)	127 (23.1)	452 (14.1)	<0.001	85 (18.8)	279 (20.5)	0.417
Current CHF, n (%)	153 (27.8)	423 (13.2)	<0.001	95 (21.0)	291 (21.4)	0.842
Past CHF, n (%)	105 (19.1)	293 (9.1)	<0.001	63 (13.9)	191 (14.1)	0.938
PVD, n (%)	154 (28.0)	569 (17.7)	<0.001	113 (24.9)	329 (24.2)	0.752
<b>BMI categories</b>						
BMI < 24, n (%)	444 (80.7)	2,670 (83.2)	0.159	369 (81.4)	1,117 (82.2)	0.724
BMI 24–29, n (%)	86 (15.6)	432 (13.5)	0.171	67 (14.8)	190 (14.0)	0.669
BMI > 29, n (%)	20 (3.6)	108 (3.4)	0.704	17 (3.8)	52 (3.8)	0.999
Hypertension, n (%)	420 (76.4)	2,215 (69.0)	<0.001	339 (74.8)	992 (73.0)	0.443
Diabetes mellitus, n (%)	213 (38.7)	1,064 (33.1)	0.011	165 (36.4)	500 (36.8)	0.888
Calcified aorta, n (%)	101 (18.4)	222 (6.9)	<0.001	59 (13.0)	172 (12.7)	0.839
Renal failure, n (%)	12 (2.2)	70 (2.2)	0.999	9 (2.0)	35 (2.6)	0.598
Preoperative dialysis, n (%)	12 (2.2)	34 (1.1)	0.035	10 (2.2)	21 (1.5)	0.402
Hepatic failure, n (%)	3 (0.5)	3 (0.1)	0.044	2 (0.4)	1 (0.1)	0.156
Immune deficiency, n (%)	13 (2.4)	23 (0.7)	0.001	6 (1.3)	22 (1.6)	0.827
Preoperative IABP, n (%)	37 (6.7)	172 (5.4)	0.195	30 (6.6)	101 (7.4)	0.565
IV NTG, n (%)	121 (22.0)	529 (16.5)	0.002	89 (19.6)	269 (19.8)	0.946
LV hypertrophy, n (%)	196 (35.6)	773 (24.1)	<0.001	139 (30.7)	424 (31.2)	0.837
Malignant ventricular arrhythmia, n (%)	24 (4.4)	72 (2.2)	0.008	19 (4.2)	45 (3.3)	0.379
Thrombolysis before surgery, n (%)	30 (5.5)	166 (5.2)	0.782	24 (5.3)	84 (6.2)	0.567
Myocardial rupture, n (%)	0 (0)	5 (0.2)	0.999	0 (0)	3 (0.2)	0.578
Previous PCI, n (%)	53 (9.6)	380 (11.8)	0.135	46 (10.2)	138 (10.2)	0.999
Smoking in past 2 weeks, n (%)	146 (26.5)	420 (13.1)	<0.001	104 (23.0)	307 (22.6)	0.871

Continued

Table 1. Continued

Variable	Unmatched Groups			Matched Groups		
	CABG With COPD (n = 550)	CABG Without COPD (n = 3,210)	p Value	CABG With COPD (n = 453)	CABG Without COPD (n = 1,359)	p Value
Smoking in previous year, n (%)	137 (24.9)	432 (13.5)	<0.001	100 (22.1)	293 (21.6)	0.818
Intraoperative variables						
Total bypass time (min), mean ± SD	109 ± 53	111 ± 51	0.313	104 ± 51	116 ± 51	<0.001
OPCAB, n (%)	41 (7.5)	205 (6.4)	0.349	29 (6.4)	104 (7.7)	0.377
BITA, n (%)	266 (48.4)	1,815 (56.5)	<0.001	211 (46.6)	755 (55.5)	0.001
SITA, n (%)	243 (44.2)	1,265 (39.4)	0.035	204 (45.0)	557 (41.0)	0.131
Only vein grafts, n (%)	41 (7.5)	130 (4.1)	<0.001	38 (8.4)	47 (3.5)	<0.001
Anastomoses, mean ± SD	3.3 ± 1.0	3.4 ± 1.0	0.127	3.2 ± 1.0	3.4 ± 1.0	0.005
Postoperative variables						
In-hospital mortality, n (%)	23 (4.2)	82 (2.6)	0.048	18 (4.0)	46 (3.4)	0.558
Length of stay (days), mean ± SD	13.6 ± 14.8	10.5 ± 11.8	<0.001	13.0 ± 13.7	11.4 ± 12.3	<0.001
Postoperative complications						
Intraoperative stroke, n (%)	18 (3.3)	80 (2.5)	0.309	15 (3.3)	39 (2.9)	0.633
Stroke >24 hours, n (%)	3 (0.5)	22 (0.7)	0.999	3 (0.7)	10 (0.7)	0.999
Postoperative MI, n (%)	4 (0.7)	19 (0.6)	0.765	4 (0.9)	7 (0.5)	0.483
Deep sternal wound infection, n (%)	5 (0.9)	35 (1.1)	0.825	3 (0.7)	19 (1.4)	0.321
Bleeding/reoperation, n (%)	8 (1.5)	58 (1.8)	0.725	7 (1.5)	26 (1.9)	0.690
Gastrointestinal complications, n (%)	14 (2.5)	36 (1.1)	0.014	11 (2.4)	20 (1.5)	0.207
Renal failure/dialysis, n (%)	4 (0.7)	21 (0.7)	0.778	4 (0.9)	14 (1.0)	0.999
Sepsis/endocarditis, n (%)	4 (0.7)	32 (1.0)	0.812	4 (0.9)	22 (1.6)	0.361
Respiratory failure, n (%)	39 (7.1)	123 (3.8)	0.001	29 (6.4)	65 (4.8)	0.178

BITA = bilateral internal thoracic arteries; BMI = body mass index; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IABP = intraaortic balloon pump; IV NTG = intravenous nitroglycerin; LV = left ventricular; MI = myocardial infarction; OPCAB = off-pump coronary artery bypass; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; SITA = single internal thoracic artery.

plications (Table 1). Matched COPD patients received less BITA grafting and they had still significantly prolonged LOS (13.0 versus 11.4 days;  $p < 0.001$ ).

Kaplan-Meier curves of the matched groups are shown in Figure 2. Freedom from all-cause mortality in COPD patients at 1, 7, and 14 years after the operation was  $89.9\% \pm 1.4\%$ ,  $65.3\% \pm 2.3\%$ , and  $43.1\% \pm 3.1\%$ , respectively, compared with  $91.8\% \pm 0.8\%$ ,  $71.9\% \pm 1.3\%$ , and  $51.8\% \pm 1.9\%$  in patients without COPD ( $p = 0.008$ ). In COPD patients, the hazard estimate was consistently increased up to 9 years postoperatively (Fig 3).

#### Cox Proportional Hazard Models

The crude HR of long-term mortality for COPD patients was 1.68 (95% CI, 1.47 to 1.93;  $p < 0.001$ ). After adjustment for preoperative factors in the entire database, the adjustment for preoperative factor in the entire database, the adjusted HR was 1.28 (95% CI, 1.11 to 1.47;  $p < 0.001$ ). For those

COPD patients who survived the first postoperative year (n 465), the adjusted HR was 1.30 (95% CI, 1.11 to 1.52;  $p < 0.001$ ). In the subgroup of BITA

Table 2. Preoperative Variables Used for Propensity Matching Between Coronary Artery Bypass Grafting Without and With Chronic Obstructive Pulmonary Disease

Variable	Odds Ratio	95% CI	p Value
Age	1.01	1.00–1.02	0.047
Urgent operation	1.3	1.1–1.6	0.006
LVEF category	0.8	0.7–0.9	0.003
Previous MI	1.5	1.2–1.8	<0.001
PVD	1.3	1.1–1.7	0.010
LV hypertrophy	1.2	1.0–1.5	0.076
Current CHF	1.4	1.1–1.8	0.004
Past CHF	1.5	1.1–2.0	0.004
Calcified aorta	2.1	1.6–2.9	<0.001
Immune deficiency	4.6	2.2–9.4	<0.001
Smoking in last 2 weeks	2.8	2.2–3.5	<0.001
Smoking in previous year	2.3	1.8–2.9	<0.001

CHF = congestive heart failure; CI = confidence interval; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PVD = peripheral vascular disease.

grafting, COPD was still an independent predictor for long-term mortality with a similar adjusted HR of 1.31 (95% CI, 1.01 to 1.70;  $p$  0.040).

### Comment

This study has two principal findings: first, COPD, excepting a slightly longer hospital stay, is not associated with operative mortality and major morbidity after CABG after propensity match analysis; second, in contrast, COPD is a detrimental factor for long-term survival after CABG.

Other studies have also failed to identify COPD as independent risk factor for operative mortality after CABG [2, 16, 17]. Yet this conclusion contradicts the majority of published series [6, 9–13] and deserves cautious interpretation. Some authors have demonstrated that operative mortality after CABG is related to the severity of COPD, with only severe COPD affecting the outcome [3, 5, 20]. Fuster and colleagues [5] showed operative mortality of 0.4% to 0.9% in patients with FEV<sub>1</sub> greater than 60% but mortality of 10.8% for FEV<sub>1</sub> 40% to 59% and 54% for FEV<sub>1</sub> less than 40%. As we were unable to stratify COPD patients according to the severity of lung disease, our result might be attributed to the proportion of patients who, although fulfilling database criteria for COPD, had rather mild to moderate disease. Had this proportion been large enough, it could have skewed the mortality difference between matched groups toward not significance. Our study indeed shows some difference in favor of matched patients without COPD: 4.0% versus 3.4% hospital mortality. Still this difference would require more statistical power to reach significance. On the other hand, Manganas and associates [16] have published on 322 patients who had spirometry soon before undergoing CABG and found mortality to be unrelated not only to the presence but also to the severity of COPD. In fact, none of their 68 patients with severe COPD died.

Regarding morbidity, the present study showed a longer hospital stay, the difference being rather small (11.6 versus 13.0 days) but statistically

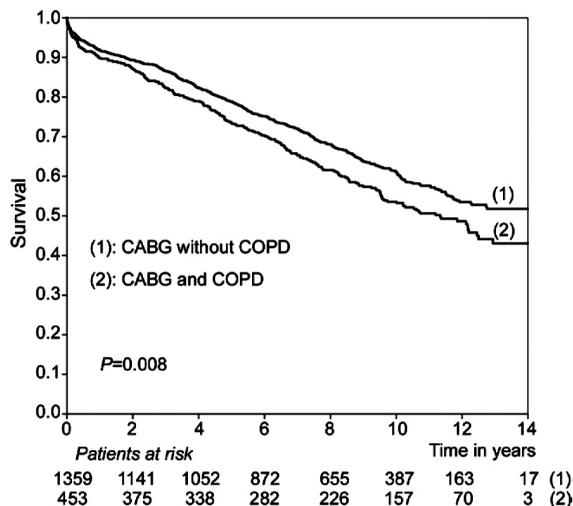


Fig 1. Kaplan-Meier survival plots of unmatched patients with and without chronic obstructive pulmonary disease (COPD) undergoing coronary artery bypass grafting (CABG).

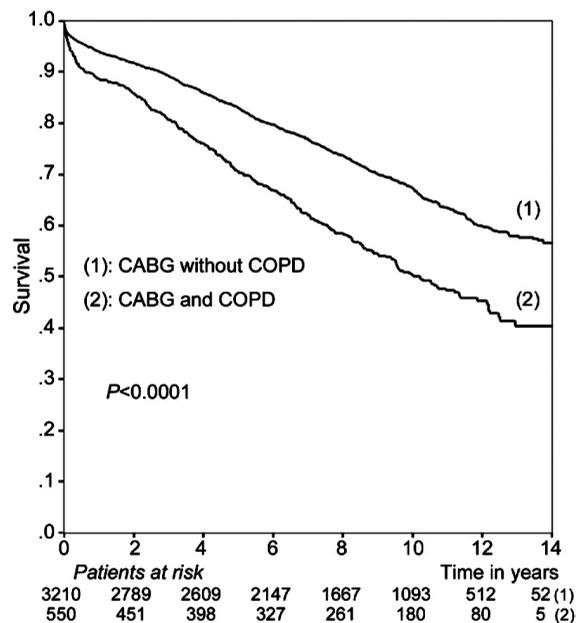


Fig 2. Kaplan-Meier survival plots of propensity-matched groups for all preoperative risk factors. Patients with chronic obstructive pulmonary disease (COPD) are compared with patients without COPD before coronary artery bypass grafting (CABG).

significant ( $p$  0.001). This is in agreement with Canver and coworkers [8] who documented that preoperative low FEV<sub>1</sub> affects the duration of care both in the intensive care unit (ICU) and in the hospital for patients younger than 70 years of age. Similarly, Herman and colleagues [21] have

recently identified COPD as an independent predictor of prolonged LOS in the ICU (odds ratio, 2.02; 95% CI, 1.55 to 2.65). However, except for LOS, we were unable to identify other significant differences in major morbidity between matched groups, including respiratory failure, deep sternal wound infection, and sepsis. The rate of BITA grafting in our series is higher than the general BITA grafting rate in the United States, and we have shown that BITA grafting is an independent predictor for deep sternal wound infection [22]. However, COPD was not an independent predictor for deep sternal wound infection when all available preoperative, intraoperative, and postoperative risk factors were used as potential predictors [22]. This observation was also confirmed in the matched groups. However, these results have been in contrast with those reported by others [3, 6, 14, 15], and this might also be explained by a relatively small proportion of patients with severe COPD in our study population. Indeed it has been shown that the post-CABG morbidity differs substantially only in patients with severe COPD, ie, those with FEV<sub>1</sub> less than 40% to 50% [5, 16, 20].

Of course, continuous progress in patient management should not be overlooked as a factor in improved outcome. More careful preoperative evaluation and preparation, implementation of aggressive fast-track extubation protocols, and so forth possibly lead to neutralization of COPD as a risk factor for operative mortality and morbidity. In such a dynamically adjusting clinical setting,

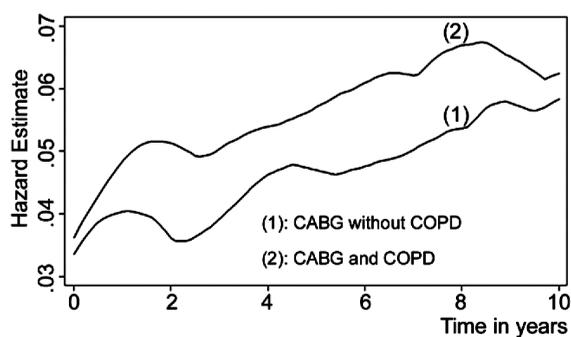


Fig 3. Hazard estimates of long-term mortality for propensity-matched patients with and without chronic obstructive pulmonary disease (COPD) undergoing coronary artery bypass grafting (CABG).

continuous reevaluation of the prognostic significance of COPD and other comorbidities appears essential [17].

On the other hand, COPD was clearly demonstrated to negatively affect long-term survival after CABG. After a mean follow-up of 7.6 years, matched COPD patients had a decreased likelihood of survival, the adjusted HR being 1.28 (95% CI, 1.11 to 1.47;  $p = 0.001$ ). We have shown in our CABG database that BITA improves 7-year survival after CABG by 21% [23]. There is, therefore, a possible advantage in the group of patients without COPD because of the use of increased number of BITA grafts. However, when risk-adjusted patients with BITA and COPD were compared with patients with BITA without COPD, COPD remained an independent predictor for long-term mortality with a similar adjusted HR of 1.31 (95% CI, 1.01–1.70;  $p = 0.040$ ).

In another study by van Domburg and associates [18], COPD was determined as a risk factor for 5-year mortality after CABG (HR, 1.9; 95% CI, 1.1 to 3.5), whereas in a study by Gao and coworkers [7], COPD was also associated with increased long-term mortality. Canver and colleagues [8] showed preoperative FEV<sub>1</sub> to be a significant predictor of 5-year survival in both young and elderly individuals undergoing CABG. In the largest relevant series to date, Leavitt and associates [4] analyzed 33,137 consecutive isolated CABG patients from the Northern New England Cardiovascular Disease Study Group prospective registry and documented that patients with COPD had worse long-term survival compared with those with no comorbidities (HR, 1.8; 95% CI, 1.6 to 2.1;  $p < 0.001$ ). Survival was even poorer for COPD patients who had additional comorbidities (HR, 3.6; 95% CI, 3.3 to 3.9;  $p < 0.001$ ) [4]. Similarly, compared with the adjusted HR of 1.28 of the present study, our group has reported elsewhere worse HRs for long-term survival in COPD patients with concomitant severely impaired left ventricular function (HR, 1.53; 95% CI, 1.13 to 2.09;  $p < 0.001$ ) [24] or diabetes (HR, 1.58; 95% CI, 1.19 to 2.11;  $p = 0.002$ ) [25]. However, it is noteworthy that the HR of 1.28 in this study compares favorably with those reported

by Leavitt and colleagues (HR, 1.8) [4] and van Domburg and associates (HR, 1.9) [18], supporting the idea of less severe COPD in our patients, as outlined before.

The cause of the invariably negative effect of COPD on long-term survival after CABG is not well understood. One could reason that COPD patients are likely to have an overall more problematic recuperation period, and are prone to postdischarge increased morbidity and mortality. This mortality, although closely related to surgery, is not reflected in hospital and 30-day mortality rates. In view of that, we separately analyzed long-term mortality of matched patients who survived the first postoperative year. This analysis yielded an equally unfavorable HR of 1.30 (95% CI, 1.11 to 1.52;  $p = 0.001$ ). The increased hazard of COPD patients extended well beyond the short and mid-term postoperative phase, up to 9 years postoperatively. Hence, it appears that the impaired long-term survival of COPD patients is a function of their progressive lung disease rather than CABG per se. In fact, COPD has also been associated with impaired long-term survival after percutaneous coronary intervention (HR, 2.16; 95% CI, 1.81 to 2.56) [26], or in patients with coronary artery disease in general (HR, 1.71; 95% CI, 1.21 to 2.42 for noncardiac mortality and HR, 1.67; 95% CI, 1.29 to 2.16 for cardiac mortality) [27]. In a small series, Medalion and colleagues [1] also documented a decreased long-term actuarial survival after CABG associated with COPD (65% versus 92% at 9 years;  $p 0.005$ ). Interestingly, after comparing their results with natural history studies of isolated COPD patients, they noted a similar long-term survival of COPD patients after CABG to the natural history of isolated COPD patients.

Moreover, they showed long-term COPD survivors after CABG to have significantly improved quality of life compared with their preoperative status and concluded that CABG apparently carries an overall beneficial long-term effect for COPD patients [1].

#### *Limitations of the Study*

First, this is a retrospective investigation. Nevertheless, all data were prospectively recorded with the highly standardized methods used for the New York State– audited database. Second, the cause of death is not documented. However, for practical purposes, estimation of overall mortality is probably more important after a long-term follow-up period. Third, as the study refers to a single-center regional database, our results require corroboration across diverse institutions and countries. Finally, as already pointed out, we were unable to stratify COPD patients according to the severity of lung disease and provide valuable subgroup analysis.

#### *Conclusions*

The present study demonstrated that COPD, although accompanied by a slightly longer hospital stay, is not associated with increased hospital mortality or major postoperative complications after CABG. However, COPD is a continuing detrimental independent risk factor for long-term survival after CABG, associated with 30% higher relative risk for long-term mortality. More frequent follow-up for those patients seems appropriate to ensure optimal therapy and potentially improve survival and quality of life.

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# Surgical Ventricular Restoration: Where Do We Go From Here?

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key words: surgical ventricular restoration, ischemic cardiomyopathy, post-infarction ventricular dilation, ventricular volume reduction

## ABSTRACT

The STICH trial concluded that the addition of surgical ventricular restoration (SVR) to coronary bypass grafting (CABG) did not lead to improved survival in patients with dilated ischemic cardiomyopathy. Observational studies at multiple centers over the last 15 years have shown consistent improvement in global ventricular function and approximately 70% long-term survival. The causes of this discrepancy are reviewed here and likely relate to how the STICH trial was conducted. Recent subset analyses from the STICH investigators have provided some additional data relating ventricular volumes to outcomes. However, including patients with unsuitable entry criteria and operations confounds the data. We recommend an analysis of the STICH data based on the trial's initial design in order to determine if there are patients who may benefit by SVR.

Surgical ventricular restoration (SVR) is an operation applied to patients with congestive heart failure and ventricular dilation following infarction. Ventricular scar tissue replaces normal muscle and the remote muscle remodels becoming more spherical. Myocardial fibers become reoriented in a more horizontal rather than elliptical formation. Left ventricular (LV) volume can increase substantially from the normal 25 ml/m<sup>2</sup>. The SVR operation reduces ventricular size by excluding the scarred segment, rebuilds a more

normal elliptical architecture and improves LV function.

SVR has been done for over 25 years and thousands of patients have undergone the operation.<sup>3,4,5</sup> Observational data of SVR from 64 published articles reported operative mortality and summarized 34 series with long-term survival. Operative mortality varied by center from 3 to 15% and five-year survival was approximately 70%, irrespective of when the operations were reported. This has led the European Task Force on Myo-

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cardial Revascularization to recommend SVR as a surgical option combined with CABG in selected patients with advanced heart failure due to ischemic cardiomyopathy who have documented scar, and a LV end-systolic volume index (LVESVI)  $\geq 60$  ml/m<sup>2</sup> if done in centers with a high level of surgical competence.<sup>7</sup>

The STICH trial (Surgical Treatment for Ischemic Heart Failure) is the first and only randomized trial comparing this treatment to coronary bypass grafting (CABG) alone.<sup>8</sup> The results showed that the addition of SVR did not improve survival when compared to CABG alone. Many experts in the heart failure community accept this conclusion because it is the only randomized trial of this therapy. Clinical guidelines depend on expert opinion derived from randomized trials and observational data. How does the clinician determine good from bad evidence-based medicine? What should we do when observational and registry data differ from randomized trial data? The case of SVR illustrates this dilemma.

The purpose of this review is to examine the design and implementation of the STICH trial since this is the framework for subsequent reported analyses. We propose a further simple inquiry that may help clinicians decide if there are some patients who may benefit by the addition of SVR to CABG alone.

STICH was originally conceived and built on observational studies from multiple centers that defined appropriate candidates for operation and the key components of a successful SVR operation. These inclusion criteria consisted of congestive heart failure following a prior anterior myocardial infarction that causes LV necrosis involving  $>35\%$  of the muscle mass, a proven scar by radionuclide (RN) or cardiac magnetic resonance imaging (CMR), LV akinesia or dyskinesia, an ejection fraction  $<35\%$ , and LV end systolic volume index (LVESVI)  $\geq 60$  ml/m<sup>2</sup>. CMR and RN were the only methods felt by experts to accurately measure LV volume.<sup>9</sup> In fact, the initially selected 50 centers were chosen *because* they had these modalities. Equally important was the definition of what constituted an effective SVR procedure, determined in consultation with experts

who had extensive prior experience and publications. An effective SVR was defined as a LV reduction of 30% or more that was measured by CMR four months postoperatively. How this was to be achieved surgically was not described because of the variability of techniques, however, centers were to be included if their surgeons could demonstrate low mortality in CABG operations on patients with low ejection fractions and experience with at least five SVR operations where LV volume was reduced by at least 30%.

Here is what actually happened in the STICH trial. The study randomized 1000 patients to SVR plus CABG or CABG alone.<sup>8</sup> Perhaps due to the challenges of enrollment, the original 50 centers were expanded to include 127 centers in 26 countries. Many centers did very few operations without prior experience. Decision to perform SVR was left to the surgeon's visual assessment of the ventricular surface at the time of surgery. In many cases this could have represented hibernating ventricle in the absence of viability data. Exactly what operation was done in such patients? Was it exploratory myotomy and some form of closure or LV volume reduction? Demonstrable scar by viability testing was an essential determinant of eligibility and was violated in the actual trial. As a result, STICH reported no history of infarction in 13% of patients and only 58% had akinesia or dyskinesia in the report by Zembala.<sup>10</sup> Volume was measured mostly by echocardiography (ECHO), a method that was rejected in the original study design due to its inaccuracy. LV baseline volume was obtained in 710 patients by ECHO, in 352 patients by CMR and in 344 patients using RM.<sup>11</sup> Bonow reported RN to detect scar in 50% of patients in hypothesis I comparing medical treatment against CABG, but his analysis has not yet reported outcomes in patients with documented necrosis in the SVR cohort.<sup>12</sup>

Furthermore, SVR in STICH reduced LV volume only 19%, significantly lower than what is reported in multiple observational data registries. This inclusion is deliberately different from the original grant submission (LV reduction  $\geq 30\%$ ). The details of the changes in the STICH protocol are available on the National Institutes of Health

website <http://clinicaltrials.gov/archive/NCT00023595>. Despite these deficiencies, subset analyses have recently been reported by the STICH investigators based on flawed data.<sup>14-16</sup>

Michler published a post hoc STICH subset analysis of preoperative LVESVI on outcome from 195 patients with paired CMR studies, 276 with paired ECHO studies, and 84 with paired RN. Among patients with a *preoperative* baseline LVESVI  $\geq 60$  ml/m<sup>2</sup>, SVR decreased volume 30% or more in only 26% of patients and in 41% of patients there was no decrease at all! Most likely, a hibernating LV was opened and simply closed. There was a trend toward improved survival in this group with small preoperative volumes ( $< 60$  ml/m<sup>2</sup>) compared to CABG alone, yet this cohort was not considered eligible for the trial in the initial design. Their data suggests a cutoff of preoperative volume where operation may be warranted. Operating on larger ventricles had worse outcomes, but only 36% and 42% of patients with LVESVI 60-90 ml/m<sup>2</sup> and  $>90$  ml/m<sup>2</sup> had greater than 30% volume reduction. This conclusion is in sharp contrast to the vast experience of SVR operations reported in many centers over many years, where more than 1500 patients had  $> 40\%$  volume reduction. Moreover, since a small number of patients received a volume reduction in the smaller ventricles in STICH, questions arise regarding what specific operation was done and what this conclusion means. Does it extend the criteria to perform SVR in smaller hearts, as the normal LVESVI is  $< 25$  ml/m<sup>2</sup>? Certainly, the LVESVI  $< 60$  ml/m<sup>2</sup> would have otherwise been excluded, so that the procedure may be useful in this subset.

The same STICH study analyzed outcomes based on *postoperative* LVESVI and revealed interesting findings. First, a postoperative LVESVI  $\leq 70$  mL/m<sup>2</sup> after CABG plus SVR resulted in improved survival compared with CABG alone, and the contrary was true with a postoperative LVESVI  $\geq 70$  mL/m<sup>2</sup> compared to CABG alone. Furthermore, among SVR plus CABG patients, a postoperative LVESVI  $< 60$  ml/m<sup>2</sup> showed significant survival advantage compared to SVR plus CABG patients with LVESVI  $> 60$  ml/m<sup>2</sup>.

What about extent of volume reduction? Michler's analysis showed that survival comparing SVR plus CABG with CABG alone was not influenced by large ( $\geq 25$  ml/m<sup>2</sup>) or small volume ( $\leq 25$  ml/m<sup>2</sup>) reductions. This becomes apparent in the larger hearts where LVESVI is  $> 90$  ml/m<sup>2</sup> (average 153 ml/m<sup>2</sup>), so that a 25 ml/m<sup>2</sup> reduction is a minor one. Among these SVR patients whose LVESVI was reduced 30% or more, there was no significant survival advantage over CABG alone. So apparently the finally achieved volume may be very important. This is consistent with findings of Di Donato who observed improved short and long-term results if postoperative LVESVI is  $< 60$  ml/m<sup>2</sup>.<sup>18</sup>

There is controversy regarding operating on larger ventricles. STICH investigators caution against operating on larger ventricles based on the trial data. However, operation on the very large ventricle has excellent long-term survival as illustrated in an observational study in patients with preoperative LVESVI  $> 80$  ml/m<sup>2</sup>. Skelley reported on SVR where volume reduction of 31% was achieved as measured by CMR. Three-year survival of 73.4% was reported in the preoperative LVESVI 80 to 120 ml/m<sup>2</sup> group and the authors concluded that this may be the group of patients most helped by operation.<sup>19</sup> The RESTORE group reported 70% five-year survival in patients with SVR among patients with LVESVI 80 - 120 ml/m<sup>2</sup>.<sup>5</sup>

Oh and STICH colleagues recently reported that 18.5 % of patients in the trial had ejection fraction  $> 35\%$ , a cohort that should have clearly been excluded from the SVR.<sup>11</sup> The analysis was aimed at identifying any subgroups that may benefit from SVR based only on *preoperative* baseline LV function. The authors concluded that patients with smaller ventricles (LVESVI  $< 60$  ml/m<sup>2</sup>) and LVEF  $\geq 33\%$  may have benefited by SVR and CABG compared to CABG alone. This is a curious finding, given that these patients were not originally even considered for operation.

Oh's conclusions further depend on how volume was measured in the STICH trial. Baseline core lab data was assigned as adequate quality, obtained in 710 patients by ECHO, in 352 patients by CMR and in 344 patients using RN.

Outcomes are based on 13 algorithms using a different hierarchy of imaging modalities and their quality. Depending on which algorithm is chosen, the results differ. One algorithm (preferential hierarchy ECHO, CMR, RN) shows significance ( $p = .037$ ) favoring CABG over SVR plus CABG for death/hospitalization. However, if a different algorithm was chosen for analysis where the hierarchy of analysis was CMR, ECHO then RN, the findings comparing CABG plus SVR vs. CABG only show different results. CABG plus SVR is favored for LVESVI  $< 60 \text{ ml/m}^2$ , CABG fared better for LVESVI 60 to  $90 \text{ ml/m}^2$  and CABG also fared better for LVESVI  $> 90 \text{ ml/m}^2$  but not significantly ( $p = 0.19$ ). However, this analysis does not consider the extent LV volume reduction, an essential factor for long-term survival<sup>18</sup>

Observational studies from registry data may influence our clinical decisions. For example, Di Donato examined residual volume after the SVR operation in a study of 216 patients from an experienced single-center that underwent SVR and grouped them according to *postoperative* LVESVI at discharge.<sup>18</sup> LVESVI decreased by 41% in the overall population reflecting a substantial volume reduction compared to the STICH data. Postoperative LVESVI  $\geq 60 \text{ ml/m}^2$  was an independent predictor of mortality at 5 years. Furthermore, a preoperative LVESVI of  $94 \text{ mL/m}^2$  was the cut-off for an optimal postoperative volume  $< 60 \text{ mL/m}^2$ . There seems to be an end-stage LV dilation that defines patients who may not benefit from the SVR procedure but the highest pre-operative LVESVI that precludes surgery has yet to be defined. The RESTORE data showed a decreased 5-year survival of 64% in preoperative hearts with LVESVI  $> 120 \text{ ml/m}^2$  compared to 80% when preoperative LVESVI is  $< 80 \text{ ml/m}^2$ .<sup>5</sup>

The magnitude of LV reduction is emphasized by Isomura. LVESVI was measured by ECHO, LV angiography and RN. ECHO underestimated LVESVI by approximately 30%, most likely due to post-ischemic ventricular asynergy. Long-term (8 years) prognosis depended on the *extent* of SVR reduction. Survival of  $> 80\%$  was achieved if there was a  $> 33\%$  reduction of LVESVI and the residual

volume was  $< 90 \text{ ml/m}^2$ . His finding in large hearts (LVESVI  $> 120 \text{ ml/m}^2$ ) implies that greater than 30% volume reduction is indicated following SVR for very large ventricles. Conversely, inadequate volume reduction of approximately 15% resulted in 100% 8-year mortality if the post-operative LVESVI was  $> 90 \text{ ml/m}^2$ . Isomura's further analysis of his data showed the advantage of reconstruction of LV size and shape, as seven-year survival improved from 61% to 72% when SVR fashioned a more elliptical ventricle. Creating an elliptical ventricle is a variant of the classical SVR operation where the intraventricular patch is oriented obliquely in the ventricle, extending from the non-scarred ventricular outflow tract beneath the aortic valve to the scarred apex. This procedure also results in a greater ventricular volume reduction than that achieved by the standard elliptical apical patch placement.

The concept of SVR has evolved from observations about size and shape in diseased ventricle. Douglas reviewed LV shape, afterload and survival in idiopathic dilated cardiomyopathy. Size (LV end-diastolic dimension) and specifically shape (sphericity index) provided the best correlation with survival. Bolognese examined the prognostic impact of LV remodeling after acute myocardial infarction successfully treated by primary percutaneous coronary angioplasty (PTCA). LV dilation (greater than 20%) occurs in about 15% and persists at six months despite patency of the infarct-related artery. Patients with LV dilation had the worse long-term (80 months). These findings are consistent with the concept of early mitral valve repair in degenerative disease to prevent ventricular dilation. Suri reports that mitral valve repair functional improvement is reduced when LVESVI exceeds  $36 \text{ ml/m}^2$ .<sup>23</sup> Guidelines suggest early surgical correction before the ventricle enlarges. Perhaps in the near future this concept will be applied in the treatment of post-infarction ventricles before massive dilation occurs.

A refinement of operative risk for SVR was reported by Wasaka who elucidated factors of mortality after SVR by creating a risk scoring system. All of their patients had either dyskinesia (31%) or akinesia (69%). This differs from the

STICH trial where 58% had these wall motion abnormalities. Four independent predictors of mortality were identified: Interagency Registry for Mechanically Assisted Circulatory Support profile (INTERMACS), left ventricular ejection fraction, severity of mitral regurgitation, and age. Three risk scores were developed from high to low and 3-year survivals were significantly different among these groups. In their series, the goal of LVESVI reduction of 30% with surgery was achieved in only 44%, 55% and 69% of patients with preoperative volumes of <60, 60-90 and >90 ml/m<sup>2</sup>. The severity of mitral regurgitation was addressed in Isomura's study that showed that mitral procedures did not affect prognosis in SVR patients if the postoperative LVESVI was < 90 ml/m<sup>2</sup>. A comparable finding was observed in the RESTORE registry when mitral procedures with SVR were compared to SVR alone.<sup>5,25</sup>

Despite its implementation flaws, the STICH trial has raised some new areas of interest and future research. Specifically, should patients with the non-massively dilated hearts (LVESVI < 60 ml/m<sup>2</sup>) undergo SVR? Such volumes have traditionally not been considered for SVR by most surgeons. Dor, however, has always advocated operation in these patients because of the known natural history of post-infarction ventricular dilation treated by CABG alone. What is the great-

est ventricular volume beyond which no improvement is expected by SVR? This is a new and inviting question since novel procedures to rebuild shape as well as size have been reported with excellent results even in large ventricles.

There will likely be more subset analyses of the STICH data. The original study design was simple and was intended to address significant issues that were based on extensive observational data. So where do we go from here? We urge the STICH investigators to analyze a subset of patients in whom accurate and complete data was recovered. STICH data should be probed to include a comparison of treatments based on the following original inclusions: 1) advanced congestive heart failure (NYHA class III and IV) after documented myocardial infarction, EF <35%, a >35% LV necrosis with a regional anterior akinetic or dyskinetic scarred segment 2) LVESVI measured preoperatively and postoperatively by CMR, and 3) postoperative LVESVI volume reduction by SVR >30%. Such a breakdown would provide clinicians valuable guidance in their management of a difficult group of patients. This analysis would also alleviate concerns and misgivings about the STICH trial that is perceived by many to have deviated significantly from its original design.

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# Resection-Plication-Release for Hypertrophic Cardiomyopathy: Clinical and Echocardiographic Follow-Up

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**Background:** Abnormal positioning and size of the mitral valve contribute to the systolic anterior motion and mitral-septal contact that are important components of obstructive hypertrophic cardiomyopathy (HCM). The RPR repair (resection of the septum, plication of the anterior leaflet, and release of papillary muscle attachments) addresses all aspects of this complex pathology. This study reports outcomes regarding effectiveness of the RPR repair.

**Methods:** Fifty consecutive unselected patients (average age, 55.8 years) undergoing RPR repair for obstructive HCM from 1997 to 2007 were studied. Each patient underwent preoperative and postoperative transthoracic echocardiograms to document gradient, ejection fraction, degree of mitral regurgitation, and systolic anterior motion. Intraoperative transesophageal echocardiogram was used to guide all surgical repairs. Clinical follow-up included patient interviews to determine New York Heart Association (NYHA) status.

**Results:** Concomitant operations were performed in 25 patients (50%). Postoperative mortality was 0%. Average mean left ventricular outflow tract gradients decreased from  $134 \pm 40$  to  $2.8 \pm 8.0$ . Mitral regurgitation improved from a mean of 2.5 to 0.1 ( $p < 0.001$ ). Average length of stay was  $6.9 \pm 2.7$  days. NYHA class improved from  $3.0 \pm 0.6$  to  $1.2 \pm 0.5$ . Follow-up was 100%, with a mean of  $2.5 \pm 1.8$  years. Average mitral regurgitation at follow-up was 0.9, with no residual systolic anterior motion.

**Conclusions:** The RPR repair is safe and effective for symptomatic obstructive HCM. Our data support repair of the mitral valve that results in good intermediate outcomes with respect to gradient, mitral regurgitation, and clinical status.

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Hypertrophic cardiomyopathy (HCM) is an uncommon, autosomal-dominant disease characterized by asymmetric septal hypertrophy that was first described by Sir Russel Brock in 1957 [ 1 ]. Morrow's transaortic approach to resection of the septum relieved the bulk of obstruction and was popularized after presentation of his results in 83 patients and their follow-up in 1975 [ 23 ]. More recently, multiple large studies have demonstrated excellent outcomes with surgical myectomy for repair of HCM for symptomatic, drug-refractory septal hypertrophy with outlet obstruction [ 4-9 ].

The anterior leaflet of the mitral valve plays an important role in obstruction in HCM. Echocardiographic data supports that it is the anterior motion of the mitral valve that causes both subaortic obstruction and loss of coaptation with the posterior leaflet, resulting in mitral valve insufficiency [ 10,11 ]. Previous treatments of mitral regurgitation (MR) with a redundant anterior mitral leaflet have included mitral valve replacement and repair [ 12,13 ]. It is the anterior displacement and the recognition of drag (pushing) forces on the mitral valve that prompted Messmer and colleagues to perform a more extensive myectomy, followed by thinning of the papillary muscle; this allows the anterior leaflet to fall more posteriorly within the ventricular chamber [4].

Our group has proposed horizontal plication of the anterior mitral leaflet, reasoning that this leaflet is often too long in an anteroposterior dimension. Shortening the leaflet horizontally limits its excursion into the outflow tract by decreasing the length in its longest dimension and stiffening the redundant tissue [ 14-16 ]. This, in addition to standard extended septal myectomy and release of abnormal papillary attachments, has been termed the resection-plication-release (RPR) repair. This study reviews the clinical and echocardiographic follow-up of our first 50 patients with this repair.

## Patients and Methods

### *Study Group and Patient Selection*

From 1997 until 2007, 50 patients underwent RPR repair for HCM at St. Luke's-Roosevelt Hospital Center. These patients were selected from a group of approximately 450 patients. Most were treated

medically to reduce their left ventricular outflow tract (LVOT) gradient and alleviate their symptoms. Patients with symptomatic LVOT obstruction (LVOTO) were given an aggressive trial of pharmacologic therapy including  $\beta$ -blockers, disopyramide, or calcium channel blockers. Those in whom medical therapy failed and who remained symptomatic with LVOTO and gradients exceeding 50 mm Hg at rest or after physiologic provocation were referred for surgical repair.

Selection criteria for patients undergoing the RPR repair included those patients who met the aforementioned criteria and in addition had significant systolic anterior motion (SAM) with an elongated and floppy mitral valve, as judged by echocardiography. The ultimate decision to proceed with an RPR repair was made preoperatively based on transthoracic echocardiography (TTE) characteristics but was subject to change based on intraoperative transesophageal echocardiography (TEE) and operative findings.

The decision involved an integrated assessment of the extent of SAM, the size of the mitral valve leaflets, the presence of abnormal papillary muscle attachments, and the slack and redundancy of the mitral valve as assessed by direct visualization. Specifically, qualitative preoperative assessment included assessment of the mitral valve as (1) being large relative to the LV chamber and (2) showing large excursion and a large angle of motion as it is pushed into the outflow tract. The intraoperative assessment by the surgeon required that the valve was redundant, enlarged, and slack, as assessed by nerve hook traction.

This study involving human subjects was approved by the St. Luke's-Roosevelt Institutional Review Board. Individual consent was waived for the study after clearance and use of an approved deidentified database.

### *Echocardiography*

Before admission, TTE was performed for assessment of the LVOT gradient, septal and anterior wall thickness, papillary muscle anatomy, SAM, and MR. Echocardiographic gradients were measured at rest, after the Valsalva maneuver, after standing, and after treadmill exercise. For

each patient, the distance between the aortic annulus and the area of mitral–septal contact was carefully measured during diastole. The furthest extent of the myectomy into the LV was determined by measuring the distance from the aortic annulus to the far side of the septal bulge. Mitral valve structure and function were also assessed during outpatient preoperative echocardiograms. Criteria for mitral valve replacement included severe MR in the setting of heavy leaflet calcification and immobility (excluded from study). Any patient with posterior mitral valve prolapse who required a standard mitral valve repair was also excluded from the study.

All patients also received TEEs to remap the location and extent of septal hypertrophy, assess mitral valve function, measure LVOT gradients, and evaluate MR. The degree of MR was scored on a standard scale from 0 to 4.

#### ***Operative Technique***

A standard median sternotomy was performed, and patients were placed on cardiopulmonary bypass (CPB) using moderate hypothermia. The aorta was cross-clamped, and both antegrade and retrograde cold crystalloid cardioplegia were delivered. Visualization of the septum was achieved with a transverse aortotomy and retraction of the aortic valve leaflets; this allowed for direct evaluation of the degree of hypertrophy.

Extended septal myectomy was performed as previously described by Messmer and colleagues [4,14]. Stabilization of the muscle was accomplished by use of a trefoil hook. This approach ensures an adequate length of resection into the LV cavity. Two parallel incisions were made into the septal bulge and connected to remove the muscle mass. Further resection was performed after careful palpation of the septum and estimation of residual LV mass. Myectomy was extended to the base of the papillary muscles, when midseptal thickening was present.

Mitral valve pathology was addressed after the myectomy was completed. The horizontal plication of the anterior leaflet was performed to reduce length and decrease leaflet and chordal slack. The leaflet and its degree of redundancy were evaluated in each case and three to four 5-0 poly-

propylene sutures were placed through the fibrotic area of the leaflet in a horizontal mattress fashion. The extent of plication was determined by integrating the preoperative echo, the degree of SAM, the size of the mitral valve, and the slack and redundancy of the anterior leaflet as assessed with the nerve hook. This usually resulted in a plication of 2 to 5 mm.

The papillary muscles were grasped and pushed medially to visualize the abnormal connections between the papillary muscles and the anterior wall of the ventricle. A blade was used to divide the thickened abnormal attachments. A pituitary rongeur may be used to resect a portion of the junction of the papillary and lateral wall. This reduces the diameter of the papillary muscle and allows for posterior displacement of the anterior mitral leaflet. Division of abnormal attachments and thinning of the papillary muscles is critical for the treatment of SAM. This is followed by extensive irrigation of the LV cavity.

Postoperative TEE was performed after withdrawal of CPB, but before removal of the cannulae, and assessed by the surgeon, anesthesiologist, and referring cardiologist. The repair was closely examined for residual SAM, degree of gradient, presence of ventricular septal defect, and MR. Intravenous dobutamine was used to provoke the patients and measurements and assessments were repeated. CPB was reinstated for a persistent gradient greater than 30 mm Hg, mitral septal contact, or MR of moderate or greater degree.

#### ***Follow-Up***

Follow-up was obtained by direct patient interview, review of patient records, and information supplied by referring physicians. TTE was used for examination of LVOT gradient, MR, and LV function at the outpatient follow-up. Patients were seen 2 weeks postoperatively, with TTE performed at 3 months. These visits were followed by yearly TTE evaluation. Patients being treated medically were evaluated with yearly echocardiography and more frequently as necessary based on changes in treatment or symptoms.

**Statistical Analysis**

All data were collected retrospectively. Data are presented as mean  $\pm$  standard deviation. MR is presented as the mean with the ranges included. Continuous variables were compared using paired *t* test, with significance accepted at values of  $p < 0.05$ .

**Results****Baseline Characteristics**

From August 1997 through May 2007, 50 patients (26 men, 24 women) underwent RPR repair at St. Luke's-Roosevelt Hospital Center. Patients were a mean age of  $55.8 \pm 14.6$  years (range, 23 to 84 years). The patients were symptomatic, with an average New York Heart Association (NYHA) functional class of  $3.0 \pm 0.6$  (range, 2 to 4). The average resting LVOTO gradient, as measured by echocardiography, was  $88 \pm 26$  mm Hg. The gradients after provocation averaged  $134 \pm 40$  mm Hg (range 66 to 230 mm Hg). Mean ventricular septal thickness was  $23 \pm 5$  mm. The preoperative ejection fraction was  $0.60 \pm 0.10$  (range, 0.35 to 0.85). SAM was present in 96% of patients. The mean degree of MR in this group was 2.5 (range, 1 to 4).

Preoperative characteristics included coronary artery disease in 13 patients (27%), hypertension in 17 (35%), diabetes mellitus in 5 (10%), and prior ventricular arrhythmias in 11 (22%). In addition, 4 patients (8%) had chronic obstructive pulmonary disease, 6 (12%) had hypercholesterolemia, 3 (6%) had a previous pacemaker in place, and 10 (20%) had a history of smoking. Two patients had previous septal myectomy at other institutions.

A positive family history for HCM was present in 15 of 50 patients (30%), of whom 6 (12%) had more than one relative with HCM. Preoperatively, 42 patients (84%) were treated with  $\beta$ -blockers, 18 (36%) were also taking disopyramide, and calcium channel blockers had been used in 6 (12%; Table 1).

Table 1. Preoperative Characteristics

<b>Baseline Characteristics</b>	<b>Results, No (%) or Mean <math>\pm</math> SD</b>
Demographic data	
Age, y	55.8 $\pm$ 14.6
Gender	
Males	26 (52)
Females	24 (48)
Positive family history	15 (30)
Clinical status	
NYHA class	3.0 $\pm$ 0.6
Coronary artery disease	13 (27)
Hypertension	17 (35)
COPD	6 (12)
Diabetes mellitus	5 (10)
Ventricular arrhythmias	11 (22)
Echocardiographic data	
Resting gradient, mm Hg	88 $\pm$ 26
Provoked gradient, mm Hg	134 $\pm$ 40
Septal thickness, mm	23 $\pm$ 5
Ejection fraction	0.60 $\pm$ 0.10
Mitral regurgitation	2.5 $\pm$ 1.1
Drug therapy	
$\beta$ -Blockers	42 (84)
Disopyramide	18 (36)
Calcium channel blockers	6 (12)

COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; SD = standard deviation.

**Intraoperative Findings**

All 50 patients underwent RPR repair as described. Half of the patients had additional procedures, including coronary artery bypass grafting in 12, aortic valve replacement in 5, repair of atrial septal defect in 2, and radiofrequency atrial ablation in 6. Not all HCM patients received the full RPR repair. Average aortic cross-clamp time of all patients was  $96.5 \pm 25$  minutes, with a CPB time of  $129 \pm 34$  minutes (Table 2).

Patients who did not require mitral valve plication due to a shortened or fibrotic anterior leaflet and those who required a mitral valve replacement due to profound MR with severely calcified leaflets (advanced rheumatic disease) were not included in this study because they did

Table 2. Operative Details

Details	Results, No. (%) or Mean $\pm$ SD
Concomitant procedures	
CABG	12 (24)
Atrial septal defect repair	2 (4)
Maze	6 (12)
Aortic valve replacement	5 (10)
Operative times, min	
Cross-clamp time	96 $\pm$ 25
CPB time, min	129 $\pm$ 34

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; SD = standard deviation.

not fulfill the criteria for the RPR repair.

Initial postoperative TEEs in the operating room demonstrated a marked reduction in LVOTO gradient to  $2.8 \pm 8.0$  mm Hg (range 0 to 23 mm Hg;  $p < 0.0001$ ). Significant improvement in MR to 0.1 (range, 0 to 2;  $p < 0.0001$ ) was also demonstrated. None of the patients had persistent SAM.

After initial assessment by TEE, the decision was made for re-resection in 3 of the 50 patients (6%). These patients required a second pump-run for inadequate initial resection. One patient had persistent and significant MR despite plication and was placed back on CPB to undergo an Alfieri (edge-to-edge) repair of the mitral leaflets, with resulting trace residual MR.

### Early Outcomes

No deaths occurred in the postoperative period. Surgical morbidity was 10% overall and included one reoperation for bleeding, one cerebrovascular accident, and one late pericardial tamponade in a patient requiring anticoagulation. Two patients required placement of a permanent pacemaker for complete heart block (4%). The incidence of postoperative atrial fibrillation was 12% (Table 3). Internal defibrillators were placed in 4 patients postoperatively for preoperative syncope or malignant ventricular arrhythmias. The average hospital length of stay was  $6.9 \pm 2.7$  days.

Table 3. Complications

Complication	No. (%)
Postoperative bleeding	1 (2)
Atrial fibrillation	6 (12)
Permanent pacemaker	2 (4)
Cerebrovascular accident	1 (2)
Sternal wound infection	1 (2)
Late pericardial tamponade	1 (2)

No ventricular septal perforations were present on follow-up echocardiography. The incidence of left bundle branch block in follow-up was 42% (21 of 50 patients). No patients required re-resection of the septum. Overall, the patients had marked improvement in clinical symptoms, with an improvement in NYHA class to  $1.2 \pm 0.5$  ( $p < 0.0001$ ).

### Follow-Up

Echocardiographic or clinical follow-up, or both (closing date, May 2007), was available for all 50 patients (100%). A mean follow-up of  $2.5 \pm 1.8$  years (range, 0.5 to 9 years) was obtained. No deaths occurred during the study period. An examination of the most recent echocardiographic data as of May 2007 for all 50 patients demonstrated that LVOT gradients remained low at  $3.4 \pm 12.7$  ( $p < 0.0001$ ). Ejection fraction was  $0.70 \pm 0.10$ . Maximal septal thickness was  $15.7 \pm 5.1$  mm. The degree of MR remained stable as well, measuring 0.9 (range, 0 to 2;  $p < 0.0001$ ; Table 4).

Table 4. Postoperative Outcomes

Outcome	Measurements		<i>p</i> Value
	Pre-op	Post-op	
LVOTO, mean $\pm$ SD, mm Hg	134 $\pm$ 40	2.8 $\pm$ 8.0	<0.0001
Mitral regurgitation	2.5	0.1	<0.0001
NYHA, mean $\pm$ SD, class	3.0 $\pm$ 0.6	1.2 $\pm$ 0.5	<0.0001

LVOTO = left ventricular outflow tract obstruction; NYHA = New York Heart Association.

### Comment

HCM has marked phenotypic variation, leading to significant differences in clinical presentation. The pathophysiology involves variation in ventricular septal thickness, SAM of the mitral valve, and papillary musculature. Detailed echocar-

diography has led to better understanding of this complex pathophysiology [ 17-22 ].

The goal of surgical intervention for HCM is to improve symptoms through relief of LVOTO. Recent large studies show excellent long-term results with extended septal myectomy alone [7-9]. However, HCM operations have been viewed as difficult, with unpredictable results, except when performed at centers with extensive experience. Postoperative SAM and MR have been reported as well as persistent LVOTO [23,24].

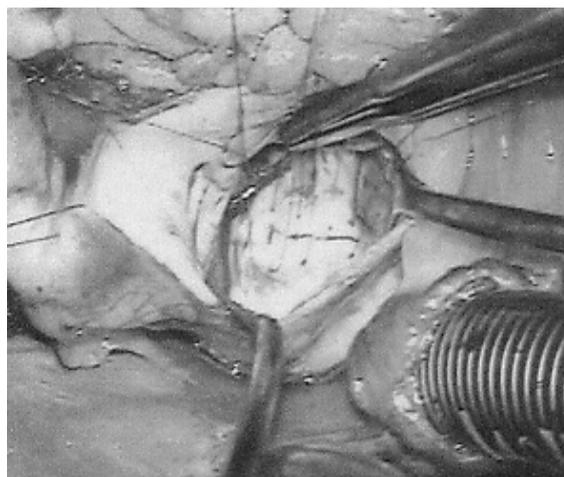
On the basis of echocardiographic data implicating the mitral valve as a key component in obstructive HCM, our group has previously published a novel method of anterior mitral leaflet plication that is performed in addition to extended septal myectomy [15,16]. This RPR repair technique addresses multiple aspects of HCM pathology. Our surgical approach specifically addresses the problem of the large protruding anterior mitral valve leaflet and its contribution to obstruction. Patients who are candidates for mitral valve plication include those with increased mobility, size, or length of the anterior mitral leaflet. These are patients who are judged morphologically to be at increased risk of residual SAM and obstruction. This study demonstrates that this repair is durable and effective over time, both from a functional and clinical standpoint.

Prior large surgical series of myectomy have not specifically addressed the problem of the mitral valve [7-9]. Repair of the mitral valve itself to relieve SAM is somewhat controversial, although the importance of the anterior leaflet of the mitral valve in the underlying pathology has long been recognized. Previous groups have used mitral valve replacement to eliminate obstruction [12,25]. Macintosh and colleagues [26] addressed the pathology of the mitral valve with selective mitral valve replacement for those patients with a septal thickness of less than 18 mm. Others have proposed a sliding leaflet or other mitral valve repair for obstructive HCM [27-30]. Redundancy in the anterior mitral leaflet has also been treated with a standard Alfieri edge-to-edge repair [31].

Some groups maintain that extended septal myectomy alone reduces LVOTO and improves

any associated MR: Yu and colleagues [32] demonstrated that preoperative MR is proportional to the degree of LVOTO and relief of the LVOTO improved MR with no additional need for an operation. This is a persistent criticism of the RPR technique; that not all steps, particularly the mitral valve plication, are necessary for surgical treatment of HCM.

We believe that the selection criteria as described are an essential aspect of our study. The patients chosen for this repair had a specific morphologic elongation of the anterior leaflet of the mitral valve. The horizontally placed mitral valve sutures are used to plicate the leaflet and reduce the length, but more importantly, these sutures serve to stiffen the leaflet and prevent its excursion into the outflow tract (Fig 1). The sutures are placed near the base of the mitral valve, and the plication is created as an even row. Although there may be a difference in the millimeters of each plication –between 2 and 5, determined by the length of the leaflet– we believe it is the stiffening of the mitral leaflet that is the important contribution in this repair.



*Fig 1. Intraoperative photograph of mitral valve plication shows the ventricular side of the anterior leaflet of the mitral valve with the horizontal sutures in place, before tying of the sutures that stiffen the base of the anterior mitral leaflet.*

McIntosh and colleagues [13] first described mitral valve plication longitudinally in the antero-posterior orientation on selected patients who were judged to be at risk for residual SAM and obstruc-

ction. Our group has reasoned that the problem of the mitral valve is that it is too long in the anteroposterior direction. This repair shortens and stiffens the leaflet to limit its entry into the LVOTO.

Aside from persistent MR and SAM reported in the surgical literature, additional evidence supports the importance of the mitral valve in this disease. Failures occur after alcohol septal ablation in which persistent SAM is present due to anterior papillary muscle displacement that persists after ablation [33]. Furthermore, echocardiography has revealed a wide spectrum of mitral leaflet abnormalities in HCM: mitral leaflets are morphologically large in HCM and positioned anteriorly in the LV cavity [34-37]. The cause of SAM appears multifactorial and related to the geometry of the anterior leaflet [38]; it depends not only on its length and redundancy but also on the LVOT area and contraction of the LV [39]. The pathophysiology of the mitral valve component has to do with the pushing force of flow as the dominant hydrodynamic force along with the mitral leaflets being large and anteriorly positioned. SAM, in the setting of mitral septal contact combined with an element of chordal slack, provides an amplifying feedback loop that leads to further obstruction [15].

Limitations of this study include its small size. Although the follow-up was consistent, the average time of follow-up echocardiography is medium-term, because most patients were operated on within the previous 5 years. We were unable to compare these patients with a control group because they were selected for the RPR repair from their specific morphology and pathology, leading to an element of selection bias. Exact measurements of the length of mitral leaflet plication are currently being studied in a retrospective fashion using preoperative and postoperative TEE.

The RPR repair is a safe, reproducible, and effective method of treatment for symptomatic obstructive HCM. The operative risk is low, with marked improved in symptom relief and clinical outcomes.

## Discussion

**DR JOHN S. IKONOMIDIS** (Charleston, SC): Do you have any data from your institution comparing this technique, which is clearly a little bit more involved, to the standard myotomy/myectomy?

**DR BALARAM:** We have an additional 20 patients who have undergone a standard myotomy/myectomy as opposed to this group of patients. I think it is very important for people to realize that not every patient who comes in for an HCM [hypertrophic cardiomyopathy] repair should have this anterior leaflet plication. These are very specific patients. One hundred percent of them had systolic anterior motion and had measured elongated anterior leaflets of their mitral valve. Some patients come in with small, somewhat fibrotic, or calcified mitral valves that need replacement, and these patients were not included in this study. Because of the low numbers, we have not directly compared the two groups.

**DR EDWARD L. WOODS** (Danville, PA): That was an excellent presentation of a very difficult topic. Could you elaborate a little bit more on how you moved or manipulated the papillary muscles, which at times is one of the biggest aspects of this SAM [systolic anterior motion] and HCM?

**DR BALARAM:** The important part of the papillary muscles is to release any of the abnormal attachments between the papillary muscles and the wall. Sometimes the papillary muscles actually appear to be completely extruding from the wall itself, and in that situation we would try and thin the papillary muscles somewhat using a rongeur and let the papillary muscles fall more posteriorly so that the whole mitral valve apparatus would fall more posteriorly as well. Of course, it is also important to make sure and irrigate thoroughly to prevent any segments of muscle from causing a stroke in the future.

**DR HAROLD G. ROBERTS** (Lauderdale Lakes, FL): I enjoyed your presentation very

much. The plication of the anterior leaflet, I would like you to elaborate, if you would, more on what guidelines you use in determining how much to reduce the height of the anterior leaflet.

**DR BALARAM:** One of the problems with this anterior leaflet is the large amount of chordal slack. We base reduction of the anterior leaflet on the preoperative echo. We have not gone back to

measure the exact measurements pre- and postoperatively as far as the length of the mitral valve leaflet. We are actually working on that data right now. We use preoperative echo and intraoperative assessment with nerve hooks to determine chordal slack and elongation to typically plicate between 2 to 5 mm of the anterior leaflet.

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# Οι Ηθικές Αξίες στην Ιατρική Πράξη

Χρήστος Σπ. Μπαρτσόκας

*Το άρθρο αυτό είναι αφιερωμένο στον εκλεκτό φίλο, εξαίρετο επιστήμονα και πιστό στον Όρκο του Ιπποκράτη καρδιοχειρουργό, Κωνσταντίνο Αναγνωστόπουλο. Στα 54 χρόνια της γνωριμίας μας εντυπωσιακή ήταν η συνεχής αφοσίωσή του στον πάσχοντα με ηθική ακεραιότητα, υπευθυνότητα, σεβασμό και φιλανθρωπία. Το αποδεικνύει η μεγάλη ευγνωμοσύνη των παιδιών από την Ελλάδα, που χειρούργησε αφιλοκερδώς, τόσο στο University of Chicago, όσο και στο SUNY στο Stony Brook. Η προσφορά του Ντίνου Αναγνωστόπουλου στα ελληνόπουλα με συγγενή καρδιοπάθεια υπήρξε ανεκτίμητη. Ο Ντίνος τίμησε τον Όρκο σε υπέρτατο βαθμό!*

*Αισθάνομαι υπερήφανος για την φιλία μας!*

Αναμφισβήτητα, η ιατρική εξελίσσεται ταχύτατα με σκοπό να περιορίσει τη ραγδαία ανθρώπινη φθορά και, με μάταιη όμως προσπάθεια, να προλάβει τον βιολογικό θάνατο. Η πολιτεία προσπαθεί συνεχώς να ελέγξει και να περιορίσει με νόμους τις προόδους της επιστήμης και της τεχνολογίας, στο πλαίσιο της νομιμότητας της ηθικής και δεοντολογίας. Δυστυχώς, οι νόμοι αυτοί μετά την παρέλευση ετών τροποποιούνται, προσαρμοζόμενοι στις ανάγκες των πολιτών και της κοινωνίας. Όμως, υπέρτατος νόμος για τους γιατρούς παραμένει ο Όρκος του Ιπποκράτη.

Είναι παράδοξο, όμως, ότι ο Όρκος του Ιπποκράτη, ακόμη και έπειτα από 2.400 χρόνια από τη «γέννηση» του, παραμένει επίκαιρος και πρακτικά καλύπτει σχεδόν όλη την καθημερινή άσκηση της σύγχρονης ιατρικής.

## Από την προσωπική επαφή στην τεχνολογία

Αρχικά, η ιπποκρατική ιατρική εξέφραζε τα τέλεια συναισθήματα της ανθρώπινης ψυχής: συμπόνια, θυσία και προσφορά προς τον συνάνθρωπο. Στη διαδρομή της, όμως, η ιατρική απέκτησε νέες γνώσεις, με θυσίες, εγωισμό και φυσικές υπερβάσεις. Οι γιατροί, αρχικά ενεργούσαν ως λειτουργοί φιλανθρωπικής αποστολής, εξελίχθηκαν αργότερα σε επιστήμονες, στη συνέχεια σε επαγγελματίες υγείας και τώρα αποκτούν, δυστυχώς, και χαρακτηριστικά επιχειρηματιών.

Φυσικά, οι απαράβατες αρχές άσκησης του ιατρικού επαγγέλματος δεν έπαυσαν να ισχύουν επί αιώνες. Όπως είναι γνωστό, περιλαμβάνουν την τιμότητα, την αντικειμενικότητα, την ακεραιότητα, την επαγρύπνηση, την ειλικρίνεια, το σεβασμό για τη διανοητική περιουσία, την εμπιστευτικότητα και την υπευθυνότητα.

Φαίνεται όμως ότι η υγεία έχει ξεφύγει από τη φροντίδα του προσωπικού γιατρού και το βάρος της εξάσκησης αυτής έχει μετακινηθεί στις κλινικές, τις διαγνωστικές και τις θεραπευτικές μονάδες, στα απρόσωπα νοσοκομεία, ακόμη και σε κυβερνητικές υπηρεσίες. Ακόμη χειρότερα, και σε ασφαλιστικά ταμεία ή σε εταιρείες υγείας, που απορροφούν ανταγωνιστικά τους αρρώστους, συλλέγοντας πόρους, παράγοντας επιχειρηματικά ενδιαφέροντα, αντικαθιστώντας ανθρώπινα συναισθήματα και προσωπικές σχέσεις με συμβόλαια, συμφωνίες και καταναλωτικές αντιλήψεις!

### Ιατρική ηθική

Για τους παραπάνω λόγους η ηθική παραμένει μη διαπραγματεύσιμη αρχή στην άσκηση της ιατρικής και στις σχέσεις γιατρού – ασθενούς. Σύμφωνα με τον Αριστοτέλη (Ηθικά Νικομάχεια), «Η ηθική και η πολιτική αποτελούν πρακτικές επιστήμες και, τελικά, η ηθική είναι η ευτυχία του ατόμου, ενώ ο τελικός στόχος της πολιτικής είναι η ευτυχία του κράτους συνολικά. Η ηθική είναι πρακτική επιστήμη, της οποίας το ενδιαφέρον συνίσταται στο απώτερο καλό των ανθρώπων... Γενικά, υφίσταται συμφωνία ότι το όνομα του καλού σκοπού είναι ευτυχία. Συνεπώς η ηθική είναι επιστήμη που ακολουθείται με σκοπό την ευτυχία».

Οι τέσσερις βασικές αρχές της ιατρικής ηθικής (να ωφελείς, να μη βλάπτεις, η αυτονομία του ατόμου και η δικαιοσύνη) έχουν οδηγήσει τον ιατρικό κλάδο σε ενδόμυχες εσωτερικές αρετές, όπως η φιλανθρωπία, η συμπόνια, η μακροθυμία, η ανεκτικότητα, στο επίκεντρο των οποίων είναι η αρετή της αγάπης. Μέσω της φιλανθρωπίας, η θεραπευτική φροντίδα αναβαθμίστηκε σε πράξη συμπόνιας και καλοσύνης και το ιατρικό επάγγελμα σε λειτούργημα και προσφορά.

Ο γιατρός σήμερα πρέπει και να τολμά ακόμη την υπέρβαση στην προσήλωση σε αναχρονιστικούς νόμους, στην πολιτική υγείας, στην οικονομική επιστήμη, όταν αυτοί επηρεάζουν θεραπευτικές στρατηγικές, ενώ απομακρύνονται από την αυθεντική φροντίδα υγείας.

Σύμφωνα με τις ιπποκρατικές απόψεις, οι γιατροί ασκούν την επιστήμη τους μέσα σε ένα λογικό και ηθικό πλαίσιο. Η θεραπευτική αποτελεί ένα λογικό επάγγελμα με ρίζες στη συμπόνια. Ο συνδυασμός, όμως, οικονομίας και υγείας οδηγεί σε απροσδόκητες εξελίξεις την ιατρική τεχνολογία (π.χ. PET, MRI, laser, γονιδιακή τροποποίηση κ.λ.π.) Έτσι, η συμβολή του γιατρού σήμερα είναι τεχνολογική, μη λησμονώντας όμως τη βασική προσωπική σχέση και την κοινωνική αντίληψη της ανθρώπινης υπάρξεως.

Ηθικοί γιατροί ασκούν ηθική ιατρική (Bill Wolf). Στο επίκεντρό της η ιατρική είναι μια ηθική επιχείρηση βασισμένη σε συμβόλαιο εμπιστοσύνης. Σήμερα, το συμβόλαιο αυτό της εμπιστοσύνης απειλείται σημαντικά. Αυτός είναι ο λόγος που απαιτούνται αξιολογήσεις και μετρήσεις ποιότητας. Ο τέως Editor-in-Chief του περιοδικού «The New England Journal of Medicine», Jerome P. Kassirer, έγραφε: «Μετρήσεις της ποιότητας που υφίστανται σήμερα είναι ακόμη αρκετά επιπόλαιες και αναξιόπιστες και αναμφισβήτητα θα βελτιωθούν, οι διαφορές ποιότητας ... είναι τόσο λεπτές, που μάλλον θα διαφεύγουν από τις πλέον εξελιγμένες τεχνικές μετρήσεις στο μέλλον».

### Η ιπποκρατική άποψη της ιατρικής – άποψη δυόμιση χιλιετηρίδων, είναι:

- Ειδική σχέση γιατρού-ασθενούς, υπόσχεση, συνεχή υποστήριξη και αφοσίωση στις ανάγκες και στην προσωπικότητα του ασθενούς.
- Ηθική υποχρέωση παροχής βοήθειας που πηγάζει από τη μοναδικότητα και την εσωτερική αξία που χαρακτηρίζει την ανθρώπινη ζωή.

Οι γιατροί αφοσιώνονται στο να πράττουν το ορθό για τους ασθενείς τους, να τους προστατεύουν, να τους ενημερώνουν για όλες τις διαθέσιμες θεραπευτικές δυνατότητες.

### Τι υψώνει ένα επάγγελμα σε επιστήμη;

- Ύπαρξη και εφαρμογή ατέγκτου κώδικα ηθικής.

- Ξεχωριστό σώμα γνώσεων.
- Παρατεταμένη ισόβια περίοδος εκπαίδευσης και άσκησης.

Η ανθρώπινη αξιοπρέπεια και η ακεραιότητα συνιστούν σημαντικές αξίες για την προαγωγή ελεύθερης, αλλά και υπεύθυνης επιστημονικής προσπάθειας.

Παρότι μεσολάβησαν τόσοι αιώνες από την

καθιέρωσή του, ο όρκος του Ιπποκράτη συνεχίζει να αποτελεί τον τελειότερο και τον πληρέστερο κώδικα άσκησης της ιατρικής επιστήμης. Νόμοι θα έρχονται και θα παρέρχονται, θα βελτιώνουν και θα συμπληρώνουν τη δεοντολογία, αλλά είναι αμφίβολο πως θα υπερκαλύψουν τις ηθικές αξίες του όρκου!

### Abstract

#### **Bartsocas CS: «The moral values in medical practice».**

Medical practice is moving ahead fast, with benefits promoting health and prolonging survival. Nonetheless, new laws and revisions are constantly needed to ensure ethical practice of health – care personnel. Although over 2.400 years have elapsed since its initiation, the Hippocratic Oath is still strong and applies to everyday medical care of patients. Technological advances may need laws , but the moral values and ethical practice have not changed as an eternal covenant over the past 24 centuries.



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# Purulent Meningococcal Pericarditis: Chronic Percutaneous Drainage with a Modified Catheter Aided by Echocardiography

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## Summary

A 7-month-old infant presented with suspected sepsis. On the third day of illness signs of cardiac tamponade developed. Tamponade was relieved by pericardiocentesis, and countercurrent immunoelectrophoresis (CIE) analysis of the fluid was positive for meningococcus group B. Antibiotic treatment was changed to penicillin G. After echocardiography demonstrated reaccumulation of fluid, a modified #16 gauge angiocatheter was placed percutaneously in the pericardial space. When drainage slowed it was repositioned using two-dimensional echocardiography. After 24 h the catheter was removed and no further accumulation occurred. The antibiotics were continued an additional 10 days and the infant recovered uneventfully. Modification of the catheter and echographic repositioning may decrease the need for surgical drainage in such patients.

**Key words:** purulent pericarditis, chronic percutaneous pericardial drainage, meningococcal pericarditis

## Introduction

Purulent pericarditis in children is an uncommon but potentially life-threatening disease. We recently diagnosed a case of meningococcal pericarditis by countercurrent immunoelectrophoresis (CIE) and treated it with penicillin and percutaneous catheter drainage (PC).

## Case Report

A 7-month-old infant was admitted to another hospital for suspected sepsis with high fever (41.1°C) and polymorphonuclear leukocytosis (28,000 white blood cell count). Initial evaluation included a lumbar puncture (85 red blood cell [RBC] and 2 WBC/mm<sup>3</sup>, glucose 98 and protein

13 mg/dl), and cultures of cerebrospinal fluid (CSF), blood, throat, and urine. The serum electrolytes were normal and the chest x-ray showed normal heart size and contour. The infant was initially treated with intravenous ampicillin 200 mg/kg per day for suspected bacteremia. Initially the temperature fell to a range of 38 to 37.5°C. All cultures were subsequently negative. Past history was remarkable only in that the infant had tracheomalacia.

On the third day of illness the infant developed tachypnea, dyspnea, and tachycardia. The heart sounds became distant and a chest x-ray showed cardiomegaly. The ECG showed low voltage and ST-T-wave changes suggesting pericarditis. The infant was then transported to the Pediatric Intensive Care Unit at Stony Brook because of suspected purulent pericarditis.

On admission to University Hospital the infant was alert, pale, and in moderate respiratory distress with grunting. The respiratory rate was 40 and the heart rate 158 beats/min. Blood pressure was 129/

88 by Dynamap and temperature was 38.8°C. Examination of the head and neck revealed a soft flat anterior fontanelle, rhinitis, and no appreciable jugular venous distention. There were rhonchi bilaterally and the heart sounds were muffled. No murmur was appreciated. The liver was enlarged with a firm edge extending 7 cm below the right costal margin. Edema of the hands and ankles was noted.

A two-dimensional echocardiogram was obtained immediately, and demonstrated a large (1.5 cm) pericardial effusion both anteriorly and posteriorly (Fig. 1). Pericardiocentesis was performed and 50 cc of yellow green, cloudy fluid was obtained. Peripheral perfusion and respiratory status immediately improved and the heart rate fell from 160 to 130 beats/min. The fluid contained 2276 WBC/mm<sup>3</sup> [98% polymorphonuclear neutrophil leukocytes (PMNs)], a glucose of 61 mg/dl, and a protein of 4 g/dl. The ampicillin was increased to 300 mg/kg per day, and chloramphenicol 100 mg/kg per day and o-

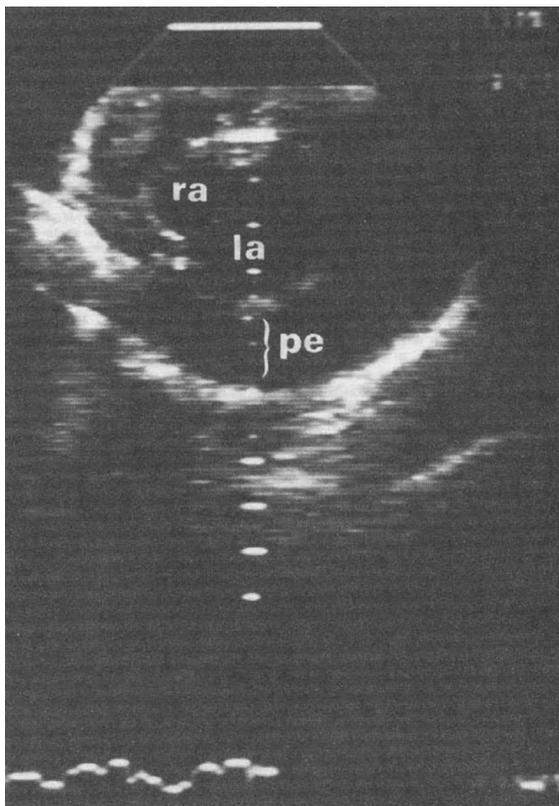


Fig. 1. Two-dimensional echocardiogram in the subcostal four-chamber view showing 1.5 cm pericardial effusion (pe). la = left atrium, ra = right atrium.

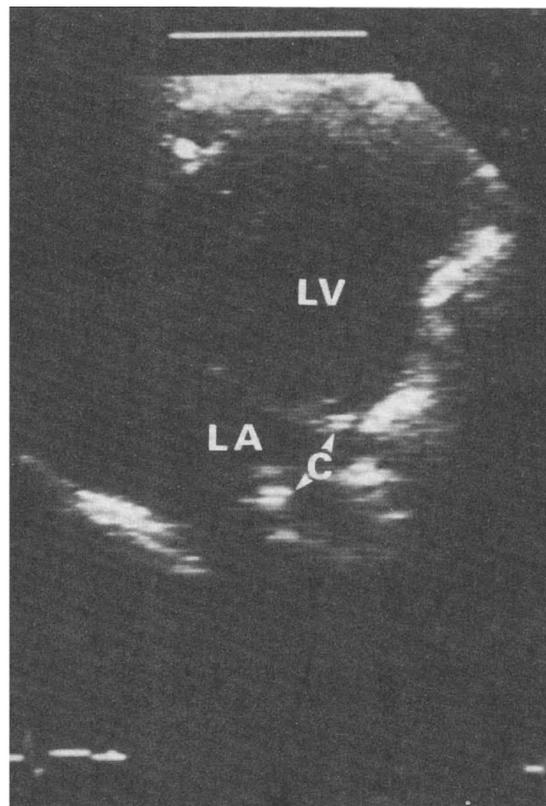


Fig. 2. Two-dimensional echocardiogram in the apical four-chamber view showing the catheter (C) curved (arrows) behind the left atrium (la). ra = right atrium.

xucillin 200 mg/kg per day added. Several hours later CIE of the pericardial fluid was positive for meningococcus group B. AH blood, CSF, and pericardial fluid cultures were negative. Purified protein derivative (PPD) was nonreactive. The previous antibiotic regimen was discontinued and 400,000 U/kg per day of aqueous penicillin G was begun. The infant became afebrile after 8 hours.

A repeat echocardiogram 10 hours after the initial tap showed reaccumulation of fluid. Repeat pericardiocentesis was performed using a #16 angiocatheter (Deseret) in which additional holes were created in the side of the catheter to enhance drainage. This was inserted over a floppy-tipped Teflon-coated guide wire and left in the pericardium, and 120 ml of yellow fluid was immediately obtained (155 WBC/mm<sup>3</sup> with 44% PMNs, 56% mononuclear cells, glucose 31 mg/dl, and protein 4 g/dl). Over the next 24 hours, 80 ml were drained. At one point two-dimensional echocardiography was used to reposition the catheter anteriorly when the drainage slowed (Fig. 2). A repeat echocardiogram showed minimal fluid and the catheter was removed after being in place for 24 hours.

The infant's clinical status remained good and follow-up echocardiogram at 4 days showed a minimal amount of fluid (2-4 mm posteriorly). The child received an additional 10 days of penicillin and was discharged after 14 days. Clinical exam two months later remained normal and echocardiography showed no fluid and normal cardiac function.

## Discussion

A large #16 gauge catheter with additional holes created on the side was used to enhance drainage. This was flushed intermittently each hour with 1 ml of heparin in an effort to prevent plugging. It has been suggested by Morgan et al. (1983) and more recently by Lock et al. (1984) that PC can be successful. Failures were due to the effusion becoming loculated and/or too thick. We believe that modification of the catheter by adding holes on the side can improve the chances of success for PC drainage.

Two-dimensional echocardiography not only allowed rapid confirmation of the clinical diagnosis, but also enabled us to reposition the catheter to a more favorable position by echocardiographic guidance when drainage slowed. This may improve the success of PC drainage because the catheter can be manipulated to obtain optimal drainage.

Countercurrent immunoelectrophoresis can be helpful in identifying certain etiologic agents when the cultures are negative and/or the patient has been pretreated with antibiotics. Purulent meningococcal meningitis has been diagnosed using CEE in a 49-year-old woman whose cultures were negative (Simon et al., 1976). Cultures of the cerebrospinal fluid and blood taken before treatment in this infant were negative. The pericardial fluid culture was negative and so the positive CIE results for meningococcus group B allowed the choice of a specific antibiotic regimen.

In summary, purulent meningococcal pericarditis was diagnosed by CIE in a 7-month-old despite negative cultures. Successful PC drainage was aided by two-dimensional echocardiographic repositioning of a modified catheter.

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*Bilfinger Thomas V.*

# A Little Monograph

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In 1975, a little monograph was published entitled “Acute Aortic Dissections.” This book has 255 pages, which is small by medical standards, and even more remarkable is that at the time, it cost \$24.50. It is a monograph based on some original work and also on some insights gained a year earlier from a conference. In November 1974, the University of Chicago sponsored a series called “Frontiers of Medicine”. At that particular conference, one topic was ‘Lethal Diseases of the Ascending Aorta’ and world-renowned specialists got together to discuss acute aortic dissections as one of the topics. Present at that conference were, among others, Randall Griep, Roque Pifarre, Victor Makusic, John Lamberti, David Sabiston, Norman Shumway, David Skinner, Denton Cooley and Robert Replogle, just to name a few. We should not forget Leon Resnekov, the world renowned Chief of Cardiology at that time at the University of Chicago.

As a foreword, the author chose a saying attributed to Hippocrates of Kos: “Life is short, art is long, opportunity fugitive, experimenting dangerous, reasoning difficult: It is necessary not only to do oneself what is right, but also to be seconded by the patient, by those who attend him, by external circumstances.” This seems to summarize in a few words what has happened with aortic dissections over the last forty years.

This little book is regarded as the first comprehensive clinical treatise on acute aortic dissection in modern times. At that time, it was very common that this condition was still misnamed and called dissecting aortic aneurysm, which we know today is not the case. At the time this book was written, the author had experience with 36 patients with aortic dissections, either operated on in the Yale, New Haven Hospital, or at the University of Chicago. This then led to a collection of patients from the literature and from discussion with colleagues. The world-renowned figure on page 130 is often quoted today. It obviously stems from a time where no treatment was offered and therefore no longer necessarily reflects what happens today with modern anti-impulse therapy. However, it is still widely taught throughout the world that an acute ascending aortic dissection has a mortality of 1% per hour for the first 48 hours. Out of this work came the insight that dissection of the ascending aorta behaves differently and has a different outcome than dissections of the descending aorta, which is an opinion propagated by Dr. Shumway at the time and led to the now well-known Stanford classification. For the first time, it was unequivocally stated that the common cause of death of ascending dissections is free perforation and cardiac tamponade, as well as dissection of the coronaries. Further, it was noted that valvar insufficiency is

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also a common cause of death. It was unequivocally stated in that book that ascending aortic dissections constitute a surgical emergency. It was estimated for the first time in the book that the incidence is 3 per 100,000 people. The anatomy, embryology and physiology section of the book is as valuable today as it was 40 years ago. At the end, there is a brief chapter on outlook on the future where it was proposed to create a registry. It is interesting that it took almost 40 years for IRAD to take up this notion.

So what has happened since? Acute aortic dissection remains a life threatening event. As the author has clearly stated, it results from a tear in the intimal layer of the aorta. Blood dissects between the intima and media creating a false and a true lumen. It is the most lethal disease affecting the aorta. As was clearly stated by the author back in 1975, this occurs from rupture, either free or into the pericardium, sudden aortic valve incompetence, myocardial infarction from shearing off of coronary arteries and cerebral or visceral ischemia. It is estimated that 21% of patients die before ever reaching a hospital. It has been confirmed since by population-based estimates, the incidence is 2 to 4 cases per 100,000 people per year. The life-threatening emergency nature of this problem does not lend itself easily for prospective randomized trials. Our understanding is entirely based on registry data and on individual efforts undertaken to understand the molecular biology and the genetics. However, why a dissection occurs at any given moment in time is still unclear.

### Circadian Variation

In recent times, we have learned through at least three studies that there seems to exist a circadian rhythm of spontaneous aortic dissection. The first study by Gallerani et al., describes 70 patients with a statistically significant circadian variation with a mean morning peak between 8 and 10 am, and then a second peak in the early evening hours around 8 pm. Subsequently, Sumiyoshi et al., de-

scribed a weaker diurnal variation in a larger population of 312 patients with a peak occurrence between 8 and 11 am, and a second peak in the evening between 5 and 7 pm. The largest study comes from the IRAD Registry where 689 patients were reviewed. A morning peak between 8 and 9 am was found. The circadian variation was present in all subgroups, including male, female, type A or type B dissections, younger or older age, and presence or absence of hypertension.

### Seasonal Variation

Vascular events with regard to seasonal variation have been studied for decades with varying methods. With regard to aortic dissection, there is less data, but there have been a number of studies over the last decade. Sumiyoshi et al. found the highest incidence in winter with the lowest incidence in summer. The highest frequency months were December, January and March and a 2.9-fold increase was found in January when the incidence was the highest compared to August with the lowest incidence. The IRAD study also found the peak incidence to be in January with the trough in summer. A smaller regional study enrolling 389 patients from Switzerland demonstrated a difference between type A and type B dissection, again with the type A having the highest incidence in winter while the type B had a delayed incidence in spring.

### Weekly Variation

There is only scant data available with regards to weekly rhythm for aortic dissection. However, the two above-mentioned papers by Sumiyoshi and IRAD have data that addresses this issue. While Sumiyoshi found a small peak on Monday with an overall homogeneous distribution, the IRAD study did not find any significant weekly variation in the occurrence. Sumiyoshi estimated the risk for acute aortic dissection on Monday to be 10.3% higher than if one would assume homogeneity.

It is interesting to note at this point that other vas-

cular catastrophes also have circadian rhythm. For instance, strokes seem to occur between 6 am and 12 noon. A similar predication of seasonal occurrence of any type of cerebral vascular accident in the winter months has also been well documented. Maybe the most expansively studied subject is the occurrence of myocardial infarctions. Again, clearly a circadian and seasonal pattern emerges. The early hours of the morning are the most dangerous with regard to myocardial infarction. Predilection of myocardial infarction to occur during the colder season is also well documented. Several investigators have further documented in large studies the preference for a myocardial infarction to occur on Monday. Perhaps the earliest data documenting a circadian rhythm for sudden cardiac deaths in a large population study stems from the Framingham study population.

A circadian rhythm to blood pressure has been observed and documented over 30 years ago. It has been shown that blood pressure reaches peak values in the morning with a second although less pronounced peak in the late afternoon or early evening. A close linkage between diurnal blood pressure and cardiovascular events has been proposed. Further, it has long been recognized that the heart rate shows a diurnal pattern as well with peak in the morning. While it is undisputed that blood pressures are elevated in the morning, the rise with regard to sleep and awake patterns is still being debated. It is entirely conceivable that there are two patterns depending on age. It has been observed that in elderly people, blood pressure seems to rise with the initiation of physical activity. In younger people, a pattern of gradual increase before awakening is being discussed. These findings are consistent with a circadian rhythm in vascular tone. Obviously, these findings have been linked to the well-known diurnal pattern of hormonal secretions, such as plasma norepinephrine levels and plasma cortisol levels with its sharp increase in the morning and the finding of a diurnal plasma renin pattern. Maybe less well known, but of similar importance, is the diurnal varia-

tion in effectiveness of coagulation and fibrinolysis. It is easy to speculate that during the time of increased shear stress due to the above mentioned mechanisms further weakened by acquired disorders, aging and in some cases, genetic predisposition, an imbalance between coagulation and fibrinolysis coincides, possibly leading to these catastrophic events. Hematocrit and fibrinogen, as well as plasma viscosity and platelet aggregability have been found to co-exist simultaneously with reduced fibrinolytic activity. Vascular shear stress during winter months appears to be increased, leading to further damage of the vascular endothelium, culminating possibly in aortic dissection, rupture or stroke. It is well known that low ambient temperature has hypertensive effects. The pulse pressure during peripheral vasoconstriction increases with little change to overall cardiac output, thus enhancing shear stress. Hematocrit, platelet count as well as viscosity and coagulation increase even during mild surface cooling. Fibrinogen levels have been found to increase during colder months, up to 23%.

## Treatment

It is astounding to point out that 40 years after this book was published, most efforts have gone into treatment. On a systematic level, the insights gained into treatment stem to a large part from the IRAD consortium, which constitutes of a number international institutions with a particular interest in aortic dissections. Maybe thanks to that consortium, the last decade has seen an unprecedented increase in interest in this subject. However, on a national basis, there remains very few efforts to gain insight on how this condition is dealt with. The two countries with probably the most advanced data in this regard are Japan and Germany. For instance, we learned from the newest edition of the German registry that type A aortic dissection repair in Germany carries a 10% mortality, which increases sharply after age 75. We are on the verge of a paradigm shift in treatment with endoluminal solutions being tried out

on a daily basis, not only for B dissections, but A dissections as well. Because of our progress, we have become aware of long-term problems such as the distal arch, which seems to be the weakest spot in type A repairs. The fundamental question, however, why does an acute aortic dissection occur at any given moment is not answered. Also not answered is the question in whom does an acute aortic dissection occur. How can these patients be identified early, and how can they be treated prophylactically before such a catastrophic event occurs?

A little book of 250 pages published back in 1975 can claim to have been an important stepping stone in the unprecedented interest and development in the treatment and understanding of aortic dissections.

*“The man whose thoughts and feelings are enlarged by history will wish to be a transmitter, and to transmit, so far as may be, what his successors will judge to have been good.”*

Bertrand Russell (1872-1970)

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# Application of the International Society for Heart and Lung Transplantation (ISHLT) criteria for primary graft dysfunction after cardiac transplantation: outcomes from a high-volume centre†

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## Abstract

**OBJECTIVES:** A standardized definition for primary graft dysfunction (PGD) after cardiac transplantation was recently proposed by the International Society of Heart and Lung Transplantation (ISHLT). We sought to characterize the outcomes associated with and identify risk factors for PGD following cardiac transplantation using these criteria at a high volume centre.

**METHODS:** Donor and recipient medical records of 201 consecutive adult cardiac transplantations performed between November 2012 and March 2015 were retrospectively reviewed. Patients undergoing isolated heart transplantation were diagnosed with none, mild, moderate, or severe PGD using ISHLT criteria. Cumulative survival was calculated according to the Kaplan–Meier method. Associations of risk factors for combined moderate/severe PGD were assessed with univariate and multivariate analyses.

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**RESULTS:** A total of 191 consecutive patients underwent isolated heart transplantation, and 59 (30%) met ISHLT criteria for PGD: 35 (18%) mild, 8 (4%) moderate and 16 (8%) severe. Thirty-day/in-hospital mortality occurred in six (3%) patients, all of whom were diagnosed with severe PGD. Patients with moderate/severe PGD also had significantly increased intensive care unit length of stay (LOS), total LOS, reoperations for bleeding and postoperative infections. Survival at 1-year was diminished with increasing severity of PGD (none 93%, mild 94%, moderate 75% and severe 44%; log-rank  $P < 0.001$ ). Elevated preoperative creatinine, pretransplantation hospitalized recipient and undersized donor were independently predictive of moderate/severe PGD.

**CONCLUSIONS:** A diagnosis of PGD portends worse outcomes including increased 30-day and 1-year mortality. The ISHLT diagnostic criteria for moderate and severe PGD identify and discriminate patients with PGD in a clinically relevant manner.

**Keywords:** Cardiac transplantation • Primary graft dysfunction • Donor selection

## INTRODUCTION

Primary graft dysfunction (PGD) is the most common cause of death within 30 days of cardiac transplantation [1]. The most recent report from the International Society for Heart and Lung Transplantation (ISHLT) Registry reported that 42.6% of deaths within 30 days after transplant were due to PGD [2]. Due to the lack of standardized criteria for its diagnosis, the incidence of PGD reported in the literature has varied widely between 2 and 24% [3–7]. Proposed definitions have included various diagnostic criteria including timing of onset, echocardiographic evidence, haemodynamic measures and/or requirements for inotropic or mechanical support. The inconsistency in applied definitions prevents generalization of results from one centre and/or era to others. The lack of standardization has also resulted in the identification of dozens of donor, recipient and procedural factors that may increase the risk for PGD [8].

To address this issue, the ISHLT recently published a consensus document with standardized criteria for PGD diagnosis following cardiac transplantation [9]. The ISHLT consensus committee also emphasized that the diagnosis of PGD must be made within 24 h after completion of the transplantation surgery and that other discernible causes such as hyper-acute rejection, pulmonary

hypertension, or known surgical complications must be ruled out in order to diagnose PGD. The new ISHLT criteria for PGD must be validated in a sample cohort, but the major transplantation databases [United Network for Organ Sharing (UNOS) and Eurotransplant] have not incorporated these criteria to document PGD. Therefore, the aim of this study is to validate the ISHLT criteria through their application to a series of adult cardiac transplantations from a high volume centre by: (1) determining the impact of PGD on outcomes up to 1-year following transplantation and (2) identifying risk factors for the development of PGD.

## METHODS

### *Patients and definitions*

This study was approved by the Institutional Review Board at Baylor University Medical Center, and informed consent was waived given the retrospective nature of the study. The medical records of 201 patients undergoing heart transplantation procedures from November 2012 to March 2015 were reviewed. Those who underwent multi-organ transplants were excluded (six kidney/heart, three liver/heart and one heart/lung). Information about the respective donors was also reviewed. Recipient characteristics examined were

**Table 1:** ISHLT definition of severity scale for primary graft dysfunction

PGD left ventricle (PGD-LV):	<p><i>Mild PGD-LV:</i> one of the following criteria must be met:</p> <p><i>Moderate PGD-LV:</i> must meet one criterion from I <i>and</i> another criterion from II:</p> <p><i>Severe PGD-LV</i></p>	<p>LVEF <math>\leq</math> 40% by echocardiography, <i>or</i> Haemodynamics with RAP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup> (lasting more than 1 h) requiring low-dose inotropes</p> <p>I. LVEF &lt; 40%, <i>or</i> Hemodynamic compromise with RAP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup>, hypotension with MAP &lt; 70 mmHg (lasting more than 1 h)</p> <p>II. High-dose inotropes—inotrope score &gt; 10<sup>3</sup>, <i>or</i> Newly placed IABP (regardless of inotropes)</p> <p>Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.</p> <p>i. Haemodynamics with RAP &gt; 15 mmHg, PCWP &lt; 15 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup></p> <p>ii. TPG &lt; 15 mmHg and/or pulmonary artery systolic pressure &lt; 50 mmHg</p> <p>iii. Need for RVAD</p>
PGD right ventricle (PGD-RV):	Diagnosis requires either both i and ii, or iii alone:	

Adopted from [9].

BiVAD: biventricular assist device; CI: cardiac index; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; MAP: mean arterial pressure; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; PCWP: pulmonary capillary wedge pressure; PGD: primary graft dysfunction; RAP: right atrial pressure; RVAD: right ventricular assist device; TPG: transpulmonary pressure gradient.

<sup>a</sup>Inotrope score = dopamine ( $\times 1$ ) + dobutamine ( $\times 1$ ) + amrinone ( $\times 1$ ) + milrinone ( $\times 15$ ) + epinephrine ( $\times 100$ ) + norepinephrine ( $\times 100$ ) with each drug dosed in  $\mu\text{g}/\text{kg}/\text{min}$ .

demographics, etiology of heart failure, comorbidities, mechanical assistance prior to transplant, UNOS status, cytomegalovirus (CMV) status, prior sternotomy, wait list time and subjective global assessment (SGA) score. Donor characteristics included demographics, cause of death, donor heart measurements and haemodynamics, CMV status and rates of prior cardiopulmonary resuscitation (CPR). Procedural characteristics included donor/recipient size mismatch [by weight ratio, body weight percent difference and predicted heart mass (pHM) percent differences], distance of donor centre from recipient centre and cold ischemia time. pHM was calculated using previously published equations that incorporate height, weight, age and sex to account for variations in heart mass due to gender and age at a constant body mass [10–12]. Donor/recipient percent difference measurements were calculated as follows:

$$[(\text{Measure}_{\text{recipient}} - \text{Measure}_{\text{donor}}) / \text{Measure}_{\text{recipient}}] \cdot 100$$

The ISHLT recently published standardized criteria to diagnose PGD following cardiac transplantation (Table 1) [9,13]. The ISHLT consensus committee introduced two new features to the diagnosis of PGD that had not been previously reported in the literature: (i) a distinction between PGD due to left ventricular or biventricular failure (PGD-LV) and PGD due to right ventricular failure (PGD-RV) and (ii) a 3-level grading system

for PGD-LV. Despite the ISHLT consensus committee's recommendation for a distinction between PGD-RV and PGD-LV, it was not feasible to incorporate this distinction in our study. Specifically, our centre's clinical approach to patients with evidence of PGD precluded such analysis. The haemodynamic criteria used to distinguish PGD-RV from PGD-LV rely on measurements not routinely collected at our centre, particularly pulmonary capillary wedge pressure (PCWP), due to safety concerns regarding the serial acquisition of such metrics by non-physicians. Additionally, no right ventricular assist devices (RVADs) were placed in our patient cohort because extracorporeal membrane oxygenation (ECMO) therapy has become our preferred therapeutic modality for all patients who require support beyond maximum inotropic therapy. Patients were therefore assigned only to none, mild, moderate, or severe PGD-LV based upon the ISHLT criteria within the first 24 h after the completion of the transplantation procedure. In order to facilitate statistical analysis, patients were separated into two groups: none/mild PGD and moderate/severe PGD. Infectious complications following transplantation were catalogued as previously defined [14].

### ***Transplant criteria and immunosuppression***

The same transplantation protocol was implemented throughout the study period. A cardioplegia needle was inserted into the ascen-

ding aorta at the initiation of organ procurement. The ascending aorta was cross-clamped, and 2 L of Belzar UW solution was used to arrest the heart. The organ was closely inspected for any pathology after cardiectomy. Then, the donor heart was placed in a sterile container, and transported in a portable cooler on ice. After the organ arrived to our centre, it was removed from the container and placed into the operating field. A 500 mL volume of cardioplegia was administered down the aortic root immediately prior to implantation. Intermittent doses of cardioplegia were given between each anastomosis, and orthotopic heart transplantation was performed using the bicaval technique. The same immunosuppression protocol was prescribed to all patients throughout the study period. At the time of transplantation, recipients were given mycophenolate mofetil 2 g intravenously [IV; or 1 g IV if white blood cell count (WBC) less than  $4 \times 10^3/\text{mL}$  or recipient age over 60] and solumedrol 1 g IV in the operating room. They also received a single dose of basiliximab 20 mg IV in the operating room and again on postoperative day 4. During the first 24 h after surgery, patients received mycophenolate mofetil 1 g IV every 12 h (or 500 mg every 12 h if WBC less than  $4 \times 10^3/\text{mL}$  or recipient age over 60) and methylprednisolone 125 mg IV every 8 h. Thereafter, patients receive a steroid taper [methylprednisolone IV, transitioned to prednisone taper orally (PO) starting at 1 mg/kg], an antiproliferative agent (mycophenolate mofetil 1000 mg PO every 12 h), and a calcineurin antagonist (tacrolimus PO with doses targeted to goal levels of 12–15 ng/mL in the first 3 months post-transplant, 10–12 ng/mL in months 3–6, 8–10 ng/mL in months 6–12, and 4–8 ng/mL after 1 year).

### *Statistical analysis*

Recipient-related, donor-related and procedure-related characteristics were summarized and compared for their association with moderate/severe PGD. These univariate associations were tested for statistical significance by using  $\chi^2$  test for categorical data or Wilcoxon ranksum test for continuous variables. All statistical analyses were

performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Univariate logistic regression results were used as a conservative screening tool to identify a subset of potential predictors for moderate/severe PGD. Donor, recipient and procedure characteristics related to moderate/severe PGD at values of  $P < 0.25$  were tested for inclusion in the final multivariate analysis. Multivariate logistic regression was used to adjust for potential confounding. A stepwise Akaike information criterion (AIC) best-subsets approach was used to identify the final multivariable model. The approach facilitates selection among AIC optimal models based on clinical and statistical considerations [15]. Final results are expressed as multivariate odds ratios (OR) and 95% confidence intervals (CI). The Kaplan-Meier method was used to estimate cumulative survival up to 1-year after cardiac transplantation procedure. Patient survival curves were compared using the log-rank test.

## RESULTS

During the 30-month study period, we performed 191 consecutive, isolated heart transplantation procedures. The mean recipient age at the time of transplantation was  $57 \pm 11$  years (range 42–65 years) and 25% of patients were female. The etiology of heart failure was evenly divided between ischemic cardiomyopathy (50%) and non-ischemic cardiomyopathy (50%). The recipient UNOS statuses were recorded as: 1A (38%), 1B (53%) and 2 (9%). Mean allograft hypothermic ischemic time was  $228 \pm 61$  min.

A total of 59 (30%) patients were diagnosed with PGD using the ISHLT criteria: 35 (18%) mild, 8 (4%) moderate and 16 (8%) severe. Patients were grouped into none/mild PGD and moderate/severe PGD groups for statistical comparisons. Recipient-related, donor-related and procedure-related variables for each group are summarized in Table 2.

Postoperative outcomes and complications for each group are summarized in Table 3 [16]. There were six (3%) in-hospital/30-day mortalities in the cohort, all of which occurred in patients with

severe PGD. Thus, short-term mortality was much higher in the moderate/severe PGD group (25%) as compared to the none/mild PGD group (0%). Patients diagnosed with moderate/ severe PGD developed more postoperative infections (pneumonia, sepsis and mediastinitis), required more transfusions and reoperations for bleeding, experienced a higher rate of acute renal failure requiring dialysis and had increased inotrope scores (Table 3). Patients who developed moderate/severe PGD also had longer intensive care unit (ICU) length of stay (LOS;  $22 \pm 21$  days vs  $4 \pm 6$  days,  $P < 0.001$ ) and total postoperative LOS ( $27 \pm 20$  days vs  $11 \pm 9$  days,  $P < 0.001$ ) as compared to patients with none/ mild PGD.

Survival to 1-year post-transplantation was diminished with increasing severity of PGD (Fig. 1; none 93%, mild 94%, moderate 75% and severe 44%; log-rank  $P < 0.001$ ). The survival curves diverged during the first 3 months following transplantation, but were similar after this initial postoperative period. To analyse the duration of the effect of PGD on survival, we also estimated conditioned mortality monthly following transplantation. Patients who survived 1 and 2 months following transplantation still demonstrated increased mortality with increasing severity of PGD (log-rank  $P = 0.002$ ). However, the conditioned survival estimates at 3-months post-transplantation was not significantly different between PGD severities (log-rank  $P = 0.37$ ).

The following preoperative variables were associated with moderate/severe PGD by univariate logistic regression analysis ( $P < 0.05$ ): increased recipient body mass index, elevated pre-operative creatinine, recipient hospitalized at the time of transplantation, ischemic cardiomyopathy, and undersized donor (by difference in pHM  $\geq 30\%$ ) and requirement for ECMO prior to transplantation (Table 4). Although a requirement for ECMO support prior to transplantation was a significant univariate predictor of moderate/severe PGD, this factor was precluded from subsequent multivariate analysis given the limited number of patients in the study cohort requiring pretransplant ECMO (5/191; 2.6%). Upon multivariate logistic regression analysis, elevated preoperative creati-

nine, undersized donor (by difference in pHM  $\geq 30\%$ ), and recipient hospitalized at the time of transplantation were independently associated with moderate/severe PGD. A graphical representation of the multivariate adjusted probability of moderate/severe PGD according to these variables is presented in Fig. 2. The model is highly discriminative (c-statistic = 0.765).

## DISCUSSION

PGD is the most common cause of death following cardiac transplantation [1]. Due to a lack of standardized criteria for PGD diagnosis, previous studies have reported widely variable rates of PGD and dozens of potential risk factors for this complication [2–8]. Recently, the ISHLT proposed a standard set of criteria for the diagnosis of PGD to address this issue [9]. To the authors' knowledge, our report is the first to apply the new ISHLT criteria to a series of patients in order to examine outcomes of and identify risk factors for PGD at a high volume transplant centre.

In our series of 191 consecutive, isolated cardiac transplantations performed within a 30-month period, the total incidence of PGD was 30%. Severity of PGD in this cohort was stratified to mild (18%), moderate (4%) and severe (8%). Other reports have described incidences of non-stratified PGD ranging from 2 to 24% [2–7]. Although the total incidence of PGD in our cohort is the highest reported in any study of adult patients, this likely reflects the liberal criteria for PGD proposed by the ISHLT. The ISHLT recognized that this definition would result in a significant number of patients being diagnosed with PGD, and therefore the committee stratified the diagnosis of PGD into mild, moderate and severe classifications [9].

The variety of non-stratified diagnostic criteria applied in published studies likely explains the significant variability in previously reported PGD incidence. Some studies have applied narrow definitions that restrict the diagnosis of PGD to the most severe cases, such as those resulting in mortality or early requirement for VAD, in an effort to implement objective, easy-to-apply criteria. These studies generally report a lower incidence of PGD

**Table 2:** Baseline recipient, donor and procedure-related characteristics

Variable <sup>a</sup>	Severity of primary graft dysfunction						P-value <sup>b</sup>
	None (N = 132)	Mild (N = 35)	None/Mild <sup>b</sup> (N = 167)	Moderate (N = 8)	Severe (N = 16)	Moderate/Severe <sup>b</sup> (N = 24)	
<b>Recipient variables</b>							
Age (years)	57.5 ± 10.0	55.7 ± 12.2	57.1 ± 10.5	50.9 ± 18.0	54.0 ± 11.6	53.0 ± 13.7	0.22
Range (years)	[20, 76]	[20, 73]	[20, 76]	[21, 68]	[32, 69]	[21, 69]	
Gender, female	36 (27)	7 (20)	43 (26)	2 (25)	3 (19)	5 (21)	0.08
Race/ethnicity							0.32
Black	25 (21)	9 (26)	34 (22)	3 (38)	2 (13)	5 (21)	
White	92 (75)	24 (69)	116 (74)	4 (50)	11 (73)	15 (65)	
Other	5 (4)	2 (6)	7 (5)	1 (13)	2 (13)	3 (13)	
Etiology of heart failure							0.03*
Ischemic cardiomyopathy	58 (44)	20 (57)	78 (47)	4 (50)	13 (81)	17 (71)	
Non-ischemic cardiomyopathy	74 (56)	15 (43)	89 (53)	4 (50)	3 (19)	7 (29)	
Diabetes	49 (38)	14 (40)	63 (38)	3 (38)	5 (33)	8 (35)	0.82
Hypertension	115 (90)	27 (79)	142 (88)	7 (100)	13 (87)	20 (90)	1.00
Creatinine (mg/dL)	1.48 ± 0.37	1.43 ± 0.43	1.47 ± 0.38	1.71 ± 0.47	1.88 ± 0.60	1.83 ± 0.55	0.002*
BMI (kg/m <sup>2</sup> )	28.5 ± 4.6	29.8 ± 5.0	28.8 ± 4.7	31.6 ± 5.8	30.5 ± 5.6	30.9 ± 5.6	0.08
Hospitalized at transplant	19 (15)	8 (23)	27 (16)	4 (50)	5 (33)	9 (39)	0.02*
ICU prior to transplant	16 (12)	2 (6)	18 (11)	1 (13)	0 (0)	1 (4)	0.48
VAD prior to transplant	37 (28)	12 (34)	49 (29)	2 (25)	3 (19)	5 (21)	0.47
ECMO prior to transplant	1 (1)	0 (0)	1 (1)	1 (13)	3 (20)	4 (17)	<0.001*
UNOS status							0.18
1A	47 (36)	16 (46)	63 (38)	3 (38)	5 (31)	8 (33)	
1B	76 (57)	15 (43)	91 (55)	5 (62)	6 (38)	11 (46)	
2	9 (7)	4 (11)	13 (7)	0 (0)	5 (31)	5 (21)	
PVR (Wood units)	2.22 ± 2.00	2.20 ± 1.51	2.22 ± 1.91	0.81 ± 2.54	2.33 ± 2.38	1.88 ± 2.45	0.45
Prior sternotomy	58 (44)	22 (63)	80 (48)	5 (63)	10 (63)	15 (63)	0.20
Wait list time (days)	133 ± 254	168 ± 296	140 ± 263	89 ± 154	79 ± 141	82 ± 142	0.10
Range	[1, 1640]	[1, 1220]	[1, 1640]	[2, 426]	[2, 499]	[2, 499]	
SGA nutrition risk							0.80
Low	61 (60)	21 (81)	82 (64)	3 (60)	5 (63)	8 (62)	
Moderate	41 (40)	3 (12)	44 (34)	2 (40)	3 (38)	5 (39)	
High	0 (0)	2 (8)	2 (2)	0 (0)	0 (0)	0 (0)	
CMV mismatch	48 (36)	8 (23)	56 (34)	3 (38)	7 (44)	10 (42)	0.49
<b>Donor variables</b>							
Age (years)	33.0 ± 12.5	36.9 ± 12.0	33.8 ± 12.4	37.9 ± 8.4	33.7 ± 12.2	35.1 ± 11.1	0.53
Range (years)	[19, 57]	[26, 49]	[19, 57]	[12, 60]	[11, 52]	[11, 60]	
Gender, female	73 (56)	22 (63)	95 (57)	5 (63)	11 (69)	16 (67)	0.51
Race/ethnicity							0.006*
Black	21 (16)	7 (20)	28 (17)	0 (0)	0 (0)	0 (0)	
White	108 (82)	28 (80)	136 (81)	8 (100)	14 (88)	22 (92)	
Other	2 (2)	0 (0)	3 (2)	0 (0)	2 (13)	2 (8)	
Cause of death							0.84
Anoxia	52 (39)	16 (46)	68 (41)	4 (50)	5 (31)	9 (38)	
Head trauma	43 (33)	10 (29)	53 (32)	2 (25)	5 (31)	7 (29)	
Other	37 (28)	9 (26)	46 (28)	2 (25)	6 (38)	8 (33)	
BMI (kg/m <sup>2</sup> )	29.3 ± 7.3	31.9 ± 6.9	29.9 ± 7.3	31.8 ± 8.6	30.4 ± 8.5	30.9 ± 8.4	0.85
LV wall thickness (>1.3 cm)	23 (17)	4 (11)	27 (16)	1 (13)	2 (13)	3 (13)	0.77
LVEF (%)	61.1 ± 8.7	62.1 ± 9.0	61.3 ± 8.7	59.8 ± 7.2	61.2 ± 8.1	60.7 ± 7.7	0.67
Range (%)	[35, 80]	[45, 79]	[35, 80]	[50, 69]	[45, 70]	[45, 70]	
Previous CPR	45 (34)	10 (29)	55 (33)	1 (13)	1 (6)	2 (8)	0.02*
<b>Procedure-related variables</b>							
Donor/recipient weight ratio	0.98 ± 0.23	1.00 ± 0.25	0.98 ± 0.23	0.88 ± 0.15	0.89 ± 0.29	0.89 ± 0.25	0.02*
Body weight % difference	2.4 ± 23.1	-0.17 ± 24.3	1.9 ± 23.3	11.5 ± 15.4	11.2 ± 28.9	11.3 ± 24.6	0.02*
Range (%)	[-63, 45]	[-59, 43]	[-63, 45]	[-19, 33]	[-54, 38]	[-54, 38]	
pHM % difference	6.8 ± 22.1	8.8 ± 21.2	7.2 ± 21.9	15.0 ± 14.2	19.5 ± 19.7	18.0 ± 17.8	0.02*
Range (%)	[-60, 47]	[-65, 36]	[-65, 47]	[-8, 39]	[-33, 42]	[-33, 42]	
Distance from donor to transplant centre (miles)	470 ± 464	507 ± 496	478 ± 470	170 ± 148	436 ± 384	348 ± 345	0.42
Range (miles)	[0, 2143]	[0, 1669]	[0, 2143]	[0, 370]	[0, 1358]	[0, 1358]	
Ischemic time (min)	224 ± 61	239 ± 60	227 ± 61	202 ± 39	249 ± 67	233 ± 63	0.79
Range (min)	[100, 383]	[127, 399]	[100, 399]	[162, 273]	[171, 425]	[162, 425]	

BMI: body mass index; CMV: cytomegalovirus; CPR: cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; LV: left ventricle; LVEF: left ventricular ejection fraction; pHM: predicted heart mass; PVR: pulmonary vascular resistance; SGA: subjective global assessment; UNOS: United Network for Organ Sharing; VAD: ventricular assist device.

<sup>a</sup>Continuous data are shown as mean ± standard deviation and categorical data as number (%).

<sup>b</sup>P-value for comparison between none/mild PGD and moderate/severe PGD groups.

\*P < 0.05 considered statistically significant.

(2–3%) [3,4]. On the other hand, studies that incorporate more liberal definitions (for example, those that incorporate additional criteria such as early inotropic support) have in contrast reported a higher incidence of PGD (9–24%) [5–7].

The majority of patients with PGD in our cohort met the criteria only for mild PGD (35/59;

59%). The remaining 24 patients with moderate or severe PGD comprise only 13% of the total cohort, an incidence that falls in the middle of the range previously reported. Of note, there was no difference in the 30-day/in-hospital or 1-year mortality of patients with mild PGD versus those without PGD. Taken together, these findings suggest

**Table 3:** Postoperative outcomes

Severity of primary graft dysfunction							
Variable <sup>a</sup>	None (N = 132)	Mild (N = 35)	None/mild <sup>b</sup> (N = 167)	Moderate (N = 8)	Severe (N = 16)	Moderate/severe <sup>b</sup> (N = 24)	P-value <sup>b</sup>
In-hospital/30-day mortality	0 (0)	0 (0)	0 (0)	0 (0)	6 (38)	6 (25)	<0.001*
ICU LOS, days	4.2 ± 5.4	5.3 ± 6.9	4.4 ± 5.8	22.9 ± 22.8	21.5 ± 21.0	22.0 ± 21.1	<0.001*
Total post-transplant LOS, days	10.4 ± 9.0	13.0 ± 9.9	11.0 ± 9.2	31.8 ± 20.7	25.1 ± 19.2	27.3 ± 19.5	<0.001*
Severe rejection (3R) <sup>c</sup>							1.00
At 1 month	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	
At 3 months	3 (2)	1 (3)	4 (2)	0 (0)	0 (0)	0 (0)	
At 1 year	3 (2)	1 (3)	4 (2)	0 (0)	0 (0)	0 (0)	
Inotrope score <sup>d</sup>	16.3 ± 7.8	22.5 ± 9.5	17.6 ± 8.5	38.0 ± 12.0	31.1 ± 20.0	33.4 ± 17.8	<0.001*
Dialysis post-transplant	0 (0)	1 (3)	1 (1)	2 (25)	3 (19)	5 (21)	<0.001*
Stroke	3 (2)	1 (3)	4 (2)	2 (25)	0 (0)	2 (8)	0.17
Reoperation for bleeding	10 (8)	4 (11)	14 (8)	3 (43)	8 (50)	11 (48)	<0.001*
Transfusion requirements, units							
PRBC	1.4 ± 2.2	1.6 ± 2.0	1.4 ± 2.2	7.5 ± 12.3	5.1 ± 6.6	5.9 ± 8.7	<0.001*
Platelets	0.2 ± 1.0	0.3 ± 0.7	0.3 ± 1.0	2.9 ± 4.9	2.3 ± 4.3	2.5 ± 4.4	<0.001*
FFP	1.0 ± 2.4	1.4 ± 3.0	1.1 ± 2.6	1.4 ± 2.7	1.7 ± 2.4	1.6 ± 2.4	0.22
Cryoprecipitate	0.3 ± 1.6	0.1 ± 0.5	0.3 ± 1.4	2.5 ± 7.0	4.8 ± 9.9	4.0 ± 8.9	<0.001*
Pneumonia	5 (4)	2 (6)	7 (4)	3 (38)	5 (31)	8 (33)	0.005*
Urinary tract infection	3 (2)	2 (6)	5 (3)	1 (13)	1 (6)	2 (8)	0.21
Sternal wound infection (without mediastinitis)	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	1.00
Sternal wound infection (with mediastinitis)	0 (0)	0 (0)	0 (0)	1 (13)	2 (13)	3 (13)	0.002*
Bacteremia	3 (2)	2 (6)	5 (3)	2 (25)	1 (6)	3 (13)	0.06
Sepsis	3 (2)	0 (0)	3 (2)	3 (38)	3 (19)	6 (25)	<0.001*

FFP: fresh frozen plasma; ICU: intensive care unit; LOS: length of stay; PRBC: packed red blood cells.

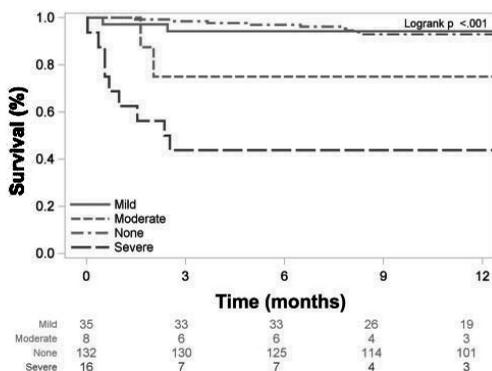
<sup>a</sup>Continuous data are shown as mean ± standard deviation and categorical data as number (%).

<sup>b</sup>P-value for comparison between none/mild PGD and moderate/severe PGD groups.

<sup>c</sup>By ISHLT Standardized Cardiac Biopsy Grading Scheme [16].

<sup>d</sup>Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in µg/kg/min [13].

\*P < 0.05 considered statistically significant.



**Figure 1:** Cumulative survival to 1-year post-transplantation. Kaplan–Meier curves are stratified by PGD severity. Patients with increased severity of PGD had decreased survival at 1-year (log-rank  $P < 0.001$ ).

that the ISHLT category for mild PGD may not have significant clinical relevance in terms of mortality. A diagnosis of mild PGD may portend an increased risk for morbidity, though the rates of post-operative complications were similar between the none and the mild PGD cohorts in our study. However, such a comparison was not the primary aim of our analysis, and a larger sample size is probably necessary to determine whether

**Table 4:** Univariate and multivariate predictors of moderate/severe primary graft dysfunction

Predictors	Odds ratio	95% CI	P-value
<b>Univariate</b>			
Recipient BMI, per 5 unit increase	1.6	1.0–2.4	0.046
Ischemic cardiomyopathy	2.8	1.1–7.5	0.032
Undersized donor <sup>a</sup>	2.8	1.0–7.2	0.033
Recipient hospitalized	3.3	1.3–8.3	0.013
Creatinine, per 1.0 mg/dL increase	6.4	2.2–18.7	<0.001
ECMO prior to transplant	34.9	4.9–702.4	0.002
<b>Multivariate</b>			
Recipient hospitalized	2.9	1.0–8.0	0.049
Undersized donor <sup>a</sup>	3.4	1.1–9.8	0.026
Creatinine, per 1.0 mg/dL increase	5.5	1.8–19.5	0.005

<sup>a</sup>By difference in pHM > 30%.

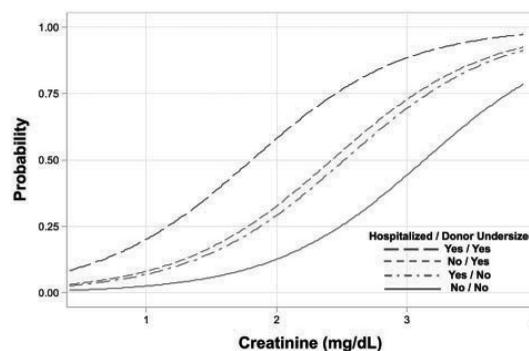
mild PGD truly reflects any increase in morbidity.

The survival of patients with mild PGD was similar to that of patients without PGD, but diagnosis of moderate or severe PGD was indeed associated with increased mortality. In-hospital/30-day mortality for patients with moderate/severe PGD was 25%, whereas none of the patients with none/mild PGD suffered early mortality. Patients diagnosed with moderate/severe PGD also experienced higher transfusion burdens and increased rates of reoperation for bleeding and post-operative renal failure requiring dialysis. Not surprisingly, ICU and total postoperative LOS were

longer in the moderate/severe PGD group as compared to the none/mild PGD group, reflecting the aggressive therapy and increased resource utilization required to treat patients with clinically significant (moderate/severe) PGD. This group also experienced increased rates of infections, most likely due to the increased LOS required following transplantation.

Although PGD was previously thought to impact survival primarily within a 30-day postoperative period, recent evidence suggests that PGD may affect survival for several months beyond the initial post-transplantation window [17]. Our study identified that moderate/severe PGD negatively impacted survival up to 3 months following transplantation, lending further credence to this new understanding of the midterm prognosis associated with PGD. Downstream consequences of PGD, including sepsis and multiorgan failure, likely increase mortality for several months following transplantation, even if patients with these unfortunate sequelae live beyond 30-days [17]. Cumulative survival analysis after 3 months, however, was similar between the two groups, suggesting that total recovery of the graft occurs by approximately 90 days and is maintained at 1-year follow-up. This finding should be reassuring for patients initially diagnosed with PGD who survive this critical period.

The pathogenesis of PGD has not been clearly delineated, though its origin is believed to be multifactorial. After multivariate regression, elevated preoperative creatinine, recipient hospitalized at time of transplant and undersized donor (by difference in pHM  $\geq 30\%$ ) were found to be independently predictive of PGD in our analysis. Numerous clinical markers indicating a more severe pre-transplant condition of the recipient, including requirement for inotropic or mechanical support, have been repeatedly identified as risk factors for PGD [3,18,19], suggesting that placing a donor heart in a 'hostile' recipient environment increases the risk for this complication. Our study identified recipient hospitalization at the time of transplantation, a potential marker for some or all of the variables that may suggest a hostile recipient environment, as a risk factor for PGD.



**Figure 2:** Predicted probabilities for moderate/severe PGD by preoperative creatinine (x-axis) and stratified by undersized donor (by difference in pHM  $\geq 30\%$ ) and recipient hospitalized at the time of transplantation.

The negative impact of compromised renal function on out-comes following essentially any cardiothoracic procedure is firmly established [20], and, thus, preoperative creatinine levels weigh heavily in the Society of Thoracic Surgeons cardiac surgery risk models [21,22]. That the likelihood for development of PGD increased with diminishing renal function in our cohort is consistent with this principle. The renal function of heart transplant recipients may face additional stressors beyond that of open-chest surgery itself. Transplant recipients are dosed with nephrotoxic immunosuppressant agents including calcineurin inhibitors. The inflammatory response induced by the transplantation of a foreign object into the recipient's body may further compromise renal function postoperatively. Therefore, the preoperative creatinine of heart transplant recipients in particular may be of even greater import as compared to other cardiothoracic procedures, especially given the increased risk for moderate/severe PGD faced by patients with elevated preoperative levels.

Undersized donor by body weight alone has previously been associated with PGD [3,18]. However, variations in age and sex have been proven to affect the heart mass of donors with the same body weight. Formulas to estimate heart mass (pHM) that incorporate donor age, sex, weight and height to account for these additional factors have therefore been developed to provide clinicians with better information regarding donor-recipient size mismatches [11,12]. Undersized donor hearts as defined by a difference in pHM have already been

shown to negatively influence survival following heart transplantation [10]. Our study is the first to demonstrate an association between undersized donor hearts by pHM and the development of PGD postoperatively. Although the transplantation of marginal donor hearts (including undersized donor hearts) can be performed safely [5], our analysis suggests that there is a limit to how far donor-recipient size mismatches can be taken before the risk of PGD over-comes the potential benefits of performing transplantation.

The only previously validated predictive model for the development of PGD is the RADIAL score (recipient: right atrial pressure > 10 mmHg, age > 60 years, diabetes and inotropic support dependence preoperatively; donor: age > 30 years; procedural: length of ischemia > 240 min) [6]. This system, however, is limited by poor calibration [9,17] and the fact that it was derived and validated in a patient cohort with a low prevalence of VADs (16/655; 2%) as compared to a modern transplant practice. Patients with VADs prior to transplantation have been shown to be at increased risk for developing PGD [3,5,18]. Given the increased utilization of bridge-to-transplant therapy in the current era of heart transplantation, pretransplant mechanical circulatory support is a key factor to study when investigating PGD. One strength of our study, therefore, is that the prevalence of VADs in the study cohort (28%) better reflects the frequency of bridge-to-transplantation therapy that occurs in the contemporary treatment of heart failure [2]. We cannot comment on the calibration of our risk model, however, without first applying it to another population.

Unfortunately, due to the significant variability in definitions of PGD, eras of heart transplantation, and published study designs currently available, the best method to assess donor-recipient mismatch that portends increased risk for PGD remains to be determined [9]. The standardized criteria set forth by the ISHLT and validated in this study should be applied to large, contemporary series that include a high percentage of patients bridged with VADs in order to identify additional PGD risk factors and validate methods to assess the risk of PGD prior to transplantation.

The limitations of this report include those expected of a single-centre, retrospective study. Although the results in our patient cohort may not be readily generalizable to other populations, we are the first to apply the standardized criteria proposed by the ISHLT to define PGD. By implementing this definition, results of future studies can more easily be compared to the findings in this report. Furthermore, our patient population better represents the demographics of modern heart transplant patients: an increased prevalence of VADs was present in the study cohort as compared to previous investigations regarding PGD, though many centres have even higher proportions of transplant recipients bridged with VAD support [2]. Survival beyond 1-year follow-up was not available at the time of the current analysis, but the impact of PGD on mid-to-long term survival appeared to disappear by 3 months post-transplantation. However, a study with an increased duration of follow-up is necessary to confirm this finding.

The ISHLT consensus committee introduced into their criteria a distinction between PGD-RV and PGD-LV, a novel conceptualization of PGD that had not been previously utilized in the literature. We did not incorporate this distinction into our assessment of PGD in the study cohort. Our centre's clinical approach to patients with evidence of PGD precluded such analysis. The haemodynamic criteria required to distinguish PGD-RV from PGD-LV, specifically PCWP, is not routinely collected at our centre due to safety concerns. Furthermore, no RVADs were placed in our cohort because we prefer to initiate ECMO for all patients with PGD who require support beyond maximum inotropic therapy. Whether this is a limitation of our study or an additional limitation to the clinical relevance of the ISHLT criteria remains to be determined.

In conclusion, we identified a total PGD incidence of 30% in a series of adult cardiac transplantations performed at a high-volume centre using ISHLT diagnostic criteria. Patients with moderate/severe PGD (13%) had decreased survival, though complete graft recovery appeared to be achieved by 3 months following transplantation. Risk factors for the development of moderate/severe PGD included elevated preoperative creati-

nine, recipient hospitalized at time of transplantation and undersized donor hearts. Ultimately, the new ISHLT diagnostic criteria for PGD appear to identify and discriminate patients in a clinically relevant manner.

**Conflict of interest:** none declared.

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# Enhanced External Counterpulsation for the Treatment of Angina Pectoris

*Peter F. Cohn*

The treatment of refractory chronic angina pectoris presents an increasing problem for all physicians caring for patients with coronary artery disease because of the large number of individuals who have either failed multiple revascularization procedures or are not appropriate candidates for such procedures. The aim of this study was to review the safety, efficacy, and clinical applicability of a noninvasive technique (external counterpulsation) for the treatment of angina pectoris. A MEDLINE search for all English language abstracts, meeting presentations, journal articles, and reviews from 1960 through December 2005 was conducted. Of the 194 citations in the literature, 60 appeared before 1983 when the enhanced version of the technique (the one that is presently used) was first reported. Criteria for further evaluation of the 134 post-1983 citations were either (1) randomized trial, (2) observational study of at least 10 patients, or (3) investigations into possible mechanisms. Of the 134 citations, 45 were used for data extraction. Observational studies from the United States, Asia, and Europe have demonstrated improvement in symptoms, reduction in anginal episodes, better quality of life, and improved exercise performance in over 5000 patients. The only randomized study (Multicenter Study of Enhanced External Counterpulsation) confirmed these findings as well as the continua-

tion of clinical benefits at least 1 year posttreatment. Although the mechanisms by which diastolic augmentation achieves these beneficial results are still under investigation, this is a promising noninvasive therapy in a group of patients with limited treatment options.

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Because of advances in both coronary risk factor modification and treatment of coronary artery disease, mortality from cardiovascular disease has declined drastically in the United States in the last 3 decades. Despite these gains, atherosclerotic heart disease remains the most common cause of death in the United States and in other developed countries. Not only do millions of people die of this disease but also many others continue to have anginal symptoms that interfere significantly with their quality of life despite aggressive anti-ischemic drug regimens combined with medical and/or surgical coronary revascularization procedures. For example, it is estimated that hundreds of thousands of patients in the United States have undergone percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery each year for the past decade, and many remain symptomatic or become symptomatic again within months or years of the original procedure. There is a limit to how many repeat revasculari-

zation attempts can be made because of the patient's coronary anatomy, conduit availability, left ventricular function, age, comorbidity, and so on.

For those patients in whom repeat (or initial) revascularization procedures are not appropriate and in whom aggressive medical therapy fails to maintain a quality of life that patients are comfortable with, several emergent therapies have been proposed. These include techniques to reduce anginal pain by neural stimulation or blockade and procedures that could potentially enhance coronary myocardial perfusion. There are several methods available to block pain associated with cardiac ischemia, including conventional sympathectomy and 2 newer techniques popular in Europe: transcutaneous electrical nerve stimulation and spinal cord stimulation.<sup>1</sup> The most encouraging approach appears to be the latter, but the main drawback to spinal cord stimulation is that it is invasive.

There are also several invasive procedures currently used to increase myocardial perfusion in patients with refractory angina with varying clinical results such as transmyocardial<sup>2,3</sup> or percutaneous laser revascularization<sup>3,4</sup> (procedures that use the myocardial sinusoids to create new channels to deliver blood to the myocardium) and the still investigational angiogenic therapy for the human heart, that is, injection of an angiogenic protein such as fibroblast growth factor 1 close to the left anterior descending artery during coronary artery bypass surgery.<sup>5</sup> The only truly noninvasive procedure currently available for which an increase in myocardial perfusion has been reported is external counterpulsation and especially the enhanced version (EECP). This systematic review of the English language literature will focus on EECP's safety, efficacy, and applicability to current clinical practice especially as it applies to the general physician.

## Methods

### Data Sources

The MEDLINE database was used to identify English language abstracts, meeting presentations, reviews, and journal articles related to external

counterpulsation. The main Medical Subject Headings of assisted circulation and counterpulsation were referenced with resulting citations divided into 2 periods, from 1960 to 1982 and from 1983 to 2005. This was done because of the historical development of the technique. Briefly stated, the concept of counterpulsation rests on an observation in the animal model reported in 1953 by Kantrowitz and Kantrowitz<sup>6</sup> that coronary blood flow could be increased significantly if the coronary artery was perfused at a higher pressure during diastole. This report led an engineer (Birtwell) to propose to a cardiac surgeon (Harken) and to colleagues at the Peter Bent Brigham Hospital that a system to implement arterial counterpulsation in humans could be developed. Studies of such a system were begun in 1957 and reported in 1961.<sup>7</sup> Experiments on intraaortic balloon pumping were also being conducted in Harken's laboratory at this time,<sup>8</sup> but this review will only focus on external counterpulsation.

The initial external devices required blood to be led outside the body to a pump, but this was soon replaced by a totally noninvasive device marked by rigid outer housing containing waterfilled bags. Sequential compression, rather than 1-stage uniform compression, was the next development under the leadership of another cardiac surgeon (Soroff). Clinical trials in patients with cardiogenic shock,<sup>9</sup> angina,<sup>10</sup> and acute myocardial infarction<sup>11</sup> were conducted in the United States during the 1970s and early 1980s. Treatment periods were short with results suggestive of benefit but not clearly so. At this point, interest in this technique waned (as perhaps best exemplified by the editorial of Kuhn in 1980).<sup>12</sup> The modern era of external counterpulsation began with modifications made in the technique by Zheng et al<sup>13</sup> in China that were reported in 1983. Zheng's system used compressed air with 3 sets of balloons sequentially compressing the vascular beds of the legs, thighs, and buttocks. The timing of the compression was controlled by the patient's electrocardiogram (ECG).

Since 1983 there have been 134 citations referring to external counterpulsation in the literature, of which 45 satisfied the selection criteria

for this review (Table 1).<sup>13-57</sup> This criteria involved either (1) a randomized trial (with 3 references concerning the Multicenter Study of EECP [MUST-EECP] trial<sup>55-57</sup>), (2) observational clinical studies of at least 10 patients (most of the remaining references), or (3) investigations into hemodynamic effects and/or possible mechanism of action of this procedure.<sup>19,21,25,27,31,37,48,52</sup>

**Table 1. EECP Patient Studies Between 1983 and 2005**

Lead Author	Year	Reference	No. of Patients
Observational Trials (in chronological order)			
Zheng	1983	[13]	52
Kern	1985	[14]	14
Lawson	1992	[15]	18*
Lawson	1995	[16]	17*
Fricchione	1995	[17]	38*
Karim	1995	[18]	15*
Kasliwal	1996	[19]	23
Lawson	1996	[20]	27*
Lawson	1996	[21]	50*
Garlichs	1998	[22]	12
Tartaglia	1998	[23]	22
Katz	1998	[24]	13
Suresh	1998	[25]	30*
Lawson	1998	[26]	60*
Qian	1999	[27]	104
Huang	1999	[28]	14
Strobeck	1999	[29]	466†
Wu	1999	[30]	43
Masuda	1999	[31]	11
Gloth	1999	[32]	18
Werner	1999	[33]	16
Karim	1996	[34]	117
Lawson	2000	[35]	33*
Lawson	2000	[36]	2289‡
Urano	2001	[37]	12
Lawson	2001	[38]	1957‡
Barsness	2001	[39]	978†
Michaels	2001	[40]	1004†
Lawson	2001	[41]	598†
Stys	2002	[42]	175†
Holubkov	2002	[43]	323†
Lakshmi	2002	[44]	2486†
Michaels	2002	[45]	10
Linnemeer	2003	[46]	1532†
Fitzgerald	2003	[47]	215†
Shechter	2003	[48]	20
Tartaglia	2003	[49]	25
Werner	2003	[50]	48
Michaels	2004	[51]	1097†
Dockery	2004	[52]	23
Lawson	2004	[53]	2861†
Michaels	2005	[54]	37
Randomized trial (MUST-EECP)			
Arora	1999	[55]	139
Cohn	1999	[56]	125
Arora	2002	[57]	71

\*Overlapping Stony Brook populations.

†IEPR.

‡Consortium.

## Study Selection and Data Extraction

### A. Safety

Adverse effects requiring hospitalization are rare with this device, although it is occasionally uncomfortable, and side effects such as skin abrasions on the legs are not uncommon. For example, in 3 large-scale observational studies cited in Table 2 in which such data were reported, the incidence of deaths or myocardial infarctions reported during the 35 to 36 hours of EECP therapy or immediately thereafter in over 3000 patients was less than 1%. In addition, no deaths or myocardial infarctions were reported in the 139 patients enrolled in the randomized MUST-EECP trial. The procedure is also well tolerated psychologically with 1 study showing a reduction in a psychosocial stress factors.<sup>18</sup>

### B. Efficacy

Although different end points were emphasized in the various studies surveyed, one common theme was a favorable change in anginal symptoms and/or quality of life, and another theme was improvement in exercise ECG or myocardial perfusion parameters.

### Observational studies

The Stony Brook study reported in 1992<sup>15</sup> was the initial prospective observational study with the enhanced device reported in the United States. Patient selection and reasons for exclusion are typical of all the other observational studies cited. The 18 patients enrolled in this study had chronic stable angina despite medical or surgical therapy or both and evidence of exertional ischemia on thallium-201 perfusion imaging. Other patients were excluded because of overt congestive heart failure, aortic insufficiency, a myocardial infarction within the previous 3 months, arrhythmias that prevent suitable ECG triggering such as frequent ventricular ectopic activity or atrial fibrillation, severe occlusive peripheral vascular disease, recurrent deep vein thrombosis, systemic hypertension (N180/110 mm Hg), or a bleeding diathesis. After completing the course of 36 hours of outpatient EECP therapy (an empiric number derived from the Chinese studies of Zheng et

al<sup>13</sup>), patients underwent a thallium-201 stress test (with usual medication continued); exercise duration was the same as that during baseline testing so as to provide a comparison of imaging test results. In addition, a maximal stress test was performed less than a week after EECF treatment to assess exercise tolerance. All 18 patients experienced substantial improvements in anginal symptoms after EECF. Thallium-201 stress testing (performed to the same exercise duration before and after EECF) showed a complete resolution of ischemic defects in 12 patients (67%), a decrease in the area of ischemia in 2 patients (11%), and no change in 4 patients (22%). Thus, 14 of 18 patients had a reduction in myocardial ischemia after EECF as assessed by thallium-201 imaging ( $P < .01$ ).

In this Stony Brook study (as in the other observational studies), patients served as their own controls; thus, a placebo effect cannot be ruled out. In addition, because the course of coronary artery disease is largely unpredictable, it is possible (but not probable) that regression of disease could occur over the 6- to 7-week trial period in a group of patients whose angina had been disabling or progressive over a period of months or years. The enrolled patients did not undergo any new therapy, such as diet, lipid reduction, or smoking cessation, during the study. Dosages of antianginal medications remained the same (or decreased) over the course of the study. Because the study cohort was predominantly male, no definitive conclusions regarding efficacy in women could be made. EECF was well tolerated by these 18 patients, and none withdrew after enrollment.

Protocols similar to the one used in the Stony Brook patients were also used in several other studies from a variety of countries and reported in a variety of medical journals. Thus, Karim et al<sup>17</sup> reported significant improvement in perfusion imaging and exercise tolerance in 38 Indonesian

patients who also had a decrease in anginal symptoms. Kasliwal et al<sup>19</sup> reported a decline in the number of anginal episodes and an increase in left ventricular myocardial function determined by echocardiology in 23 Indian patients. In the United States, Tartaglia et al<sup>23</sup> reported increased exercise tolerance and prolongation of time to ST depression in 22 patients, as well as in radionuclide perfusion scores and functional class,<sup>49</sup> whereas Michaels et al<sup>54</sup> found clinical and exercise improvement but no changes in radionuclide measurements, and Glothen and Oken<sup>32</sup> reported improvement in anginal functional class in 18 patients.

As impressive as the data from these small studies are the reports from several large cooperative multicenter ventures. For example, Strobeck et al,<sup>29</sup> Lawson et al,<sup>38</sup> and Barsness et al<sup>39</sup> reported data from the International EECF Registry (IEPR) centered at the University of Pittsburgh. These investigators found improvement in anginal class and decrease in nitroglycerin use in 466, 1957, and 978 patients, respectively. The report of Barsness involving 43 centers found that 81% of patients reported improvement of at least one anginal class immediately after the last treatment<sup>39</sup> (Table 2). Even with ejection fractions less than 35% and a history of congestive failure,<sup>29,38</sup> many patients were still able to complete the treatment course with good results.

In more recent studies, the IEPR investigators found that improvement in anginal symptoms and quality of life were sustained for 2 years, and quality of life were sustained 2 years posttreatment,<sup>51</sup> that even patients with left main disease who were not operated on could be helped,<sup>53</sup> that diabetic patients had similar degrees of improvement as did nondiabetics,<sup>46</sup> and that EECF also is efficacious as initial therapy, that is, in those patients who chose not to have invasive revasculari-

**Table 2. Effect of EECF in 3 Large Observational Trials**

	EECF International Consortium (n = 2289) [36]	IEPR (n = 978) [39]	International Study (n = 175) [40]
Beneficial effect: improvement in at least 1 anginal class	73%	81%	85%
Serious adverse effect (death/MI)	0.7% (8/8)	0.6% (2/4)	0

zation procedures.<sup>47</sup> Another large observational study<sup>40</sup> enrolled 175 patients in 7 countries in the United States, Europe, and Asia and specifically compared radionuclide stress testing before and after therapy. In the 4 centers performing post-EECP radionuclide stress tests to the same level of exercise, 81 of 97 patients (83%) had improved perfusion images, whereas in the 3 centers using maximal exercise testing, 42 of 78 (54%) showed improvement. Improvement in anginal functional class was reported in 85% of patients. The EECP Clinical Consortium (a forerunner of the IEPR) enrolled 3788 patients from 1997 to 2000 with complete follow-up data available in 2289 patients from 84 centers.<sup>36</sup> The average Canadian Cardiovascular Society (CCS) anginal class before treatment was 2.78 compared with 1.81 after treatment ( $P < .001$ ). The greater the impairment at baseline, the greater the degree of improvement. Overall improvement in at least 1 angina class was reported in 74% of patients. Although the results from the various observational trials—both large and small—were encouraging in the extremely symptomatic populations studied, it cannot be emphasized strongly enough that by definition the observational studies lacked a suitable control group. This was one of the reasons a randomized multicenter trial was begun in 1995. Its goal was measuring the effect of EECP versus placebo on both symptoms and various exercise parameters.

#### *Randomized trial*

The MUST-EECP was a randomized, placebo (sham)-controlled, multicenter trial designed to evaluate EECP in patients with angina and documented coronary artery disease.<sup>55</sup> Treatment effect was determined by comparing changes in exercise treadmill test parameters (exercise duration and time  $\geq 1$ -mm ST segment depression) and symptoms (frequency of anginal episodes and nitroglycerin use). The MUSTEECP trial was conducted at 7 medical centers in the United States, with the Core Laboratory and Data Coordinating Center at the State University of New York at Stony Brook and the Data and Safety Monitoring Committee located at the University of Florida in Gainesville.

Approximately 500 patients with chronic stable angina were considered for inclusion, of whom 139 were randomized between May 1995 and May 1997.

Main reasons for nonenrollment included failure to satisfy inclusion/exclusion criteria and patient refusal. To be eligible, patients had to meet the following inclusion criteria: between 21 and 81 years of age; symptoms consistent with CCS angina levels I, II, or III; documented evidence of coronary artery disease; and positive exercise test result for ischemia.

Evidence of coronary artery disease required at least one of the following criteria: angiographically proven stenosis greater than 70% in at least one major coronary artery; history of myocardial infarction (MI) documented by characteristic creatine kinase elevation and development of Q waves on ECG; or positive result of nuclear exercise stress test for infarction or ischemia.

Exclusion criteria were similar to those cited earlier. Before a patient underwent randomization, medical history, physical examination, and a baseline treadmill test were performed. The baseline treadmill test used a standard or a modified Bruce protocol and was performed within 4 weeks of treatment initiation. All medications (except on-demand nitroglycerin) remained unchanged for the duration of the study. Once randomized, patients underwent 35 hours of either active counterpulsation (EECP) or inactive counterpulsation (sham). Within 1 week of completion of 35 treatment sessions, a posttreatment exercise test was performed. Baseline and posttreatment treadmill tests were performed by personnel who were blinded to whether the patient was in the active or inactive counterpulsation group.

Tracings of each treadmill test from each study center were sent to the core laboratory, where exercise duration (in seconds) and time  $\geq 1$ -mm ST-segment depression (in seconds) were confirmed by personnel unaware of both treatment assignment of each patient and whether the treadmill test was baseline or after treatment. Diaries were evaluated for frequency of angina episodes and nitroglycerin use.

There was no significant difference between

**Table 3. Effect of EECp in the randomized MUST-EECP trial**

	Active Treatment	Sham Treatment	<i>P</i>
Improvement in exercise parameters: change in time to 1 mm ST depression (s)*	37 ± 1	-4 ± 12	<.01
Improvement in symptoms: Change in daily anginal episodes from baseline*	0.15 ± 0.3	-0.01 ± 0.3	<.05
Continued reduction in symptoms 1 y later (%)†	70	37	<.01

\*[55].

†[56].

groups in change in exercise duration from baseline to after treatment, but time to  $\geq 1$ -mm ST-segment depression was  $337 \pm 18$  seconds at baseline  $379 \pm 18$  seconds after treatment in the EECp group. In the sham group, time to  $\geq 1$  mm ST-segment depression was  $326 \pm 21$  seconds at baseline and  $330 \pm 20$  seconds after treatment. There was a significant difference between groups in change in time to exercise-induced ischemia from baseline to after treatment (Table 3).

In patients who completed 34 sessions or more, angina counts were  $0.72 \pm 0.14$  at baseline and  $0.57 \pm 0.38$  after treatment in the EECp group and  $0.77 \pm 0.14$  at baseline and  $0.76 \pm 0.22$  after treatment in the sham group. The difference between groups in the change in angina counts from baseline was statistically significant (Table 3). A similar number of patients in each group showed a 0% to 25% level of improvement, but more patients reported greater than 50% improvement in angina frequency, and fewer worsened in the EECp group compared with the sham group ( $P < .05$ ). Nitroglycerin use was similar in both groups.

The MUST-EECP trial confirmed the conclusions of the observational studies: EECp can reduce exercise-induced ischemia in patients with symptomatic coronary artery disease. The lack of significant treatment effect on exercise duration, despite reduction in other measures of ischemia, has been seen in other clinical trials involving antianginal agents and may be because of a fixed exercise duration in patients heavily medicated with antianginal drugs, especially  $\beta$  blockers. Just as the observational studies reported improvement in symptoms, the randomized trial demonstrated a trend toward angina reduction after treatment with EECp in the intention-to-treat analysis. This trend reached statistical significance when the

analysis included only those subjects completing at least 34 sessions. This latter observation confirms the prior experience that a certain number of treatment hours are required to maximize the antianginal benefit of this device.

#### Effect of Treatment on Prognosis

Follow-up studies from the Stony Brook series were published at means of 3<sup>16</sup> and 5 years<sup>38</sup> after completion of treatment. Of the first 33 patients studied, 4 died 1 to 5 years after therapy. Only 9 other patients required interim hospitalization for acute ischemic events, leaving 20 of the original 33 without new events 4 to 7 years after EECp treatment, which is an impressive accomplishment. Most of the new events occurred in the 7 patients (of the 33) who had not responded satisfactorily to the initial therapy. Karim et al<sup>34</sup> also reported 5 years of follow-up data in their Indonesian patients. They treated 117 patients between 1992 and 1999, with a follow-up from 1 to 6 years. There were 5 deaths and only 4 other acute events. (A control group of 198 patients had a significantly greater event rate, but the criteria for enrollment in the control group were unclear.) The IEPR reported 1-year follow-up data on 589 patients: death occurred in 3 patients, with major cardiac events requiring hospitalization in 94 other patients (a total of 17% of the original cohort).<sup>42,43</sup> Two-year follow-up of 1097 patients showed 9 deaths with 40% requiring hospitalization.<sup>51</sup> Long-term follow-up data are not yet available from the EECp consortium patients except for a subset of patients with a history of heart failure<sup>38</sup> who were less likely to maintain their angina reduction than nonfailure subjects 6 months after treatment. In the randomized MUST-EECP trial, 2 different prognostic protocols have demonstrated

the same result: an improvement in quality of life that has persisted up to 1 year posttreatment.<sup>56,57</sup> One protocol used follow-up questionnaires administered by nurse clinicians at each site. As seen in Table 3, 70% of actively treated patients reported persistent improvement compared with 37% in the sham group ( $P < .01$ ). The other protocol used more sophisticated and comprehensive questionnaires (the SF-36 and QLI-HF instruments). All instruments showed better results in the active versus sham patients, with 3 questionnaires achieving statistically significant intergroup differences. Perhaps, the most striking was the observation that the favorable 1-year follow-up data were dramatically similar to the initial post-treatment results in the actively treated patients.

#### Hemodynamic Effects

The acute hemodynamic effects of an enhanced version of the external counterpulsation device were first demonstrated invasively by Kern et al<sup>14</sup> in 1985 and later noninvasively by Suresh et al in 1998.<sup>25</sup> Using finger plethysmography to measure the amplitude and area of the peak diastolic and peak systolic pressure waves, Suresh et al found that an effectiveness ratioQ of 1.5 to 2 (the peak diastolic amplitude divided by the peak systolic amplitude) was associated with an optimal enhancement of diastolic retrograde aortic flow. More recently, Michaels et al<sup>45</sup> were able to invasively demonstrate the beneficial acute effects of EECP on intracoronary and left ventricular hemodynamics in 10 patients studied with Doppler flow measurements during cardiac catheterization. Arterial stiffness is, however, not altered.<sup>52</sup>

Attempts to confirm a relationship between the effectiveness ratios established by Suresh et al and clinical benefits have generally been successful. For example Michaels et al<sup>41</sup> and Lakshami et al,<sup>44</sup> using the IEPR data base, reported that patients with the greatest increase in the ratio had the greatest reduction in angina class at 6 months follow-up, yet investigators have noted that some patients with lower ratios also demonstrated clinical improvement.

Because diastolic augmentation and systolic unloading are the major features of both the in-

ternal and external counterpulsation devices, it was noteworthy—but not that surprising—when the degree of diastolic augmentation achieved with EECP was similar to that of intraaortic balloon counterpulsation (the current gold standard) in a Doppler study measuring internal mammary artery flow with both techniques in the same patient.<sup>24</sup> One difference between the 2 techniques is the increase in venous return during EECP, which results in a greater improvement in cardiac output but could also theoretically worsen heart failure. Several groups—including the IEPR investigators<sup>29,38</sup>—have not found this to be as worrisome as first feared, and in fact, a future application for this device might well be as adjunctive therapy for heart failure patients.<sup>58</sup>

#### Possible Mechanisms of Action

Several mechanisms of action have been postulated to explain both the short- and long-term benefits seen with EECP. These include beneficial effects on endothelial function, coronary collateralization, left ventricular function, and even the peripheral circulation.<sup>48,59</sup> They are not mutually exclusive. A relationship between improved endothelial function and collateral formation is suggested by several studies. For example, improvement in myocardial perfusion using N-13 ammonia positron emission tomography scanning was reported by Masuda et al<sup>31</sup> in 11 Japanese patients. Nitric oxide production was enhanced in this study, as it was in 18 Chinese patients reported by Qian et al,<sup>27</sup> suggesting coronary vasodilation resulted from enhanced endothelial function that in turn was induced by EECP therapy. Reduction in a potent vasoconstrictor (serum endothelin—1) in these studies also indicates a vasodilator effect. Urano et al<sup>37</sup> measured atrial and brain natriuretic peptide levels before and after EECP therapy. The latter decreased along with improvement in myocardial perfusion and exercise performance. The production of these various vasoactive and neurohumoral substances—perhaps associated with the increased shear forces produced by EECP—may diminish or stabilize atheromatous plaques in coronary arteries and/or help form new collateral

vessels or open previously present channels. Anatomic data confirming this collateralization in humans have not yet been reported in more than an anecdotal manner, but there is some encouraging animal data to suggest it may have validity.<sup>60</sup>

### Clinical Applicability

Physicians treating cardiac patients want to know first and foremost whether this procedure works and if it is safe. If so, which patients would benefit most from this procedure by being referred to appropriate treatment centers? When the federal government approved Medicare reimbursement for coronary patients, it specified its use in patients with chronic angina refractory to conventional medical and/or anaginal therapy, and this still defines its status at the present time. Some private insurers will also consider reimbursement for those patients whose coronary anatomy is unsuitable for revascularization procedures, a policy that appears reasonable based on this review. As noted earlier, common limitations include patients with arrhythmias (especially atrial fibrillation and frequent ventricular extra systoles that prevent triggering and severe peripheral vascular disease and/or aortic regurgitation that prevents adequate counterpulsation). Other exclusion criteria reflect possible complications related to the high pressures created in the legs (severe systolic hypertension, history of thrombophlebitis, recent MI, etc). Werner et al<sup>50</sup> estimated that as many as two thirds of possible candidates may not meet inclusion criteria, and a third of the treated patients may find therapy too timeconsuming. This German study highlights some practical limitations of EECp therapy.

In the United States alone, there are probably hundreds of thousands of patients who fit the Medicare guidelines and who do not have the ex-

clusion criteria cited above (as well as others noted earlier in the review) and therefore are suitable candidates for EECp. Our experience at Stony Brook has allowed us to further identify those patients who would benefit most from EECp based on coronary angiographic studies. Our findings suggest that at least one open conduit is necessary for improvement in symptoms whether native vessel or bypass graft. Fifty consecutive patients were studied<sup>21</sup> in this analysis, with improvement in radionuclide stress perfusion seen in 80% of the overall group and in 93% of those with a patent conduit. Prior surgical revascularization also improves clinical benefits.<sup>26</sup>

### Conclusions

Although there are no panaceas for the treatment of refractory angina, a systematic review of the recent medical literature suggests that EECp appears to be an efficacious and clinically reasonable approach to help manage patients with chronic stable angina who are refractory to conventional measures. Because of its proven ability to noninvasively use the beneficial effects of diastolic augmentation on the coronary circulation, it has been advocated as therapy in selected patients—especially before using an invasive procedure such as transmyocardial revascularization that has an appreciable morbidity and mortality.<sup>61</sup> The American College of Cardiology/ American Heart Association's 2002 Guideline Update for the Management of Chronic Stable Angina<sup>62</sup> recommends laser revascularization therapy, EECp, and spinal cord stimulation as class 2 alternative therapies for chronic refractory angina patients. Although the latter 2 therapies are both limited by a paucity of randomized trial data, the general physician should consider that EECp (unlike spinal cord stimulation) is a noninvasive, outpatient procedure with little risk of adverse events.

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# Ηλεκτρονική Διαδικτυακή Εφαρμογή Υγείας: Εθνικό Μητρώο Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία στην Ελλάδα

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## Summary

**Εισαγωγή:** Η παχυσαρκία αποτελεί ένα από τα πιο σημαντικά προβλήματα δημόσιας υγείας του 21ου αιώνα. Οι επιπλοκές της παχυσαρκίας είναι πολλές και περιλαμβάνουν ινσουλινοαντοχή, διαβήτη τύπου 2, υπέρταση, υπερλιπιδαιμία και καρδιαγγειακά νοσήματα, και ευθύνονται για ένα σημαντικό υψηλό ποσοστό των δαπανών της δημόσιας υγείας. Στην Ελλάδα το ποσοστό υπέρβαρων και παχύσαρκων παιδιών και εφήβων υπερβαίνει το 30-35%.

**Σκοπός:** Η ανάπτυξη Ηλεκτρονικής Διαδικτυακής Εφαρμογής (Εθνικό Μητρώο Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία) για την καταγραφή των παιδιών και εφήβων πανελλαδικά και για την καθοδήγηση Παιδιάτρων και Γενικών Ιατρών σχετικά με τη διακίνηση ενός υπέρβαρου ή παχύσαρκου παιδιού, καθώς και η αξιολόγησή του σε ένα μεγάλο αριθμό υπέρβαρων και παχύσαρκων παιδιών και εφήβων.

**Μέθοδος:** Με τη χρήση Τεχνολογιών Πληροφορικής και Επικοινωνιών, αναπτύξαμε την Ηλεκτρονική Καρτέλα Ασθενούς. Διασφαλίσαμε ασφαλή διαδικτυακή σύνδεση, κρυπτογράφηση των δεδομένων, Άδεια από την Αρχή Προστασίας Δεδομένων Προ-

σωπικού Χαρακτήρα και πιστοποίηση των Παιδιάτρων και Γενικών Ιατρών μέσω ΗΔΙΚΑ ΑΕ. Ο φάκελος ασθενούς περιλαμβάνει πληροφορίες σχετικά με το παρόν και προηγούμενο ιατρικό ιστορικό, οικογενειακό ιστορικό, λήψη φαρμάκων, εμβολιασμούς, ευρήματα κλινικής εξέτασης και εργαστηριακών εξετάσεων, καθώς και υπηρεσία ραντεβού.

**Αποτελέσματα:** Η πρόσβαση γίνεται από την ιστοσελίδα <http://app.childhood-obesity.gr/>. Ο Φάκελος Ασθενούς περιλαμβάνει τα δημογραφικά στοιχεία, και πληροφορίες σχετικά με το περιγεννητικό, αναμνηστικό και οικογενειακό ιστορικό, τη διατροφή και άσκηση. Σε κάθε κλινική αξιολόγηση συμπληρώνονται οι ανθρωπομετρικές παράμετροι, υπολογίζεται αυτόματα ο Δείκτης Μάζας Σώματος (ΔΜΣ) και η ηλεκτρονική εφαρμογή συμβουλεύει τον Ιατρό για το πώς πρέπει να διακινήσει τον ασθενή με βάση έναν ειδικά σχεδιασμένο Θεραπευτικό Αλγόριθμο, ο οποίος παρέχει συγκεκριμένες, σαφείς και αναλυτικές οδηγίες σχετικά με το πώς θα καθοδηγήσει ένα υπέρβαρο ή παχύσαρκο παιδί, καθώς και ένα παιδί με φυσιολογικό ΔΜΣ. Έτσι διασφαλίζεται ένας ενιαίος τρόπος αντιμετώπισης της παχυσαρκίας σε όλη τη χώρα, καθώς και η καθοδήγηση Παιδιάτρων και Γενικών Ιατρών που βρίσκονται μακριά από εξειδικευμένα κέντρα. Πρόσφατη ανάλυση δεδομένων μας από 1.270 περίπου παιδιά και εφήβους έδειξε ότι οι παρεμβάσεις που προτείνονται οδήγησαν σε ελάττωση του ποσοστού παχυσαρκίας κατά 30% και της υπερβαρότητας κατά 35% μέσα σε ένα έτος.

**Συμπεράσματα:** Τα παραπάνω αποτελέσματα υποδηλώνουν ότι το Έργο αυτό μπορεί να δώσει λύσεις οριστικές και αποτελεσματικές στο πρόβλημα της παχυσαρκίας στη χώρα μας.

**Χρηματοδότηση:** Το Έργο υλοποιήθηκε στο πλαίσιο του Επιχειρησιακού Προγράμματος “Ανάπτυξη Ανθρώπινου Δυναμικού” (ΕΠ.ΑΝ.Α.Δ) 2007-2013 και συγχρηματοδοτήθηκε από το Ευρωπαϊκό Κοινωνικό Ταμείο (Ε.Κ.Τ.) και από Εθνικούς Πόρους.

## Εισαγωγή

Η παχυσαρκία αποτελεί ένα από τα πιο σημαντικά προβλήματα δημόσιας υγείας του 21ου αιώνα και ο όρος επιδημία χρησιμοποιείται για να περιγράψει τον αυξανόμενο επιπολασμό της παχυσαρκίας παγκοσμίως τις τελευταίες τρεις δεκαετίες. Στις Ηνωμένες Πολιτείες, ο επιπολασμός του Δείκτη Μάζας Σώματος (ΔΜΣ) [υπολογίζεται από το βάρος σε χιλιόγραμμα διαιρούμενο με το τετράγωνο του ύψους σε μέτρα] πάνω από την 95η Εκατοστιαία Θέση (Ε.Θ.) παιδιών ηλικίας 6-11 ετών αυξήθηκε από 4,2% το 1963-1965 σε 15,3% το 1999-2002, ποσοστό που έχει φτάσει υψηλότερα επίπεδα κατά τη διάρκεια της πρώτης δεκαετίας του 21ου αιώνα. Κατά την προσχολική ηλικία (μέση ηλικία: 5,6 έτη), ποσοστό 12,4% των παιδιών είναι παχύσαρκα και 14,9% είναι υπέρβαρα, ενώ κατά την εφηβεία (μέση ηλικία: 14,1 έτη) το 20,8% των εφήβων είναι παχύσαρκα και

το 17,0% είναι υπέρβαροι. Τα υπέρβαρα παιδιά ηλικίας 5 ετών έχουν τέσσερις φορές περισσότερες πιθανότητες από τα παιδιά φυσιολογικού βάρους σώματος να γίνουν παχύσαρκα μέχρι την ηλικία των 14 ετών.<sup>1</sup> Στο Ηνωμένο Βασίλειο, το 30% των ενηλίκων είναι παχύσαρκοι, ενώ το 30% των παιδιών ηλικίας 2 έως 15 ετών είναι υπέρβαρα ή παχύσαρκα.<sup>2</sup> Ο επιπολασμός της παχυσαρκίας αναμένεται να ανέρθει στο 75% μέχρι το 2030 στις Ηνωμένες Πολιτείες Αμερικής<sup>3</sup> και στο 50% μέχρι 2050 στο Ηνωμένο Βασίλειο.<sup>2</sup> Στην Ελλάδα το ποσοστό των υπέρβαρων και παχύσαρκων παιδιών και εφήβων υπερβαίνει πλέον το 30-35%.<sup>4</sup> Με δεδομένο ότι στη χώρα μας έχουμε περίπου 100.000 γεννήσεις ετησίως, και κατά συνέπεια 1.800.000 παιδιά και εφήβους (από τη γέννηση μέχρι τα 18 έτη), την παρούσα χρονική στιγμή 540.000 – 630.000 (30-35% σε 1.800.000) παιδιά και έφηβοι στην Ελλάδα είναι υπέρβαροι ή παχύσαρκοι. Η επίπτωση της παιδι-

κής υπερβαρότητας και παχυσαρκίας είναι παρόμοια υψηλή σε άλλες Ευρωπαϊκές και μη Ευρωπαϊκές χώρες.<sup>2</sup>

Η υπερβαρότητα και παχυσαρκία στην παιδική και εφηβική ηλικία οδηγούν σε παχυσαρκία κατά την ενήλικη ζωή και συνδέονται με σημαντική νοσηρότητα και θνησιμότητα.<sup>5-10</sup> Είναι πιθανό ότι η “επιδημία της παχυσαρκίας” μπορεί να αντιστρέψει την τρέχουσα τάση της μείωσης του ποσοστού θνησιμότητας από καρδιαγγειακά αίτια, οδηγώντας σε μικρότερη διάρκεια ζωής για τα σημερινά παιδιά. Οι επιπλοκές της παχυσαρκίας περιλαμβάνουν υπέρταση, δυσλιπιδαιμία, υπερινσουλιναίμία, ινσουλινοαντοχή, διαβήτη τύπου 2, αθηροσκληρωτική καρδιαγγειακή νόσο, υπογοναδισμό, ορθοπεδικές επιπλοκές, διαταραχές του ενδοθελίου, χολοκυστίτιδα, κοινωνικό στιγματισμό, καθώς και αυξημένη επίπτωση εμφάνισης κακοηθειών.<sup>5-10</sup>

Εκτός από την αυξημένη νοσηρότητα και θνησιμότητα, οι επιπλοκές της παχυσαρκίας ευθύνονται και για ε’να σημαντικάνηλο ποσοστό των δαπανών της δημόσιας υγείας. Το κόστος για την αντιμετώπιση της παχυσαρκίας και μόνο είναι ιδιαίτερα υψηλό ακόμη και χωρίς να συμπεριληφθεί το τεράστιο κόστος από την αντιμετώπιση των επιπλοκών των παχυσαρκίας και του κοινωνικοοικονομικού αντικτύπου της. Στις ΗΠΑ, οι εκτιμώμενες ιατρικές δαπάνες που αποδίδονται στην υπερβαρότητα και παχυσαρκία είναι 78,5 δισεκατομμύρια δολάρια ΗΠΑ ετησίως.<sup>11</sup> Πρόσφατη μελέτη που βασίστηκε σε εθνικά αντιπροσωπευτικά δεδομένα που συλλέχθηκαν τις τελευταίες τρεις δεκαετίες στις ΗΠΑ έδειξε ότι τα άμεσα κόστη υγειονομικής περίθαλψης που οφείλονται στην παχυσαρκία και την υπερβαρότητα θα υπερδιπλασιάζονται κάθε δεκαετία. Μέχρι το 2030, το κόστος αναμένεται να κυμανθεί από 860,7 έως 956,9 δισεκατομμύρια δολάρια ΗΠΑ, που αντιπροσωπεύουν 1 στα 6 δολάρια που δαπανώνται για την υγειονομική περίθαλψη. Στο Ηνωμένο Βασίλειο, μέχρι το 2030, η παχυσαρκία και οι επιπλοκές που συνδέονται με αυτή, προβλέπεται να κοστίζουν περίπου 2 δισεκατομμύρια λίρες στερλίνες ετησίως.<sup>2</sup>

Κατά συνέπεια, είναι απαραίτητο να δοθεί έμφαση τόσο στην πρόληψη, όσο και στην αντιμε-

τώπιση της παχυσαρκίας κατά την παιδική και εφηβική ηλικία, ώστε να βοηθήσουμε αποτελεσματικά στη βελτίωση της υγείας των πολιτών κατά την ενήλικη ζωή, καθώς και στην ελάττωση του κόστους νοσηλείας τους λόγω των επιπλοκών της παχυσαρκίας.

Η προοδευτικά αυξανόμενη επικράτηση της υπερβαρότητας και παχυσαρκίας στην Ελλάδα και ενδεχομένως σε άλλες χώρες, παρά τις σημαντικές προσπάθειες που καταβάλλονται για να αντιμετωπιστούν οι επιδημικές διαστάσεις, δείχνουν ότι οι τρέχουσες πολιτικές μας για την υγεία και οι εφαρμοζόμενες στρατηγικές δεν είναι αποτελεσματικές. Αίτια της μη ικανοποιητικής αυτής αντιμετώπισης περιλαμβάνουν:

1. Πλημμελή καταγραφή του ΔΜΣ σε παιδιά και εφήβους που προσέρχονται σε Παιδιάτρους ή Γενικούς Ιατρούς για οξεία ή χρόνια ιατρικά προβλήματα. Κατά την κλινική εξέταση/αξιολόγηση, οι γιατροί συχνά επικεντρώνονται στη διαχείριση των οξέων ή χρόνιων ιατρικών προβλημάτων και δεν καταγράφουν το βάρος και το ύψος κατά την επίσκεψη. Σε άλλες περιπτώσεις, ακόμη κι αν καταγράψουν αυτές τις μετρήσεις δεν υπολογίζουν τον ΔΜΣ ή δεν τοποθετούν το αποτέλεσμα του υπολογισμού του ΔΜΣ στην καμπύλη του ΔΜΣ. Έτσι, δεν αναγνωρίζουν την υπερβαρότητα ή παχυσαρκία έγκαιρα και, ως εκ τούτου, δεν διαχειρίζονται αυτούς τους ασθενείς με τον κατάλληλο τρόπο.
2. Έλλειψη σαφούς καθοδήγησης των Παιδιάτρων, Γενικών Ιατρών και άλλων επιστημόνων υγείας σχετικά με το πώς θα διακινήσουν ένα υπέρβαρο ή παχύσαρκο παιδί. Παρόλο που κατανοούν τη σημασία και τις συνέπειες του προβλήματος, δεν γνωρίζουν τις εθνικές κατευθυντήριες οδηγίες ή την προσέγγιση βήμα προς βήμα σχετικά με το πώς να κατευθύνουν τους ασθενείς και τις οικογένειές τους.
3. Σε πολλές χώρες, οι Γενικοί Ιατροί πραγματοποιούν ετήσιες εξετάσεις για την προληπτική υγεία των παιδιών και εφήβων και θεωρείται ότι παίζουν σημαντικό ρόλο στην πρόληψη, τον εντοπισμό και τη διαχείριση των υπέρβαρων παιδιών και εφήβων. Σε ένα τέτοιο πενταετές πρόγραμμα πρόληψης,

περίπου το ένα τρίτο των υπέρβαρων παιδιών εκτιμήθηκε ότι ήταν φυσιολογικό βάρος από τους Γενικούς Ιατρούς.<sup>12</sup> Επιπλέον, λίγοι είναι εκπαιδευμένοι στη χρήση στρατηγικών τροποποίησης συμπεριφοράς και ο διαθέσιμος χρόνος μπορεί να μην επαρκεί για τον προσδιορισμό των στόχων και των στρατηγικών για αλλαγή συμπεριφοράς.<sup>13</sup>

4. Έλλειψη συντονισμού των φορέων που εμπλέκονται στην υγεία του παιδιού σχετικά με την αντιμετώπιση της υπερβαρότητας και παχυσαρκίας
5. Έλλειψη ικανοποιητικής ενημέρωσης των γονέων καθώς και όλων των φορέων που σχετίζονται με την εκπαίδευση, τη διατροφή και την άσκηση του παιδιού σχετικά με την πρόληψη και αντιμετώπιση της υπερβαρότητας και παχυσαρκίας.

Στόχος μας ήταν η ανάπτυξη ενός ολοκληρωμένου και εξατομικευμένου σχεδίου δράσης παρέμβασης για την πρόληψη και αντιμετώπιση της υπερβαρότητας και παχυσαρκίας κατά την παιδική και εφηβική ηλικία, λαμβάνοντας υπ' όψιν τόσο τις δομές του υπάρχοντος δημοσίου συστήματος υγείας όσο και όλους τους εμπλεκόμενους δημόσιους και ιδιωτικούς φορείς

Ειδικότερα, σχεδιάσαμε και αναπτύξαμε ένα Ηλεκτρονικό Σύστημα Βάσης Δεδομένων (ΗΣΒΔ) που αποτελείται από α) ένα Ηλεκτρονικό Φάκελο Υγείας (ΗΦΥ) για την καταγραφή και μακρόχρονη παρακολούθηση όλων των παιδιών και των εφήβων (από τη γέννηση έως την ηλικία των 18 ετών), και β) μια πληθώρα αρχείων Ηλεκτρονικών Θεραπευτικών Αλγορίθμων (ΗΘΑ) που παρέχουν συγκεκριμένες και σαφείς οδηγίες για την πρόληψη και τη διαχείριση της υπερβαρότητας και παχυσαρκίας, ανάλογα με την ηλικία, το φύλο, τον ΔΜΣ και όλες τις άλλες σχετικές πληροφορίες που καταχωρούνται στον ΗΦΥ.

Αξιολογήσαμε επίσης την αποτελεσματικότητα αυτού του συστήματος σε ένα μεγάλο αριθμό υπέρβαρων και παχύσαρκων παιδιών και εφήβων. Η μελέτη μας έδειξε ότι οι παρεμβάσεις που προτείνονται οδήγησαν σε ελάττωση του ποσοστού παχυσαρκίας κατά 30% και της υπερβαρότητας κατά 35% μέσα σε ένα έτος από την εφαρμογή της.

## Μεθοδολογία

Με τη χρήση Τεχνολογιών Πληροφορικής και Επικοινωνιών (ICT)<sup>14-16</sup>, προχωρήσαμε στην ανάπτυξη Ηλεκτρονικής Διαδικτυακής Εφαρμογής, το *Εθνικό Μητρώο Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία*, η οποία υποστηρίζει διαλειτουργικότητα με άλλες εθνικές διαδικτυακές υποδομές (π.χ. ηλεκτρονική συνταγογράφηση) και πολυεπίπεδη ασφάλεια που καλύπτει προληπτικούς, διερευνητικούς και διαχειριστικούς ελέγχους. Αυτό περιλαμβάνει μεταξύ άλλων κρυπτογράφηση, επεξεργασία δεδομένων, ιχνηλασιμότητα των εργασιών, κεντρικό σύστημα διαχείρισης χρηστών και καθορισμού δικαιωμάτων, διαδικασία ταυτοποίησης και πιστοποίησης και ασφάλεια εφαρμογών. Η Εγκατάσταση και Φιλοξενία της Κεντρικής Βάσης Δεδομένων προσφέρεται από την Ιατρική Εταιρεία Αθηνών, και το έργο υλοποιήθηκε από την εταιρεία Datamed A.E. - εξειδικευμένη εταιρεία Ιατρικής Πληροφορικής, η οποία ανακηρύχθηκε Ανάδοχος σχετικού δημόσιου διαγωνισμού.<sup>17</sup>

Το έργο εντάσσεται στη γενικότερη προσπάθεια, τόσο σε Ελλαδικό όσο και σε Ευρωπαϊκό επίπεδο, λειτουργίας αξιόπιστων Μητρώων Ασθενών, και ως τέτοιο σχεδιάστηκε και υλοποιήθηκε, ώστε να ικανοποιεί όλες τις τελευταίες ευρωπαϊκές οδηγίες και κανονισμούς. Επιπλέον το έργο ικανοποιεί όλες τις τελευταίες θεσμικές εξελίξεις στην Ελλάδα που αφορούν στη δημιουργία του Πρωτοβάθμιου Εθνικού Δικτύου Υγείας (ΠεδΥ) και στην ανάπτυξη εργαλείων κλινικής διακυβέρνησης.

Συγκεκριμένα, αναπτύξαμε ένα ΗΦΥ Ασθενούς για την ηλεκτρονική καταγραφή των ευρημάτων του ιατρικού ιστορικού και της κλινικής αξιολόγησης, καθώς και αρχείων Θεραπευτικών Αλγορίθμων, τα οποία παρέχουν συγκεκριμένες και σαφείς οδηγίες για τη διαχείριση της υπερβαρότητας και παχυσαρκίας κατά την παιδική και εφηβική ηλικία. Υπάρχουν Θεραπευτικοί Αλγόριθμοι που εφαρμόζονται στο Ηλεκτρονικό Σύστημα Βάσης Δεδομένων για να επιτρέψουν στο Ηλεκτρονικό Σύστημα Βάσης Δεδομένων να επιλέξει το καταλληλότερο για κάθε περίπτωση

ασθενούς. Παρέχουμε σε κάθε Παιδίατρο και Γενικό Ιατρό έναν προσωπικό κωδικό αναγνώρισης (password) μέσω του οποίου μπορούν να έχουν πρόσβαση στον ΗΦΥ μέσω κεντρικής πύλης προσβάσιμης από συγκεκριμένη διεύθυνση ιστότοπου. Διασφαλίσαμε ασφαλή διαδικτυακή σύνδεση, κρυπτογράφηση των δεδομένων, και υποστήριξη για όλες τα ερωτήματα/διευκρινίσεις που θα προκύψουν. Επίσης, λάβαμε έγκριση από την Επιτροπή Ηθικής και Δεοντολογίας, Άδεια από την Αρχή Προστασίας Δεδομένων Προσωπικού Χαρακτήρα και πιστοποίηση των Παιδιάτρων και Γενικών Ιατρών μέσω ΗΔΙΚΑ ΑΕ.

Αυτό που ξεχωρίζει το παρόν έργο, όμως, από ένα σύστημα απλής καταγραφής και διαχείρισης στοιχείων ασθενών, είναι ο δυναμικός του χαρακτήρας, που προκύπτει από την ενσωματωμένη ευφυία του συστήματος, μέσω ολοκληρωμένων θεραπευτικών πρωτοκόλλων και αλγορίθμων, ώστε να παρέχει κλινικές οδηγίες και κατευθύνσεις προς τους Παιδιάτρους και Γενικούς Ιατρούς, τόσο για την πρόληψη όσο και για την αντιμετώπιση της υπερβαρότητας και παχυσαρκίας.

Τα δεδομένα που καταγράφονται στον ΗΦΥ περιλαμβάνουν:

- **Προσωπικά Δεδομένα του Παιδιού/Εφήβου** και αφορούν γενικά στοιχεία: ΑΜΚΑ, επώνυμο, όνομα, ονοματεπώνυμο πατέρα και μητέρας, ημερομηνία γέννησης, διεύθυνση, τηλέφωνο, email και στοιχεία ασφαλιστικού φορέα, καθώς και δημογραφικά στοιχεία: φύλο, εθνικότητα, περιοχή διαμονής, κατάσταση οικογένειας, σχολείο, επιδόσεις του παιδιού, αλλά και επάγγελμα και εκπαίδευση των γονέων
- **Δεδομένα Ιστορικού Υγείας**, που αφορούν συνοπτικό και αναλυτικό ιστορικό υγείας: διατροφή, επίπεδο δραστηριότητας και άσκησης του παιδιού, επιβλαβείς συνήθειες (κάπνισμα, αλκοόλ, ναρκωτικά), πιθανές αλλεργίες, περιγεννητικό ιστορικό (κύηση και τοκετός), εμβολιασμοί, νοσηλείες και χειρουργικές επεμβάσεις, νοσήματα, γυναικολογικό ιστορικό, πιθανές φαρμακευτικές αγωγές, αλλά και το ιστορικό αυξημένου βάρους που ενδέχεται να εμφανίσει το παιδί.

- **Οικογενειακό Ιστορικό:** ύψος, βάρος και ΔΜΣ πατέρα και μητέρας, καθώς και κληρονομικό ιστορικό και νοσήματα
- **Δεδομένα Επίσκεψης**, όπου τα στοιχεία περιλαμβάνουν βιομετρικούς δείκτες που χρησιμοποιούνται για την εξαγωγή της θεραπευτικής οδηγίας και είναι: ηλικία, βάρος, ύψος, ΔΜΣ, περιφέρεια μέσης, ισχίων, καθώς και δεδομένα αντικειμενικής εξέτασης: αρτηριακή πίεση, διατροφική συμπεριφορά και άσκηση, εξαρτήσεις και επιπλέον κλινικά δεδομένα. Επίσης, εξάγεται το διάγραμμα επίσκεψης, ενώ δίνεται η δυνατότητα στον γιατρό να συμπληρώσει δικές του παρατηρήσεις
- **Συγκατάθεση Ασθενή.** Αξίζει να σημειωθεί ότι, σεβόμενοι την ανάγκη για συμμόρφωση με την Αρχή Προστασίας Δεδομένων Προσωπικού Χαρακτήρα, η εφαρμογή περιλαμβάνει πρόβλεψη, προκειμένου ο ασθενής να δώσει τη συγκατάθεση του για πρόσβαση του γιατρού στα στοιχεία του φακέλου του. Ο γιατρός εκτυπώνει μία δήλωση συγκατάθεσης για πρόσβαση στα στοιχεία του φακέλου του ασθενή, η οποία υπογράφεται από το γονέα, ενώ στο σύστημα αποθηκεύονται τα στοιχεία της αστυνομικής ταυτότητας του γονέα ο οποίος έχει δώσει τη συγκατάθεση του.

Οι βασικές λειτουργίες της εφαρμογής είναι οι εξής:

- **Διαχείριση ιατρικού φακέλου ασθενούς.** Η διαχείριση ασθενών γίνεται σύμφωνα με διεθνή πρότυπα (ICD-10). Δίνεται επίσης η δυνατότητα για την καταχώρηση ελεύθερου κειμένου.
- **Διατήρηση ιστορικού.** Κάθε πληροφορία που καταχωρείται διατηρείται στην βάση δεδομένων και εμφανίζεται με κατάλληλο τρόπο ώστε να είναι ευανάγνωστη και διαθέσιμη στον ιατρό όταν την χρειάζεται.
- **Διάγνωση.** Αξιοποίηση του διεθνούς standard ταξινόμησης διαγνώσεων ICD-10 (επίσημη μεταφρασμένη έκδοση)
- **Αλλεργίες.** Ειδοποίηση για καταχωρημένες αλλεργίες με κατάλληλη σήμανση.
- **Επισκέψεις.** Διαχείριση πλήρους ιστορικού

- επισκέψεων και θεραπευτικών οδηγιών που έχουν εκδοθεί από το γιατρό.
- **Εμβόλια.** Πλήρης διαχείριση ημερομηνιών για εμβόλια με βάση την τρέχουσα ημερομηνία και την κατάσταση εμβολιασμών του ασθενή.
  - **Παραπομπές.** Διαχείριση ιστορικού παραπομπών.
  - **Εργαστηριακές εξετάσεις.** Δυνατότητα για αναλυτική καταγραφή δεδομένων από εργαστηριακές εξετάσεις. Η καταχώρηση μπορεί να γίνεται και από την Γραμματεία.
  - **Υπενθυμίσεις.** Οι υπενθυμίσεις προορίζονται στον ιατρό ή στον ασθενή (αν έχει δώσει email) μέσω email.
  - **Χρήσιμες εκτυπώσεις.** Μηχανισμός για δημιουργία εκτυπώσεων όπως π.χ. ιατρική βεβαίωση, διατροφή για βρέφη, ερωτηματολόγια και συστάσεις προς γονείς κτλ.

## Αποτελέσματα

Το *Εθνικό Μητρώο Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία*, ολοκληρώθηκε το Σεπτέμβριο 2015, και η πρόσβαση γίνεται από την ιστοσελίδα <http://app.childhood-obesity.gr/>. Η Εικόνα 1, απεικονίζει την Αρχική Σελίδα, το Κεντρικό Μενού, τον ΗΦΥ, την Εκτέλεση της Θεραπευτικής Οδηγίας (Θεραπευτικός Αλγόριθμος, και το Εθνικό Πρόγραμμα Εμβολιασμών). Όπως αναφέρθηκε ανωτέρω, πρόκειται για μια Ηλεκτρονική Διαδικτυακή Εφαρμογή, η οποία υλοποιήθηκε σε περιφερειακό και εθνικό επίπεδο, προκειμένου να εκπληρώσει δύο κύριους στόχους: πρώτον, την ηλεκτρονική καταγραφή όλων των παιδιών και εφήβων (από τη γέννηση μέχρι 18 ετών) πανελλαδικά, και δεύτερον την καθοδήγηση των Παιδιάτρων και Γενικών Ιατρών σχετικά με την διακίνηση και αντιμετώπιση ενός υπέρβαρου ή παχύσαρκου παιδιού. Η εισαγωγή και υλοποίηση αυτής της Ηλεκτρονικής Διαδικτυακής Εφαρμογής είναι μοναδική και καινοτόμα καθώς απ' όσο γνωρίζουμε, δεν έχει χρησιμοποιηθεί προηγουμένως σε κάποια άλλη χώρα.

Με την είσοδο στην εφαρμογή, κάθε ιατρός

έχει την ευκαιρία να δημιουργήσει ένα νέο ΗΦΥ για τους νέους ασθενείς που θα καταγράψει και έχει πρόσβαση μόνο στους ασθενείς που ο ίδιος έχει καταχωρήσει στο σύστημα. Στον ΗΦΥ, ο γιατρός καταγράφει πληροφορίες σχετικά με το ιατρικό ιστορικό, το οικογενειακό ιστορικό, όλες τις ανθρωπομετρικές παραμέτρους (π.χ. βάρος, ύψος, ΔΜΣ, λόγος μέσης προς ισχίο), καθώς και τα ευρήματα της κλινικής εξέτασης. Πρόσθετες πληροφορίες αναφορικά με τη διατροφή και την άσκηση μπορούν επίσης να καταχωρηθούν στον ΗΦΥ. Η εφαρμογή στη συνέχεια υπολογίζει αυτόματα τον ΔΜΣ, και ενημερώνει τον ιατρό εάν ο ασθενής έχει φυσιολογικό ΔΜΣ ή είναι υπέρβαρος ή παχύσαρκος. Επιπλέον, στην οθόνη του υπολογιστή εμφανίζεται η αντίστοιχη καμπύλη ανάπτυξης του ΔΜΣ (διαφορετική για τα αγόρια και τα κορίτσια), προκειμένου ο γιατρός να έχει άμεσα την σχετική πληροφόρηση, την οποία μεταβιβάζει στους γονείς/κηδεμόνες προς ενημέρωσή τους. Επιπλέον, το σύστημα προχωρά αυτόματα στην επιλογή του καταλληλότερου θεραπευτικού αλγορίθμου για τον συγκεκριμένο ασθενή, ανάλογα με τον ΔΜΣ του, ηλικία, φύλο, ιατρικό ιστορικό, συνήθειες διατροφής και άσκησης και αρκετούς άλλους παράγοντες, οι οποίοι παρέχουν ένα ολοκληρωμένο και εξατομικευμένο πλάνο για την πρόληψη και αντιμετώπιση του προβλήματος. Ο ειδικά σχεδιασμένος Θεραπευτικός Αλγόριθμος, παρέχει συγκεκριμένες, σαφείς και αναλυτικές οδηγίες σχετικά με το πώς ο Παιδίατρος ή/και Γενικός Ιατρός θα καθοδηγήσει ένα υπέρβαρο ή παχύσαρκο παιδί, καθώς και ένα παιδί με φυσιολογικό ΔΜΣ, πχ: τι θα συμβουλευτεί αρχικά, πότε θα επανεξετάσει τον ασθενή, πώς θα διακινήσει τον ασθενή αν έχει απαντήσει στις παρεμβάσεις και πώς αν συνεχίζει η αύξηση του ΔΜΣ, παρά την εφαρμογή των παρεμβάσεων, πότε θα ζητήσει εργαστηριακές εξετάσεις και ποιές θα είναι αυτές, πότε θα παραπέμψει σε Διατροφολόγο, Καθηγητή Φυσικής Αγωγής ή Παιδοψυχολόγο, πότε θα παραπέμψει σε εξειδικευμένο Κέντρο Παχυσαρκίας.<sup>17</sup>

Έτσι διασφαλίζεται ένας ενιαίος τρόπος αντιμετώπισης της παχυσαρκίας σε όλη τη χώρα, καθώς και η καθοδήγηση Παιδιάτρων και Γενικών Ιατρών που βρίσκονται μακριά από εξειδικευμένα κέντρα.

### **Αξιολόγηση της αποτελεσματικότητας των παρεμβάσεων**

Η αξιολόγηση της αποτελεσματικότητας των παρεμβάσεων που προτείνονται στην Ηλεκτρονική Διαδικτυακή Εφαρμογή πραγματοποιήθηκε μέσα στα πλαίσια λειτουργίας του Ιατρείου Αντιμετώπισης Αυξημένου Βάρους Σώματος, το οποίο λειτουργεί καθημερινά στη Μονάδα Ενδοκρινολογίας, Μεταβολισμού και Διαβήτη της Α' Παιδιατρικής Κλινικής της Ιατρικής Σχολής Πανεπιστημίου Αθηνών, στο Νοσοκομείο Παίδων «Η Αγία Σοφία». Σήμερα, 2.500 περίπου παιδιά και εφηβόι παρακολουθούνται στο Ιατρείο Αντιμετώπισης Αυξημένου Βάρους Σώματος ανά τακτά χρονικά διαστήματα. Για την μελέτη έχει ληφθεί έγκριση από την Επιτροπή Ηθικής και Δεοντολογίας του Νοσοκομείου Παίδων «Η Αγία Σοφία» καθώς και έγγραφη συγκατάθεση από τους γονείς/κηδεμόνες όλων των παιδιών που συμμετείχαν.

Μελετήσαμε 1.270 παιδιά και εφήβους [μέση ηλικία ( $\pm$  τυπική απόκλιση): 10·06  $\pm$  3·29 έτη, 573 αγόρια και 697 κορίτσια, 608 ήταν προεφηβικά και 508 στην εφηβεία] που εντάχθηκαν στο πρόγραμμα και παρακολούθησαν για περισσότερο από ένα έτος. Κατά την αρχική αξιολόγηση έγινε καταγραφή του ατομικού και οικογενειακού ιστορικού, και των ανθρωπομετρικών παραμέτρων (ύψος, βάρος, ΔΜΣ, λόγος περιμέτρου μέσης/ισχίων). Επίσης, έγινε κλινική εξέταση, λιπομέτρηση και πλήρης αιματολογικός, βιοχημικός, και ενδοκρινολογικός έλεγχος. Στη συνέχεια, κάθε παιδί έλαβε εξατομικευμένο πρόγραμμα διατροφής και άσκησης και έγινε ψυχολογική παρέμβαση σε όσα παιδιά έρχονταν αυτής. Η παρακολούθηση συνεχίστηκε στα παχύσαρκα παιδιά ανά ένα μήνα, στα υπέρβαρα ανά δύο μήνες και στα φυσιολογικού ΔΜΣ ανά τρεις μήνες. Σε ένα έτος έγινε εκ νέου αξιολόγηση με κλινικό και εργαστηριακό έλεγχο.

Κατά την αρχική αξιολόγηση, 60,2% των παιδιών και εφήβων ήταν παχύσαρκοι, 28,4% υπέρβαρα και 11,4% είχαν φυσιολογικό ΔΜΣ. Τα αγόρια είχαν υψηλότερα ποσοστά παχυσαρκίας (68,5% vs. 53,3%,  $p < 0·001$ ), ενώ ένα υψηλότερο ποσοστό κοριτσιών ήταν υπέρβαρα (30·7% vs. 25·6%,  $p < 0·001$ ). Η εμφάνιση αύξησης του σω-

ματικού βάρους παρατηρήθηκε μετά την ηλικία των 5 ετών και ήταν προοδευτική σε όλη την παιδική και εφηβική ηλικία. Μετά από ένα χρόνο από τις προτεινόμενες παρεμβάσεις, ο επιπολασμός της παχυσαρκίας και της υπερβαρότητας μειώθηκε κατά 30% και 35% αντίστοιχα, ο φυσιολογικός ΔΜΣ αυξήθηκε κατά 8% και οι δείκτες καρδιομεταβολικού κινδύνου βελτιώθηκαν σημαντικά. Τα αποτελέσματα αυτά υποδηλώνουν ότι το προτεινόμενο εξατομικευμένο πρόγραμμα διατροφής, σωματικής δραστηριότητας και ψυχολογικής παρέμβασης έχει ιδιαίτερα σημαντικά αποτελέσματα ως προς την αποτελεσματική αντιμετώπιση και πρόληψη της παχυσαρκίας κατά την παιδική και εφηβική ηλικία.<sup>18</sup>

### **Συζήτηση**

Η αντιμετώπιση της παιδικής παχυσαρκίας και η διατήρηση φυσιολογικού ΔΜΣ για τα παιδιά και τους εφήβους υπήρξε ο κύριος στόχος πολλών διαφορετικών πρωτοβουλιών. Παρά τις προσπάθειες αυτές, τα ποσοστά υπερβαρότητας και παχυσαρκίας σε παγκόσμιο επίπεδο, καθώς και στην Ελλάδα, συνεχίζουν να αυξάνονται. Οι αυξανόμενοι ρυθμοί της υπερβαρότητας και παχυσαρκίας είναι ως επί το πλείστον αποτέλεσμα πολλών κοινωνικών και συμπεριφορικών τροποποιήσεων που έχουν οδηγήσει σε ένα περιβάλλον που συμβάλλει στην αύξηση του σωματικού βάρους. Επιπλέον, η παχυσαρκία πρέπει να θεωρείται ως χρόνιο νόσημα που απαιτεί μια διαρκή, πολυτομεακή και πολυδιάστατη συνεργασία από το σύστημα υγείας μιας χώρας σε όλα τα επίπεδα.<sup>19</sup>

Διάφορες διεθνείς επιστημονικές και υγειονομικές οργανώσεις υποστήριξαν τη χρήση νέων τεχνολογιών για την αντιμετώπιση της επιδημίας της παχυσαρκίας κατά την παιδική ηλικία και την εφηβεία.<sup>20</sup> Όπως δήλωσαν οι συντάκτες του πλαισίου<sup>7, 21</sup> «Η ηλεκτρονική υγείας (e-Health), έχει μετακινηθεί από τον προσανατολισμό της περίθαλψης οξέων περιστατικών στην πρόληψη και τη διαχείριση των ασθενειών, από την εστίαση στο άτομο στην εστίαση στον πληθυσμό, και από το θεσμικό πλαίσιο στις κοινωνίες και στον κυβερνο-

χώρο. Ταυτόχρονα, τα μοντέλα παροχής υγειονομικής περίθαλψης έχουν εξελιχθεί από την ιατρική και κλινική εστίαση, σε μοντέλα φροντίδας με επίκεντρο τον ασθενή που βασίζονται σε συμμετοχικές διαδικασίες λήψης αποφάσεων.<sup>22</sup> Αυτά τα συστήματα ηλεκτρονικής υγείας διαφέρουν στο πεδίο εφαρμογής τους, στον πληθυσμό-στόχο, στα συστατικά μέρη τους και στην τεχνολογική πλατφόρμα που χρησιμοποιείται.<sup>23</sup>

Λίγες δημοσιευμένες μελέτες έχουν διερευνήσει την επίδραση της χρήσης των εφαρμογών ηλεκτρονικής υγείας στις παρεμβάσεις απώλειας βάρους και έχουν αξιολογήσει την αποτελεσματικότητά τους για περισσότερο από ένα χρόνο. Μεταξύ αυτών είναι το Child Health and Obesity Informatics System (CHOIS), εναρμονισμένο με τις αποφάσεις HIPAA (Health Insurance Portability and Accountability Act) & FERPA (Family Educational Rights and Privacy Act), το οποίο ενσωματώνει μεγάλες βάσεις δεδομένων σε περιβάλλον τεχνολογίας υψηλής απόδοσης. Πρόκειται για μια διαδικτυακή εφαρμογή που παρέχει φόρμες για την καταχώρηση δεδομένων (όπως δημογραφικά στοιχεία, ύψος και βάρος για τον υπολογισμό ΔΜΣ, καθώς και πληροφορίες γονιδιώματος), που επιτρέπει στις σχολικές νοσοκόμες να εισάγουν δεδομένα από παιδιά σχολικής ηλικίας, προκειμένου να εντοπίζουν αυτά που βρίσκονται σε κίνδυνο παχυσαρκία, έτσι ώστε να τα εντάξουν σε προγράμματα πρόληψης και αντιμετώπισης.<sup>24</sup>

Το Resource Information Program for Parents on Lifestyle and Education (RIPPLE), αντιπροσωπεύει ένα συνοπτικό πρόγραμμα παρέμβασης και παραπομπής σε θεραπεία (SBIRT) για τους γονείς για να βοηθήσουν στην πρόληψη της παιδικής παχυσαρκίας στην πρωτοβάθμια φροντίδα υγείας. Θεωρήθηκε από τους συμμετέχοντες ως πρακτικό, καλά σχεδιασμένο και καινοτόμο. Παρόλα αυτά πρότειναν βελτιώσεις σε ορισμένα χαρακτηριστικά, όπως οι όροι που σχετίζονται με το βάρος, επειδή αντιλήφθηκαν ότι μπορεί να προκαλέσει ανεπιθύμητες ανταποκρίσεις από μερικούς γονείς.<sup>25</sup>

Το MINSTOP (Mobile-based Intervention Intended to Stop Obesity in Preschoolers) είναι μια παρέμβαση με βάση το διαδίκτυο και το κινητό

τηλέφωνο που έχει σχεδιαστεί για να βοηθήσει τους γονείς να προωθήσουν την υγιεινή διατροφή και τη σωματική άσκηση στα παιδιά. Η αποτελεσματικότητά του δεν έχει ακόμη αναφερθεί.<sup>26</sup>

Το HopSCOTCH (Shared-Care Obesity Trial in Children) περιλάμβανε την ανάπτυξη ενός λογισμικού μέσω διαδικτύου με τους ακόλουθους στόχους: i) να επιτρέψει στους ειδικούς για την παχυσαρκία και στους Γενικούς Ιατρούς να συνεργαστούν και να επικοινωνήσουν στενά για την καλύτερη φροντίδα των ασθενών τους, ii) να παράσχει μια δομημένη αλλά αποτελεσματική προσέγγιση στην καθοδήγηση για την διαχείριση του βάρους, iii) να παράσχει ένα μηχανισμό που θα επιτρέπει τόσο στους Γενικούς Ιατρούς όσο και στους ειδικούς να καταγράφουν και να παρακολουθούν την πρόοδο του ασθενούς ταυτόχρονα, και, iv) να διαλειτουργεί με το υπάρχον λογισμικό που έχουν εγκαταστήσει οι Γενικοί Ιατροί στον υπολογιστή τους για την παρακολούθηση των ασθενών τους. Το έργο υπερέβη κατά πολύ τον προϋπολογισμό και παρουσιάστηκαν προβλήματα αναφορικά με την εγκατάσταση, τα μηνύματα καθώς και καθυστερήσεις κατά τη λήψη (download delays). Ήταν δύσκολο να εφαρμοστεί και να εκτιμηθεί επαρκώς σε πραγματικές συνθήκες λειτουργίας.<sup>27</sup>

Τέλος, το Child-Teen Obesity Treatment Service Platform αναπτύχθηκε μέσω συνεργασίας μεταξύ i) παρόχων υπηρεσιών υγείας, π.χ. νοσοκομεία και κέντρα υγείας, ii) παχύσαρκα παιδιά και εφήβους (που ήταν οι ουσιαστικοί χρήστες της εφαρμογής), και iii) ιδρυμάτων και εταιρειών ανάπτυξης εφαρμογών πληροφορικής και τηλεπικοινωνιών. Η ολοκληρωμένη πλατφόρμα υπηρεσιών περιελάμβανε, i) δύο εφαρμογές για κινητά ασθενών/γονέων, ii) μια ηλεκτρονική διαδικτυακή εφαρμογή για το ιατρικό προσωπικό, iii) μια εφαρμογή για κινητό για παρακολούθηση της λήψης τροφής (food-craving endurance), και iv) και μια εφαρμογή για κινητό για ιατρικές εξετάσεις. Η εγκατάσταση ολοκληρώθηκε επιτυχώς στο νοσοκομείο όπου πραγματοποιήθηκε το πιλοτικό πρόγραμμα. Η αποτελεσματικότητά της θα επαληθευτεί στο μέλλον όταν θα συμμετάσχουν και άλλοι οργανισμοί.<sup>28</sup>

Από όσο γνωρίζουμε, το *Εθνικό Μητρώο Πρό-*

ληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία της Ελλάδας είναι η πρώτη επαγγελματική διαδικτυακή εφαρμογή ηλεκτρονικής υγείας παγκοσμίως που προσφέρει μέσω προκαθορισμένων θεραπευτικών αλγορίθμων ένα σχεδιασμένο ολοκληρωμένο και εξατομικευμένο πρόγραμμα παρέμβασης. Οι παρεμβάσεις που προτείνονται εφαρμόστηκαν και αξιολογήθηκαν για την αποτελεσματικότητά τους σε 1.270 παιδιά και εφήβους, οι οποίοι παρακολούθησαν για τουλάχιστον ένα χρόνο. Η συχνότητα εμφάνισης παχυσαρκίας και υπερβαρότητας μειώθηκε κατά 30 και 35% αντίστοιχα, ο φυσιολογικός ΔΜΣ αυξήθηκε κατά 8%, ενώ οι δείκτες καρδιομεταβολικού κινδύνου βελτιώθηκαν σημαντικά. Ως εκ τούτου, αυτή η ηλεκτρονική πλατφόρμα θα μπορούσε να χρησιμοποιηθεί αποτελεσματικά για την πρόληψη και αντιμετώπιση της υπερβαρότητας και παχυσαρκίας κατά την παιδική και εφηβική ηλικία. Μπορεί να μεταφραστεί σε διάφορες γλώσσες για να χρησιμοποιηθεί σε άλλες χώρες, έχοντας προηγουμένως πραγματοποιήσει τις απαραίτητες προσαρμογές στις προτεινόμενες παρεμβάσεις και λαμβάνοντας υπόψη τις πολιτισμικές και κοινωνικές διαφορές.<sup>29</sup> Επιπρόσθετα, μπορεί να λειτουργήσει ως μητρώο καταγραφής εμβολιασμών (υποστηρίζει την πλήρη διαχείριση ημερομηνιών για εμβόλια με βάση την τρέχουσα ημερομηνία και την κατάσταση εμβολιασμών του παιδιού/εφήβου), και να επεκταθεί και για την καταγραφή και αντιμετώπιση ενηλίκων με παχυσαρκία ή άλλα χρόνια νοσήματα. Είναι σημαντικό να σημειωθεί ότι η μακροπρόθεσμη αποτελεσματικότητα

αυτού του συστήματος ηλεκτρονικής υγείας για την πρόληψη της παιδικής παχυσαρκίας απαιτεί την υποστήριξη των αρχών δημόσιας υγείας, τη μακροπρόθεσμη χρηματοδότηση από τις εθνικές αρχές και τη δέσμευση των Παιδιάτρων και Γενικών Ιατρών να καταγράφουν όλα τα παιδιά και τους εφήβους στο σύστημα.<sup>21,30</sup>

## Ευχαριστίες

Το έργο αυτό ήταν ο κύριος πυλώνας του Προγράμματος με τίτλο: “Ανάπτυξη Εθνικού Συστήματος Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία” και σύνθημα “Χάνω Βάρος – Κερδίζω Ζωή” (MIS 370545), το οποίο υλοποιήθηκε στο πλαίσιο του Επιχειρησιακού Προγράμματος “Ανάπτυξη Ανθρώπινου Δυναμικού” (ΕΠ.ΑΝ.Α.Δ) 2007-2013 και συγχρηματοδοτήθηκε από το Ευρωπαϊκό Κοινωνικό Ταμείο (Ε.Κ.Τ.) και από Εθνικούς Πόρους. Επιστημονική Υπεύθυνη είναι η κ. Ευαγγελία Χαρμανδάρη, Καθηγήτρια Παιδιατρικής-Παιδιατρικής Ενδοκρινολογίας.

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Επιστημονική Υπεύθυνη  
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Με τη Συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης

Το "Εθνικό Μητρώο Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας" υλοποιήθηκε στο πλαίσιο της ενταγμένης Πράξης "Ανάπτυξη Εθνικού Συστήματος Πρόληψης και Αντιμετώπισης της Υπερβαρότητας και Παχυσαρκίας κατά την Παιδική και Εφηβική Ηλικία", (MIS 370545), του Επιχειρησιακού Προγράμματος "Ανάπτυξη Ανθρώπινου Δυναμικού" (ΕΠ.ΑΝ.Α.Δ) 2007-2013 και συγχρηματοδοτήθηκε από το Ευρωπαϊκό Κοινωνικό Ταμείο (Ε.Κ.Τ.) και από Εθνικούς Πόρους

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# Does leukofiltration reduce pulmonary infections in CABG patients?

## A prospective, randomized study with early results and mid-term survival

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**Background** — We present the first prospective randomized study of primary coronary artery bypass grafting (CABG) patients who were analyzed for postoperative infections after undergoing blood and/or blood product transfusion (BBPT) with a Pall Purecell leukoreducing filter.

**Methods and results** — One hundred and four patients were enrolled between March 1998 and March 1999. Seventy-two of the patients received BBPT (average 5.6 units BBPT/filter patient and 5.6 units/control patient). Three patients who had CABG without extracorporeal circulation or mixed transfusions of filtered and unfiltered BBPT were excluded. The remaining 69 transfused patients (38 filtered, 31 control) were analyzed and the incidence of culture proven infections was recorded. Mid-term survival data were obtained from the National Death Index and Kaplan-Meier survival plots were constructed. All patients were stratified and matched according to the EuroSCORE. Thirty-day mortality was 2.6% and 3.2% for the filtered and control patients, respectively. There were 5 cases of culture proven infections in 38 filtered patients (13.2%) and 8 in 31 controls (25.8%),  $P=0.224$ . No pulmonary tract infections were recorded in the filter group vs. 4 (12.9%) in controls,  $P=0.048$ . Reduced length for mechanical ventilation (16.3 hours vs. 57.8,  $P=0.103$ ), length of stay (9.1 vs. 10.8 days,  $P=0.685$ ), as well as increased 50-month actuarial survival, (45.5 vs. 42.3 months,  $P=0.695$ ) in filtered vs. control, respectively, were recorded.

**Conclusions** — The use of leukoreduced BBPT reduced the incidence of pulmonary tract infections in patients undergoing CABG. (*Acta Cardiol* 2005; 60(3): 285-293)

**Keywords:** CABG – blood transfusion – leukofiltration – randomized study – mid-term survival.

## Introduction

Blood transfusion in patients undergoing coronary artery bypass grafting (CABG) is a significant contributor to postoperative complications<sup>1-6</sup>. Transfusion-associated immunosuppression predisposes patients to postoperative infections. Indeed, homologous blood transfusion increases the risk of post-CABG infections and has been identified as the most significant predictor of all postoperative infections among other variables such as age, gender, diabetes, number of grafts, pump time, etc.<sup>3</sup> The mechanism for the immunosuppression may involve the donor leukocytes bearing HLA class II antigens, which downregulate the immune system<sup>7</sup>. Leukocyte depleted blood is not used universally because of increased cost<sup>8</sup>.

Leukofiltration has been reported to reduce the incidence of infections and mortality following open-heart surgery such as valve replacement, CABG or both<sup>9</sup>. However, its impact on specific infections and complications in patients undergoing exclusively CABG has not yet been studied in a prospective randomized study. We report on a prospective randomized study involving primary CABG patients with extracorporeal circulation analyzed for specific infections following Pall Purecell leukoreducing filter use<sup>10</sup>. This study was designed to examine whether leukocyte depletion of homologous blood results in less complications and offers mid-term advantages.

## Material and methods

### PATIENTS

The study population consisted of 104 patients who provided a written, informed consent and were prospectively randomized between March 1998 and March 1999. Of those, 72 patients were transfused and 32 were not. In addition, three patients were excluded because they had CABG without extracorporeal circulation or mixed transfusions of filtered and unfiltered blood products. Thus, 69 patients who underwent CABG with extracorporeal circulation were eventually analyzed. Investigational protocols were approved by the Institutional Review Board for Human Studies at St. Luke's / Roosevelt Hospital

Center. The procedures were in accordance with the recommendations of the Helsinki Declaration of 1975<sup>11</sup>.

### Data collection

Upon entry into the operating theater, the patient was assigned to a filter vs. control group. Randomization was performed by an independent anesthesiologist. In patients with filter use, the Pall Purecell filter (Pall Biomedical Products Company, 2200 Northern Blvd., East Hills, NY 11548 516-484-5400) was used in all operating theater and post-operative blood or blood products transfusions (BBPT). Intraoperative blood transfusion was given to maintain hematocrit > 20 and postoperative blood transfusion was given to maintain haematocrit > 25. There was no filtration of cardiopulmonary bypass circuits or cardioplegia solution. No autotransfusion of preoperatively stored blood was employed in this study.

Data were fed into the New York State database. Variables tracked are shown in Tables 1 and 2. Infections were defined as culture proven, clinically suspected events that were treated. Additionally, the infections were subdivided into categories: wound, pulmonary tract infection (PTI), or urinary tract infection (UTI). Separate analyses were performed for diabetic patients and for those patients requiring more than three units of BBPT. The length of mechanical ventilation (total postoperative intubation time at the intensive care unit) and timing of transfusion were recorded (preoperative, intraoperative, postoperative, 3 days, 10 days, total use). The presence of fever and antibiotics were also recorded. All patients received 1.5 g cefuroxime intravenously approximately 30 minutes before incision and an additional 1.5 g after separation from cardiopulmonary bypass. Survival and postoperative data were collected.

### DATA ANALYSIS

Mid-term patient survival data were obtained from the United States Social Security Death Index database (<http://ssdi.genealogy.rootsweb.com>)<sup>12</sup>, which was queried in September 2002. This corresponds to a minimum and maximum follow-up time of 44

months (March 1999 patients) and 54 months (March 1998 patients), respectively. Then the database was updated for all deceased patients with the exact date of death; mid-term Kaplan-Meier survival plots<sup>13</sup> were determined and compared for the filtered and control patients. All charts were scrutinized by authors who did not participate in the random assignment of patients. There was no role of the funding organization in the collection of data, its analysis and interpretation, as well as in the right to approve or disapprove publication of the finished manuscript.

### STATISTICAL ANALYSIS

The study was powered to have 80% power ( $b=0.20$ ) to detect a reduction in PTI from 15% in controls (based on observational studies and our CABG database) to 2% in filtered patients, as well as a reduction in total infections from 30% in controls to 10%, at an  $\alpha$  value of 0.05. With these assumptions we estimated that at least 60 patients with BBPT would be needed. Numerical variables are presented as the mean  $\pm$  standard deviation for both patient groups and compared using the independent *t*-test or the Mann-Whitney *U* test where appropriate. Patient characteristics, postoperative complications and infections are compared using the Fisher's exact test or the  $\chi^2$  test where appropriate. The survival Kaplan-Meier curves were compared by using the log-rank test. A logistic regression analysis was conducted in order to determine the relationships between filtered and control transfused patients and infections following CABG surgery. A *P* value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS software version 11.0 (SPSS, Inc, Chicago, Ill).

## Results

### COMPOSITION OF STUDY GROUPS

Preoperative characteristics of the two groups as illustrated in Table 1 ensure that the two groups were appropriately matched in thirty-six characteristics. The only difference between the two groups was in body mass index; the filtered patients had increased

body mass index ( $P=0.006$ ). One early death occurred in each group, thus we could not address the issue of mortality reduction. There were no differences in intraoperative characteristics and postoperative outcome and complications after CABG between the two groups (Table 2). Although there was a trend for reduced postoperative length of stay (pLOS) in the filtered group (9.1 days vs. 10.8 in controls) this reduction was not statistically significant ( $P=0.685$ ). Of note is the decreased length of postoperative ventilation time in the filter group (16.3 hours vs. 57.8 hours in the control group), although this difference was not statistically significant ( $P=0.103$ ).

### TOTAL INFECTIONS

Among the 32 patients who did not receive BBPT, there were 2 cases (6.3%) of culture proven infections, one PTI and one surgical wound infection. The 69 transfused patients (38 filtered, 31 controls) were analyzed. The volume of blood transfused was identical in the filtered and non-filtered group. The total infections are shown in Table 3. There were 5 cases of culture proven infections in 38 filtered patients (13.2%) and 8 in 31 controls (25.8%). Even though filtered patients had half the infections of the non-filtered group, this trend did not reach statistical significance ( $P=0.224$ ).

All available risk factors were analyzed by logistic regression analysis for possible association with an increased rate of infections. The results are shown in Table 4. Only pLOS was associated with infections after CABG (odds ratio: 1.071, 95% confidence interval: 1.007-1.140,  $P=0.028$ ) from thirty-two analyzed risk factors. Among them, filtered patients (odds ratio: 0.410,  $P=0.161$ ), number of BBPT units (odds ratio: 1.089,  $P=0.144$ ), length of postoperative ventilation (odds ratio: 1.007,  $P=0.191$ ) and diabetes mellitus (odds ratio: 2.269,  $P=0.192$ ) were not associated with an increased rate of infection.

### SEPARATE CATEGORIES OF INFECTIONS

Analyses of the separate categories of infections were performed. UTIs were present in 4 of 38 filtered patients (10.5%) and 3 of 31 (9.7%) controls

Table 1. — *Preoperative characteristics of the two groups.*

Variable	Leukofiltration (n=38)	Control (n=31)	P value
EuroSCORE	6.43 ± 3.16	6.24 ± 2.71	0.907
Age (years)	62.9 ± 10.9	66 ± 7.5	0.184
Female (%)	11 (29)	8 (25.8)	0.794
One-vessel disease (%)	1 (2.6)	1 (3.2)	1.000
Two-vessel disease (%)	6 (15.8)	5 (16.1)	1.000
Three-vessel disease (%)	31 (81.6)	25 (80.7)	1.000
Unstable angina (%)	30 (79)	25 (80.7)	1.000
Previous MI (%)	37 (97.4)	29 (93.6)	0.584
Transmural MI (%)	18 (47.4)	18 (58.1)	0.469
Previous cardiac operation (%)	3 (7.9)	2 (6.5)	1.000
Previous PCI (%)	5 (13.2)	5 (16.1)	0.745
Emergency (%)	10 (26.3)	7 (22.6)	0.784
Urgent (%)	19 (50)	14 (45.1)	0.810
Elective (%)	9 (23.7)	10 (32.3)	0.589
Ejection fraction %	36.7 ± 16.1	40.5 ± 14.8	0.335
Hemodynamic instability (%)	4 (10.5)	3 (9.7)	1.000
More previous MI (%)	13 (34.2)	8 (25.8)	0.600
Current CHF (%)	13 (34.2)	11 (35.5)	1.000
Past CHF (%)	4 (10.5)	6 (19.4)	0.327
PVD (%)	7 (18.4)	7 (22.6)	0.767
Body mass index (kg/m <sup>2</sup> )	20.9 ± 3.4	18.6 ± 3.1	0.006
Hypertension (%)	29 (76.3)	25 (80.7)	0.773
Left ventricular hypertrophy (%)	8 (21.1)	6 (19.4)	1.000
COPD (%)	8 (21.1)	5 (16.1)	0.760
Diabetes mellitus (%)	12 (31.6)	13 (41.9)	0.453
Calcified aorta (%)	2 (5.3)	2 (6.5)	1.000
Dialysis (%)	1 (2.6)	0 (0)	1.000
Preop IABP (%)	5 (13.2)	2 (6.5)	0.446
Thrombolysis (%)	2 (5.3)	1 (3.2)	1.000
Smoking past 2 weeks	12 (31.6)	7 (22.6)	0.432
Smoking last year (%)	9 (23.7)	5 (16.1)	0.552
Stent thrombosis (%)	0 (0)	1 (3.2)	0.449

COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, IABP = intra-aortic balloon pump, MI = myocardial infarction, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease.

Table 2. — *Intraoperative characteristics and postoperative outcome of the two groups.*

Variable	Leukofiltration (n=38)	Control (n=31)	P value
30-day mortality (%)	1 (2.6)	1 (3.2)	1.000
pLOS (days)	9.1 ± 8.1	10.8 ± 12.2	0.685
BITA (%)	23 (60.5)	18 (58.1)	1.000
Two or more arterial grafts (%)	24 (63.2)	19 (61.3)	1.000
# Anastomoses	3.51 ± 0.93	3.52 ± 0.95	0.973
Time surgery minutes	305 ± 69	309 ± 58	0.766
Time on pump minutes	141 ± 47	148 ± 44	0.510
Ventilation time hours	16.3 ± 19	57.8 ± 144.6	0.103
Preoperative hematocrit (%)	37.4 ± 4.7	37.6 ± 5.4	0.689
Postoperative hematocrit (%)	29.6 ± 3.4	29.1 ± 3.4	0.703
None complication (%)	32 (84.2)	24 (77.4)	0.545
Complications (%)	6 (15.8)	7 (22.6)	0.545
Intraoperative stroke (%)	1 (2.6)	1 (3.2)	1.000
Over 24 hours stroke (%)	0 (0)	2 (6.5)	0.198
New Q waves (%)	0 (0)	0 (0)	1.000
Deep sternal wound infection (%)	0 (0)	0 (0)	1.000
Bleeding/reoperation (%)	1 (2.6)	2 (6.5)	0.584
Sepsis/endocarditis (%)	0 (0)	0 (0)	1.000
GI bleeding, perforation or infarction (%)	1 (2.6)	0 (0)	1.000
Renal failure/dialysis (%)	0 (0)	1 (3.2)	0.449
Respiratory failure (%)	1 (2.6)	4 (12.9)	0.166

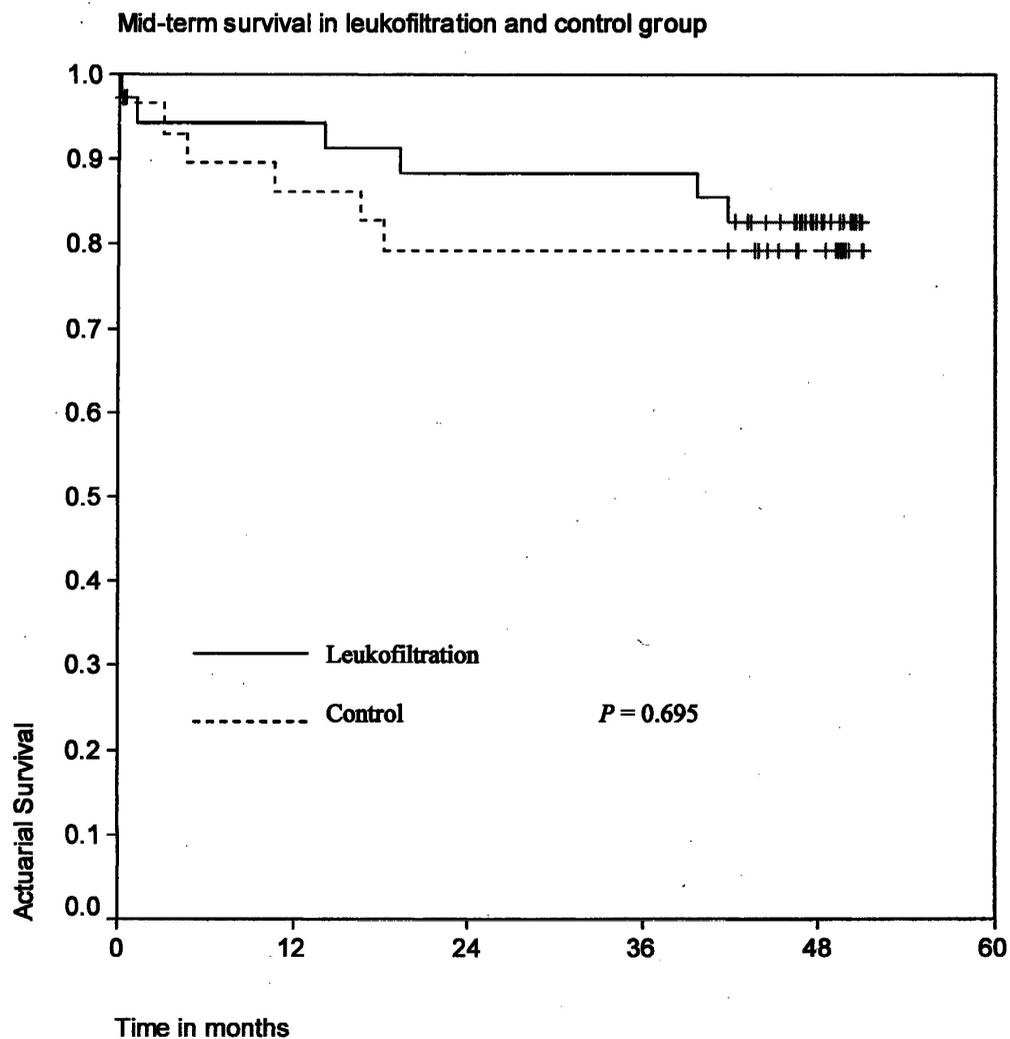
BITA = bilateral internal thoracic arteries, GI = gastrointestinal; pLOS = postoperative length of stay.

Table 3. — Infections in the two groups.

Variable (n=38)	Leukofiltration (n=31)	Control	P value
BBPT units per patient	5.6 ± 13.3	5.6 ± 10.1	0.280
Culture proven infections (%)	5 (13.2)	8 (25.8)	0.224
Sternal infections (%)	0 (0)	0 (0)	1.000
Pulmonary tract infections (%)	0 (0)	4 (12.9)	0.048
Site of surgery infections (%)	1 (2.6)	1 (3.2)	1.000
Urinary tract infections (%)	4 (10.5)	3 (9.7)	1.000
Pulmonary tract infections in diabetics (%)	0/13 (0)	3/13 (23.1)	0.220
Pulmonary tract infections in BBPT ≥3 units (%)	0/16 (0)	3/15 (20)	0.101

BBPT = blood and/or blood product transfusions.

Figure 1. — Actuarial mid-term survival as estimated by Kaplan-Meier curves in the two groups.



Patients at risk.

months	0	12	24	36	48
Filter	38	33	31	31	16
Control	31	27	25	25	16

( $P=1.000$ ). Surgical wound infections occurred in a single filtered patient (2.6%) and a single control patient (3.2%) ( $P=1.000$ ).

Of interest, however, was the analysis of PTIs where infection had not occurred in filtered patients but 4 cases of PTI were diagnosed and treated among 31 control patients (12.9%,  $P=0.048$ ). When we looked at all subacute complications there was one additional respiratory failure without pulmonary infection in each group plus one subacute stroke without infection in the control group. In such an analysis of complications there were 1/38 filtered patients with events against 6/31 control patients with events ( $P=0.040$ ). In addition when filtered patients and non-transfused patients were considered as a single group ( $n=70$ ) and compared with the transfused but non-filtered group ( $n=31$ ), there was 1 PTI (1.4%) in the group with leukofiltration or no transfusion versus 4 PTIs in the non-filtered group ( $P=0.030$ ). Diabetic patients were numerically equal in the filtered and unfiltered group. No PTIs occurred among 13 filtered diabetic patients and 3 PTIs were recorded among 13 diabetic controls (23.1%) but the  $P$  value of 0.22 did not reach significance even though 3/4 of the PTIs were in control diabetics versus none in filtered diabetic patients. In addition, when three units of BBPT or more were used, there were no PTIs among 16 filtered patients although, 3 cases out of 15 controls (20%,  $P=0.101$ ). Regarding timing of transfusion and fever and antibiotics the analysis showed no significant difference.

Mid-term survival between the two groups as estimated by Kaplan-Meier curves is shown in Figure 1. Although, there was a trend in favor of filtered patients  $45.5 \pm 2.3$  months vs.  $42.3 \pm 3.2$  months in control group or  $82.6\% \pm 6.5\%$  actuarial survival rate at 50 months after CABG in the filtered group vs.  $79.3\% \pm 7.5\%$  in the control group, this difference was not statistically significant ( $P=0.695$ ).

## Discussion

CABG surgery is one of the most common major operations performed worldwide. Fortunately, post-operative infectious complications are uncommon. However, when they do occur, they can be the cause of significant patient morbidity and

contribute greatly to prolonged pLOS and increased cost. Previous studies have shown that homologous blood transfusion was associated with an increased risk of infection in patients undergoing surgery for colorectal carcinoma<sup>14</sup> or hip replacement surgery<sup>15</sup> compared to equivalent risk patients receiving similar volumes of autologous blood transfusion. A retrospective study from the University of Rochester identified homologous blood transfusion as the most significant predictor of postoperative infectious complications in patients undergoing CABG on cardiopulmonary bypass<sup>3</sup>.

There is significant clinical data attesting to the immunosuppressive effects of homologous blood transfusion. Although the etiology of this transfusion-associated immunosuppression is unclear, it has been shown that donor leukocytes are associated with several post transfusion immunomodulatory effects including reduction in delayed hypersensitivity, natural killer cell function, recipient T-cell anergy, helper/suppressor ratio, and antigen presentation<sup>7,16</sup>. Chelemer et al.<sup>17</sup> recently published the results of a prospective cohort study of primary isolated CABG surgery patients investigating the association of homologous packed red blood cells transfusion and infection. They found that the patients were significantly more likely to develop a bacterial infection (wound, pulmonary, urinary, etc.) in a dose related relationship to the number of units of packed red blood cells transfused when controlling for other variables. Similar to our study, they found that this relationship was especially true for PTIs where 1.6% of their patients who were not transfused developed PTIs compared to 13.7% of those who received greater than 6 units of packed red blood cells. Diabetes was the only other variable that was significantly associated with infection in their study.

Our study represents the first randomized comparison aimed at investigating whether the use of leukocyte depleted blood results in a reduced risk of PTI or total infections, in patients requiring BBPT during CABG surgery on cardiopulmonary bypass, between groups with similar preoperative characteristics, including mid-term survival results. Our data indicate that the use of leukofiltration

Table 4. — Logistic regression analysis of all available risk factors for possible association with an increased rate of infections.

Variable	Odds ratio	95% confidence interval	P value
Filtered group	0.41	0.12-1.43	0.161
Units of BBPT	1.09	0.97-1.22	0.144
Age	1.00	0.94-1.06	0.939
Gender	1.92	0.53-6.92	0.317
Vessels diseased	0.50	0.24-1.04	0.065
Previous cardiac operation	3.03	0.45-20.35	0.254
Previous PCI	0.41	0.05-3.54	0.416
Emergency	1.70	0.44-6.56	0.443
Urgency	1.79	0.52-6.19	0.357
Elective	0.18	0.02-1.47	0.109
Ejection fraction	1.00	0.96-1.04	0.987
Hemodynamic instability	0.65	0.07-5.95	0.706
Current CHF	1.67	0.49-5.70	0.416
Past CHF	1.97	0.43-8.97	0.380
PVD	1.91	0.49-7.48	0.352
Body mass index	0.88	0.73-1.06	0.188
Hypertension	3.14	0.37-26.85	0.295
Left ventricular hypertrophy	0.62	0.12-3.20	0.569
COPD	1.29	0.30-5.57	0.733
Diabetes mellitus	2.27	0.66-7.76	0.192
Calcified aorta	1.39	0.13-14.55	0.784
Preoperative IABP	0.80	0.09-7.50	0.845
Smoking past 2 weeks	1.37	0.36-5.19	0.646
Smoking last year	2.17	0.55-8.63	0.270
EuroSCORE	1.15	0.93-1.41	0.193
pLOS	1.07	1.01-1.14	0.028
BITA	0.97	0.28-3.38	0.961
Two or more arterial grafts	0.97	0.26-3.67	0.967
# Anastomoses	0.56	0.28-1.12	0.104
Time of surgery	1.00	0.99-1.01	0.958
Time on pump	1.00	0.98-1.01	0.620
Postoperative hematocrit (%)	1.02	0.87-1.19	0.847
Ventilation time	1.01	1.00-1.02	0.191

BBPT = blood or blood product transfusions, BITA = bilateral internal thoracic arteries, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, IABP = intra-aortic balloon pump, PCI = percutaneous coronary intervention, pLOS = postoperative length of stay, PVD = peripheral vascular disease.

tion (Table 3) reduces PTIs (0 vs. 4 in controls,  $P=0.048$ ), but this difference was not highly significant.

This reduction in PTI among filtered patients is confirmed (but not significantly) by another randomized study including CABG patients and patients with aortic valve or mitral valve replacement singly or in combination with CABG<sup>18</sup>. It is also confirmed in our study when we considered non-transfused and filtered patients as a single group versus transfused and non-filtered patients ( $P=0.030$ ) or when we looked at all subacute complications including pulmonary failure and subacute stroke ( $P=0.040$ ). This observation may be related to pulmonary and cerebral protection effects of leukofiltration which removes platelet activating substances. There was a trend for reduced PTIs in diabetics (0 vs. 23.1%,  $P=0.220$ ) or when more than three units of BBPT were transfused (0 vs. 20%,  $P=0.101$ ).

Reduction in overall infection rate (13.2% vs. 25.8%,  $P=0.224$ ) failed to achieve statistical significance; this was also the case for pLOS (9.1 vs. 10.8,  $P=0.685$ ). The results for reduction in the hours of mechanical ventilation with filter appear more promising, particularly if outliers and mixed transfusions are excluded (11.8 hours among 35 filtered patients vs. 21.6 hours among 31 controls,  $P=0.017$ ), while this has been confirmed by another study<sup>19</sup>. This finding may be correlated with the observed reduction in PTIs or the improved pulmonary function<sup>20</sup> and may have implications for potential reduction in cost of care and intensive care unit length of stay.

In the present study we did not use leukocyte filtration methods either in blood cardioplegia solution or in the cardiopulmonary bypass circuits because such techniques have not proved to reduce infections after cardiac surgery (the focus of our study). However, these techniques have

shown beneficial effects in other outcomes. Blood cardioplegia filtration has been suggested as an approach to minimize myocardial injury, predominantly in high-risk cardiac surgery<sup>21</sup>, while arterial line filters have shown beneficial effect in reducing cerebral microemboli following CABG<sup>22</sup>. We also had no data regarding the age of BBPT used and the manipulations during the donation and conservation to the blood bank. Although there is an association between the length of storage of transfused red blood cells and the development of postoperative PTI after CABG (1% per day of increase in the mean storage time of the transfused red blood cells)<sup>5</sup>, other large studies have failed to demonstrate a significant effect of storage age of BBPT on the reduction of infections after cardiac surgery<sup>9,23</sup>.

Our results are in keeping with those reported by van de Watering et al.<sup>9</sup> The apparent differences with that study may be related to their inclusion of other than CABG patients, larger numbers, and different filter use. Newer reports exist, either in CABG patients, but not randomized, which failed to demonstrate an association between postoperative infections and the use of leukofiltration<sup>24</sup>, or randomized but not limited to CABG, which showed only a trend for less PTIs and mainly in high-risk patients with the need of a high volume of BBPT<sup>18</sup>. Regarding other clinical aspects and outcomes such as postoperative complications we found no differences in major complications between the compared groups and this was in concordance with another published study which showed that leukocyte depletion does not influence significantly the overall clinical outcome of patients undergoing elective cardiac surgery<sup>19</sup>.

It has been found recently that blood transfusions during or after CABG surgery were associated with increased long-term mortality<sup>25</sup>. Our study was designed to examine the mid-term advantages in survival between filtered and control patients. Although, survival as estimated by Kaplan-Meier curves favors the filtered group, there was no statistical significance (Fig. 1). This is the first study of its kind in the literature with mid-term results.

Patients undergoing CABG on cardiopulmonary bypass who are transfused with homologous blood may do better clinically with leukocyte depletion of transfused blood when compared to patients receiving blood filtered in the standard manner. This difference was not highly significant for PTI ( $P=0.048$ ) and there was only a trend favoring filtered patients where a reduction of all infections was encountered. It should be noted, however, that the filtered group was burdened by an excess of fat (body mass index significantly higher in filtered patients,  $P=0.006$ ). A larger study in CABG and/or other than CABG patients including higher risk patients (i.e. diabetics with re-operative aneurysm surgery, or combined valve and CABG patients) might provide additional information as to specific subsets of patients that may benefit from leukocyte filtration.

#### LIMITATIONS OF THE STUDY

Interim analysis of our data as presented to the Annual Meeting of the American College of Chest Physicians<sup>10</sup> showed significant results with Fisher's exact test and the study was interrupted. Subsequent more detailed probing resulted in the current thinking of this paper. It should be noted that the great majority of the patients was not at high-risk (EuroSCORE > 6 only 27% of patients). This was due to the composition of our referred patients, more than 2/3 of whom were emergencies or urgent cases. We did not approach particularly high-risk patients with a EuroSCORE > 6, thus excluding the very sick patients that we should have included. Regarding the quality of the filter there is an improvement since 1999. The filter used in our study had  $2 \times 10^5$  residual leukocytes per transfusion and > 85% red blood cell recovery. These characteristics have been improved and the newer filter has  $5 \times 10^4$  residual leukocytes per transfusion and > 90% red blood cell recovery, however, we do not know what the impact is of the quality of the filter on the results since there is no published study comparing the two filters. In addition, we could not perform a logistic regression analysis for PTIs because there were no events in the filtered group. The identification of

significantly heavier individuals in the filtered group leads us to believe that body mass index matching could have improved the results. Another limitation of the study is that we examined all-cause mortality and were unable to determine the cause of death (cardiac or noncardiac or infective death).

## Conclusion

This prospective, randomized study of primary CABG patients on cardiopulmonary bypass indicates that the use of leukoreducing filters results

in reduced PTI but does not significantly improve other clinical outcomes over the first four years. Further studies, with sufficient power, are needed to detect a reduction in PTIs of about 10% or less between filtered patients versus transfused and non-filtered patients.

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**Christidi Nancy (with S. Prapas-Papandreopoulou)**

Reprinted from the book «Νίκες Καρδιάς» (Victories of the Heart), period six «Recognitron» 1993-1991: The leading figures «Κωνσταντίνος Αναγνωστόπουλος» (Constantine Anagnostopoulos), with permission of the Publisher S. Prapas-Papandreopoulou and the Greek Society of Thoracic Cardiac and Vascular Surgeons, Editors 2105;6:414-419

# Κωνσταντίνος Αναγνωστόπουλος

*Ένας Homo Universalis... στην κοινωνία των ιατρικών ιδεών*

Ο ορισμός Homo Universalis χρησιμοποιήθηκε στην Αναγέννηση, ώστε να αποδώσει τα χαρακτηριστικά του καθολικού, οικουμενικού ανθρώπου. Εκείνου που λειτουργεί σε πραγματικά περιβάλλοντα, αντιμετωπίζοντας πραγματικά προβλήματα, που προσεγγίζει τις καταστάσεις αιτιοκρατικά, συνδυάζοντας λογική και αιρετική διάθεση ώστε να μην οδηγείται σε μονοσήμαντες αλήθειες, εκείνου που δεν επείγεται να ενσωματώσει εις εαυτόν υποστάσεις χωρίς να κατανοεί πλήρως τον ίδιο του τον εαυτό. Του επιστήμονα που χαρακτηρίζεται από υπευθυνότητα, του δασκάλου που χαρακτηρίζεται από ανήσυχο πνεύμα, του ανθρώπου που χαρακτηρίζεται από πολυπραγμοσύνη. Μοναχικός, ιδιοφυής, φιλοπερίεργος και πολυμαθής αποτελεί για τη σύγχρονη κοινωνία στην οποία η μήτρα του οικουμενισμού δεν ωρίμασε ποτέ αρκετά, είδος σπάνιο και δυσεύρετο. Ο κ. Κωνσταντίνος Αναγνωστόπουλος είναι ένας τέτοιος άνθρωπος. Ως γνήσιος Homo Universalis δεν είναι μια ακόμη διασημότητα, είναι ένας λαμπρός επιστήμονας.

## **1944, Θεσσαλονίκη**

Η πόλη βομβαρδίζεται ανελέητα από τα συμμαχικά στρατεύματα σε μια μάχη που θα σημάνει και την αποχώρηση των Γερμανικών κατοχικών δυνάμεων από τη χώρα. Οι πολίτες τρομαγμένοι αναζητούν προστασία στα καταφύγια. Αλλά δεν είναι μόνο οι βομβαρδισμοί που στιγματίζουν τις μνήμες όσων η μοίρα επιφυλάσσει να καταγρά-

ψουν στα ημερολόγια της ζωής τους τα εν λόγω συμβάντα. Ένας τρομερός κατακλυσμός λαμβάνει χώρα, θέτοντας σε κίνδυνο τις ζωές των ανθρώπων που κρύβονται στα καταφύγια, στις οπές των βράχων, στα χαλάσματα... Η φωνή μιας νεαρής μητέρας που χάνει τον τετράχρονο μοναχογιό της μέσα στα λασπόνερα της πλημμύρας καλύπτει ακόμη και τον ήχο των βομβαρδιστικών. Επικρατεί πανικός... Ευτυχώς, ο μικρός, που



Henry Dunant Hospital Cardiac Surgery, Athens Greece EU

από την στιγμή που γεννήθηκε, έμαθε να επιβιώνει στις αντιξοότητες του πολέμου, είναι καλά. Η μοίρα του περιέλασε τις πιθανότητες... Ο Δημιουργός έχει για εκείνον άλλα σχέδια... Κάποια στιγμή, ο κόσμος θα τον αποκαλεί Dr Κωνσταντίνο Αναγνωστόπουλο...

### 1953, Κολλέγιο «Georgetown», Washington, ΗΠΑ

Η μετάθεση του πατέρα οδηγεί την οικογένεια Αναγνωστόπουλου στην πρωτεύουσα της Αμερικής. Ο νεαρός Κωνσταντίνος καλείται να επιλέξει ποιον κύκλο σπουδών θα ακολουθήσει. Ο ίδιος ονειρεύεται πυρηνικά εργαστήρια και εφαρμογές που θα αλλάξουν το αύριο του κόσμου. Ο πατέρας, όμως, διακρίνοντας μια σπάνια ευφυΐα στο γιο του, τον ωθεί στην Ιατρική. *«Με τρόμαζαν τα χρόνια που χρειαζόταν να περάσουν μέχρι να αρχίσω να ασκώ την Ιατρική. Βλέπετε, ως Έλληνας, έπρεπε να ολοκληρώσω πρώτα τα γενικά μαθήματα του Κολλεγίου και κατόπιν να προχωρήσω στην Ιατρική Σχολή. Και δεν σας κρύβω ότι, η Πυρηνική Φυσική με συνέπαιρνε. Έβλεπα τον εαυτό μου μέσα σε λευκά, αποστειρωμένα εργαστήρια, με δεκάδες κουμπιά μπροστά μου, να πειραματίζομαι σε πρωτοποριακές εφαρμογές. Ο πατέρας όμως επέμενε. Έτσι, επισκεφτήκαμε το Κολλέγιο «Georgetown», ο κοσμήτορας του οποίου δέχτηκε να δώσω ειδικές εξετάσεις και να ενταχθώ ανάλογα με το επίπεδο γνώσεων μου. Μπήκα στο τρίτο έτος και ολοκλήρωσα το κολλέγιο σε 11 μήνες, πράγμα σπουδαίο για την εποχή». Τον Σεπτέμβριο της επόμενης χρονιάς, ο κ. Αναγνωστόπουλος είναι πια πρωτοετής φοιτητής της Ιατρικής Σχολής του Πανεπιστημίου «Georgetown».*

### 1962, Εργαστήρια Ιατρικής Σχολής Πανεπιστημίου «Georgetown», Washington, ΗΠΑ

Ο διάσημος Καρδιοχειρουργός της εποχής Charles Hufnagel καλεί φοιτητές της Ιατρικής Σχολής, στην οποία διδάσκει, να συμμετέχουν εθελοντικά στα εργαστήρια του. Ο Καθηγητής C. Hufnagel έχει καθιερωθεί παγκοσμίως ως ο άνθρωπος που δημιούργησε την πρώτη πλαστική εμφυτεύσιμη βαλβίδα. *«Όλοι οι φοιτητές, θυμάμαι, θέλαμε τότε να ενταχθούμε στα εργαστήρια του Hufnagel. Εγώ ξεκίνησα εκεί αρχικά για δυο εβδομάδες, αλλά αναπτύχθηκε με τον ίδιο και*

*μετέπειτα και με την ειδικότητα μια σχέση ζωής. Κάπως έτσι βρέθηκα στην Καρδιοχειρουργική, ενώ ο Hufnagel στάθηκε αρωγός σε αυτή μου την απόφαση».*

Υπό την καθοδήγηση του σπουδαίου αυτού επιστήμονα και με περγαμηνές που θα ζήλευαν πολλοί, μια χρονιά αργότερα, το «Columbia University» ανοίγει τις πόρτες του για να δεχτεί τον κ. Αναγνωστόπουλο ως πρωτοετή ειδικευμένο στην Γενική Χειρουργική. Όμως ακόμη και αυτό το σημαντικότατο ίδρυμα μοιάζει να μην μπορεί να «στεγάσει» την ιδιοφυΐα του... Πολύ σύντομα, ο κ. Αναγνωστόπουλος ανοίγει φτερά για το περίφημο Πανεπιστήμιο του «Yale».

### 1969, Καρδιοχειρουργική Κλινική, Πανεπιστημιακό Νοσοκομείο «Chicago», ΗΠΑ

Δεν ωφελεί σε τίποτε το να φιλονικείς με το αναπόφευκτο, έγραφε ένας σπουδαίος ποιητής, προσθέτοντας «Το μόνο δυνατό επιχείρημα, που μπορείς να φέρεις σ' ένα δυνατό άνεμο, είναι να φορέσεις το παλτό σου». Το «αναπόφευκτο» οδηγεί τον κ. Αναγνωστόπουλο στην ανάληψη της θέσης του Επίκουρου Καθηγητή Καρδιοχειρουργικής στο Πανεπιστημιακό Νοσοκομείο του Chicago, ως διάδοχο του Dr Magdi Yacoub, που αποχωρεί για να αναλάβει την Διεύθυνση του Καρδιοχειρουργικού Τμήματος του Νοσοκομείου «Harefield» του Λονδίνου. Το παλτό του είναι απαραίτητο... *«Έκανε τόσο κρύο εκεί, που οι άνθρωποι δεν είχαν άλλη επιλογή από το να δουλεύουν μέρα-νύχτα σε κλειστούς χώρους. Το ίδιο έκανα κι εγώ. Το Πανεπιστήμιο του Chicago ήταν τότε γνωστό παγκοσμίως, καθώς αποτελούσε «μηχανή» παραγωγής βραβείων Νόμπελ. Με την ανάληψη της θέσης του Επίκουρου Καθηγητή, επι-*



Με την πολυαγαπημένη του μητέρα.

φορτίστηκα και με την οργάνωση και Διεύθυνση της Καρδιοχειρουργικής Πανεπιστημιακής Κλινικής. Ήταν ένα καινούριο νοσοκομείο και οι ιθύνοντες ήθελαν κάποιον που να εργαστεί σκληρά για να εγερθεί την εξέλιξη της κλινικής». Η πρώτη επέμβαση που πραγματοποιείται στην Καρδιοχειρουργική Κλινική μεταδίδεται ως «σημαινύσα είδηση» από το τηλεοπτικό κανάλι NBC. Ο κ. Αναγνωστόπουλος, αν και απολαμβάνει διεθνή αποδοχή, παραμένει αφιερωμένος στα πειραματικά εργαστήρια. «Κάθε απόγευμα, όταν τελειώνω τα χειρουργεία, περιμένα τους φοιτητές και ξεκινούσαμε το πειραματικό έργο. Είχαμε εξοπλίσει έναν τεράστιο χώρο, δίπλα από το γραφείο μου κι εκεί πειραματιζόμασταν σε διάφορα πρωτόκολλα. Πολλά από αυτά, έχουν παρουσιαστεί σε συνέδρια ως εργασίες, οι οποίες μάλιστα με καθιέρωσαν ως σημαντικό ερευνητή και επιστήμονα».

#### 1974, Παγκόσμιο Συνέδριο

##### Καρδιολογίας, Buenos Aires, Αργεντινή

Ο κ. Αναγνωστόπουλος φτάνει στην πρωτεύουσα της Αργεντινής έτοιμος να καταπλήξει την ιατρική κοινότητα. Οι πειραματικές του μελέτες αναφορικά με τη νόσο της μετάθεσης μεγάλων αγγείων και τα ανευρύσματα αορτής θα αποδείξουν πως η καταξίωσή του δεν είναι τυχαία. Με το πέρας της παρουσίασης δέχεται μια αμφιλεγόμενη πρόταση. «Αφού παρουσίασα την πειραματική μου μελέτη για τη νόσο της μετάθεσης των μεγάλων αγγείων, με πλησίασε ο Αργεντινός Καρδιοχειρουργός



Στο 1ο Συνέδριο της ΕΑΒ, 2004, στην Παλαιά Βουλή.

Α. Jatene, προτείνοντάς μου να εφαρμόσουμε τα πειραματικά πρωτόκολλα σε παιδιά. Εκείνη την εποχή, η Αργεντινή είχε μια μεγάλη συχνότητα εμφάνισης της συγγενούς αυτής καρδιοπάθειας, με θνητότητα της τάξεως του 95%. Αν δεχόμουν, θα έμενα στην Ιστορία, ως ο Καρδιοχειρουργός που εφάρμοσε πρώτος τη μέθοδο στην κλινική πράξη...». Ο κ. Αναγνωστόπουλος αμφιταλαντεύεται και τελικά αρνείται την πρόταση... Ένα χρόνο αργότερα, ο Α. Jatene, βασιζόμενος στην εμπειρία και τα πρωτόκολλα του κ. Αναγνωστόπουλου, παρουσιάζει σε παγκόσμιο συνέδριο τα αποτελέσματα επιτυχών περιπτώσεων μετάθεσης μεγάλων αγγείων. Η μέθοδος περνά στην Ιστορία της Καρδιοχειρουργικής ως «Jatene procedu-re».

#### 1991, Παγκόσμιο Συνέδριο Ελάχιστα Επεμβατικής Καρδιολογίας, Βουδαπέστη, Ουγγαρία

Κάποιοι πιστεύουν πως δεν υπάρχουν τυχαία περιστατικά, μέσα σ' ένα τέλεια συγχρονισμένο σύμπαν. Όμως γεγονότα, όπως η «τυχαία» συνάντησή του κ. Αναγνωστόπουλου με τους κ.κ. Ράπτη και Μπαρτσόκα στην πρωτεύουσα της Ουγγαρίας, αποδεικνύουν πως το σύμπαν, κάποιες φορές, απλά σφουρίζει αδιάφορα... «Η συνάντησή μου με τους δυο αγαπητούς συναδέλφους έσπειρε μέσα μου το «μικρόβιο» του «Ωνασείου» και της επιστροφής στην Ελλάδα. Με γοήτευσε το project της δημιουργίας ενός αμιγώς Καρδιοχειρουργικού Κέντρου στην πατρίδα, από την στιγμή που γνώριζα τα προβλήματα που αντιμετώπιζαν οι συνάδελφοι εδώ στο να πείσουν τους ασθενείς, που έφευγαν για το εξωτερικό για να χειρουργηθούν. Μέχρι τότε, δεν είχα σκεφτεί ποτέ αυτή την προοπτική. Μετά την συνάντησή αυτή, άρχισαν τα τηλέφωνα από τη διοίκηση του «Ωνασείου» για να υπογράψουμε συμβόλαιο συνεργασίας. Την ίδια περίοδο είχα δεχτεί και μια πρόταση από το Πανεπιστήμιο «Columbia», την οποία σκεφτόμουν σοβαρά. Τελικά, έκανα και τα δυο».

#### 1993, «Ωνάσειο

##### Καρδιοχειρουργικό Κέντρο», Αθήνα

Η συνεργασία του κ. Αναγνωστόπουλου με το «Ωνάσειο Κ. Κ.» ξεκινά με τη μορφή περιοδικής παρουσίας του ως επιστημονικού συνεργάτη και

έχει ορίζοντα πενταετίας. «Στα χρόνια που έμεινα στο «Ωνάσειο», το πιο σημαντικό κομμάτι της δουλειάς μου αφορούσε την Παιδοκαρδιοχειρουργική. Όχι ότι δεν χειρουργούσαμε ενήλικες. Απλά, επειδή δεν υπήρχε αυτόνομη κλινική, ήταν συναρπαστική ευκαιρία να μπορείς να βοηθάς παιδιά που είχαν κάποια συγγενή καρδιοπάθεια. Εκείνα τα χρόνια, πριν την επίσημη δημιουργία αμιγούς Παιδοκαρδιοχειρουργικής Κλινικής, πραγματοποιήσαμε περί τις 400 επεμβάσεις σε παιδιά. Κατά τη διάρκεια της παρουσίας μου εκεί, συνεργαζόμουν με τους κ.κ. Αζαριάδη και Πράπα –ο πρώτος επέστρεψε αργότερα εκεί ως Διευθυντής με συνεργάτη τον κ. Μητρόπουλο, που είχα επιλέξει στη θητεία μου στο Πανεπιστήμιο Αθηνών. Είχαμε την αμέριστη συμπαράσταση καταπληκτικών Παιδο-Καρδιολόγων, όπως ο κ. Ράμμος που είχε έρθει από την Γερμανία, κι έτσι τα αποτελέσματά μας ήταν εξαιρετικά. Νομίζω ότι σε αριθμό περιστατικών είχαμε ξεπεράσει και την κλινική του Νοσοκομείου Παίδων «Αγ. Σοφία».

#### 1996, Νέα Υόρκη, ΗΠΑ

Για δεύτερη φορά στη ζωή του κ. Αναγνωστόπουλου, το σύμπαν σφυρίζει αδιάφορα... Σε ένα ταξίδι του στη Νέα Υόρκη, συναντά «τυχαία» τον κ. Π. Σουκάκο, Καθηγητή Ορθοπαιδικής στο Πανεπιστήμιο Ιωαννίνων και καλό του φίλο, ο οποίος τον φέρνει αντιμέτωπο με ένα απρόσμενο δίλλημα... «Ο κ. Σουκάκος άρχισε να μου περιγράφει τις προσπάθειες που έκανε να οργανώσει μια Καρδιοχειρουργική Κλινική στα Ιωάννινα. Μου είπε για μια ομάδα που είχε έρθει από τη Θεσσαλονίκη για να χειρουργήσει εκεί χωρίς συνέχεια, για ελλείψεις σε κλίνες ΜΕΘ και άλλα προβλήματα που έπρεπε να αντιμετωπιστούν. –Αν πετύχει, θα έρθω, του είπα. –Θα πετύχει, μου απάντησε. Αν δεν το κάνεις εσύ, δεν θα το κάνει κανένας ποτέ, μου είπε χαρακτηριστικά. Με πίεσε και η σύζυγός μου, η οποία έβλεπε θετικά την μόνιμη επιστροφή μας στην Ελλάδα. Έτσι, αποφάσισα να δεχτώ». Η θετική απάντηση του κ. Αναγνωστόπουλου καθώς και η εμπλοκή του κ. Σουκάκου σε θέματα διοίκησης του νοσοκομείου ρίχνουν «λάδι» στα βραδυκίνητα «γρανάζια» του ελληνικού συστήματος υγείας. Μέσα σε λίγο διάστημα, η κυβέρνηση δίνει εντολή για αξιοποίηση ενός

σημαντικού χρηματικού ποσού προς αγορά εξοπλισμού που θα χρησιμοποιηθεί στην υπό οργάνωση Καρδιοχειρουργική Κλινική του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων.

#### 1998, Καρδιοχειρουργική Κλινική Πανεπιστημιακού Νοσοκομείου Ιωαννίνων, Ιωάννινα

Ο εξοπλισμός έχει αγοραστεί, το προσωπικό έχει εκπαιδευτεί, η κοινωνία των Ιωαννίνων έχει ενθουσιαστεί και αναμένει εναγωνίως την έναρξη της δραστηριότητας της Πανεπιστημιακής Καρδιοχειρουργικής Κλινικής. Οι Καρδιοχειρουργοί κ.κ. Γ. Δρόσος, Σ. Συμινελάκης και Ο. Γαλανός προσλαμβάνονται ως συνεργάτες του κ. Αναγνωστόπουλου. Αλλά η έναρξη λειτουργίας της κλινικής καθυστερεί. Η κωλυσιεργία δεν οφείλεται αυτή τη φορά σε «εξωγενείς» παράγοντες, αλλά σε αντιδράσεις που προέρχονταν από το «εσωτερικό»... «Τα είχαμε όλα έτοιμα και δεν είχαμε αίθουσα να χειρουργήσουμε. Κανένας από τους συναδέλφους, βλέπετε, δεν ήταν διατεθειμένος να δώσει «χώρο» από τον δικό του για να ενταχθούμε κι εμείς στο πρόγραμμα των χειρουργειών. Κάποιοι ενδεχομένως ζήλευαν το «καινούριο» και «εντυπωσιακό» που εμείς θα ξεκινούσαμε. Τότε, για ακόμη μια φορά, ο φίλος κ. Π. Σουκάκος, μεσολάβησε, «δανείζοντάς» μας μια χειρουργική αίθουσα. Κι έτσι ξεκινήσαμε...». Στις 24 Σεπτεμβρίου του 1998, η Καρδιοχειρουργική Κλινική του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων ξεκινά επίσημα τη δραστηριότητά της, πραγματοποιώντας, την ίδια ημέρα, δυο επεμβάσεις ανοιχτής καρδιάς. Στις 31 Δεκεμβρίου του ίδιου έτους, η κλινική συμπληρώνει ήδη 26 επεμβάσεις...

#### 1998, Ιδιωτικό Θεραπευτήριο «Ευρωκλινική», Αθήνα

Η παρουσία του κ. Αναγνωστόπουλου στην Ελλάδα και οι αδιαμφισβήτητες ικανότητές του, όχι μόνο χειρουργικά αλλά και οργανωτικό επίπεδο, τον καθιστούν πολύπληθη «μεταγραφή» στα μεγαλύτερα ιδιωτικά Καρδιοχειρουργικά Κέντρα της πρωτεύουσας. Δέχεται προτάσεις σχεδόν από όλους, αλλά εκείνος, ως σπουδαίος «δάσκαλος», επιλέγει να «χτίσει» μια καινούρια «γέφυρα»... «Έχοντας τη δυνατότητα από το Νόμο να χειρουργώ ως Πανεπιστημιακός και σε ιδιωτικά

θεραπευτήρια, άρχισα να σκέφτομαι και αυτή την εκδοχή. Άλλωστε, είχα προσεγγιστεί από όλες σχεδόν τις διοικήσεις των μεγάλων κέντρων. Γιατί επέλεξα την «Ευρωκλινική», θα με ρωτήσετε εύλογα. Γιατί έμαθα στην Αμερική να κάνω πάντα το δικό μου. Να εκφράζομαι, να απαιτώ, να διεκδικώ, ώστε να μπορώ να διασφαλίζω το καλύτερο δυνατό για τους ασθενείς μου. Με την διοίκηση της «Ευρωκλινικής» είχα αυτή την πολυτέλεια. Ξεκινήσαμε μια κλινική άριστων προδιαγραφών σε πολύ γρήγορο διάστημα...». Αλλά οι ασθενείς δεν φαίνονται έτοιμοι να εμπιστευτούν το νέο αυτό εγχείρημα... Ο κ. Αναγνωστόπουλος καλείται για δεύτερη φορά να βρεθεί αντιμέτωπος με το «κατεστημένο». «Είχε περάσει ένας μήνας και δεν είχε εμφανιστεί ασθενής. Στην Αθήνα λειτουργούσε ένα «σύστημα», στο οποίο εμείς δεν είχαμε ενταχθεί. Έπρεπε, λοιπόν, να σκεφτώ κάτι. Αποφασίσαμε, λοιπόν, να δεχόμαστε τα πλέον «απαιτητικά» περιστατικά, ώστε να κερδίσουμε την εμπιστοσύνη του κόσμου. Έτσι κι έγινε».

Το πρώτο περιστατικό που χειρουργείται από τον κ. Αναγνωστόπουλο στο Ιδιωτικό Θεραπευτήριο «Ευρωκλινική» είναι ασθενής που νοσηλεύεται στην Μ.Ε.Θ. του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων, αναμένοντας την έναρξη λειτουργίας της Καρδιοχειρουργικής Κλινικής. Σε λίγες ημέρες επιστρέφει σπίτι του, ενώ φτάνει από τα Ιωάννινα και δεύτερος ασθενής...

#### **2004, Καρδιοχειρουργική Κλινική Πανεπιστημιακού Νοσοκομείου «Αττικών», Αθήνα**

Τα οράματα, όσο και αν είναι άφραστα, είναι και αέναα δημιουργικά. Για να γίνουν πραγματικότητα, χρειάζονται ανθρώπους που να μετουσιώσουν τις σκέψεις σε πράξεις. Το όραμα της δημιουργίας Καρδιοχειρουργικής Πανεπιστημιακής Κλινικής στην Ιατρική Σχολή Αθηνών «ταλάνιζε» επί χρόνια Πολιτεία και Πανεπιστημιακούς, αλλά λύση δεν δίνονταν. Ο Καθηγητής κ. Π. Σουκάκος παίζει για ακόμη μια φορά το ρόλο του «καταλύτη». «Με την «κάθοδό» του από τα Ιωάννινα στην Αθήνα, ο κ. Σουκάκος άρχισε να μου συζητά την ενδεχόμενη δική μου «κάθοδο». Επέμενε πως είμαι ο πιο κατάλληλος υποψήφιος για να ολοκληρώσω αυτό που χρόνια έμενε στο «ράφι». Στο τέλος πείστηκε. Κατέθεσα υποψηφιό-



Στο νοσοκομείο «Ερρίκος Ντυνάν» με τους μαθητές του Σ. Πράπα, Β. Κοτσή και τον αείμνηστο Αργύρη Μιχαλόπουλο, Δ/ντή της ΜΕΘ.

τητα και έλαβα παμψηφεί τη θέση του αποχωρούντος κ. Π. Ασημακόπουλου. Στην αρχή συζητάγαμε για δημιουργία κλινικής στο Νοσοκομείο «Ερρυθρός Σταυρός», αλλά τελευταία στιγμή, ο υπουργός αποφάσισε να αναπτυχθεί η Πανεπιστημιακή Καρδιοχειρουργική Κλινική στο Νοσοκομείο «Αττικών». Και εκεί, πάντως, δυσκολίες αντιμετώπισα. Αν δεν επέμενε ο κ. Σουκάκος να επιταχύνουμε, μπορεί ακόμη να παλεύαμε να ξεκινήσουμε. –Κάντε το τώρα που είναι εδώ ο Αναγνωστόπουλος, έλεγε στους υπουργούς. Αν δεν ξεκινήσει εκείνος, δεν θα τα καταφέρει κανείς άλλος». Δυο χρόνια αργότερα, Ιούνιο του 2006, ο τότε υπουργός Υγείας, κ. Δ. Αβραμόπουλος, επισκέπτεται τον πρώτο χειρουργημένο ασθενή από την ομάδα του κ. Αναγνωστόπουλου, στην Καρδιοχειρουργική Κλινική της Ιατρικής Σχολής του Πανεπιστημίου Αθηνών στο Νοσοκομείο «Αττικών»...

#### **Ιούλιος 2010, Πλάκα, Αθήνα**

Από το μπαλκόνι του διαμερίσματός του, η μυσταγωγία της φύσης απαιτεί σιωπή. Βρισκόμαστε λίγο πριν τη δύση του ήλιου και καθυστερούμε επίμονα την αρχή της συζήτησης για να μπορέσουμε να απολαύσουμε ένα Polaroid μαγικό, που όσες φορές και αν το έχει δει κανείς στη ζωή του, τον γοητεύει πάντα σαν να το αντικρίζει για πρώτη φορά. Το θέαμα εγείρει φιλοσοφικά ζητήματα. Το πεπερασμένο της ύπαρξης, το «αθεράπευτο» του πεπρωμένου, την υποκειμενικότητα της ευτυχίας. Η ψυχή του «μαύρισε» με τη γέννησή του. «Όταν γεννιόμουν, η Θεσσαλονίκη βομβαρ-

δίζονταν από τους Γερμανούς. Ο πατέρας μου αναγκάστηκε να κλειδώσει την πόρτα της κλινικής για να μην φύγουν οι γιατροί και αφήσουν τη μητέρα μου και μένα αβοήθητους, την ώρα της γέννας. Από την πρώτη μέρα της ζωής μου έμαθα να υπάρχω και να τρέφομαι στα καταφύγια. Κατά τη διάρκεια της μεγάλης πλημμύρας, τέσσερα χρόνια αργότερα, παρά λίγο να πνιγώ μέσα στις λάσπες. Τέτοια στιγμιότυπα στιγματίζουν την ψυχή σου και θέτουν έναν αόρατο πήχη για τον βαθμό δυσκολίας. Στα χρόνια που ακολούθησαν, όποια δυσκολία και αν αντιμετώπιζα, έλεγα με χιούμορ: *Αν δεν σε βομβαρδίζουν και δεν πνίγεσαι, τότε no problem*. Έχει χαρακτηριστεί «παιδί-θαύμα», «σπουδαίος δάσκαλος», «αμφιλεγόμενη προσωπικότητα». Θυμάται τη ρήση ενός φιλοσόφου που έλεγε πως η τύχη είναι ανεξερεύνητη, κολοσσιαία. Υψώνει τον άνθρωπο στην κορυφή της φήμης, αλλά και τον μεταβάλλει σε στάχτη. *«Η ζωή μου τα είχε όλα. Στα 37 μου μετρούσα ήδη 1.500 χειρουργεία και 13 χρόνια κλινικής πράξης και ερευνητικού έργου. Στην Ελλάδα, οι συνάδελφοί μου δεν είχαν τέτοιες δυνατότητες. Θυμάμαι βρισκόμασταν σε συνέδρια με τον κ. Ανδριτσάκη, τον κ. Λαζαρίδη ή τον κ. Τόλη και μου περιέγραφαν τις δύσκολες συνθήκες που αντιμετώπιζαν για να καθιερώσουν την ειδικότητα στην χώρα. Εγώ είχα την τύχη να βρίσκομαι σε περιβάλλοντα ώριμα, που προωθούσαν την ανάπτυξη νέων μεθόδων. Ακόμη και η επιστροφή μου στην Ελλάδα ήταν ομαλή. Ήταν ήδη ανεπτυγμένα σπουδαία κέντρα, η εμπιστοσύνη είχε κερδηθεί και εγώ κλήθηκα να βάλω το δικό μου λιθαράκι. Με όποιο ίδρυμα και αν συνεργάστηκα, έχω να θυμάμαι καλές στιγμές. Από το «Ωνάσειο», το Πανεπιστημιακό Νοσοκομείο Ιωαννίνων, την «Ευρωκλινική», το «Αττικόν» και το «Ερρίκος Ντυνάν» με το οποίο συνεργάστηκα για κάποιο διάστημα. Αυτό βέβαια δεν σημαίνει ότι δεν έζησα και τις «στάχτες».*

Η χροιά της φωνής του αλλάζει. Η συγκίνηση περισσεύει. Η μοίρα δεν ήταν πάντα καλή απέναντί του. Αλλά εκείνος φρόντιζε πάντα να επιστρέφει στον μοναδικό «πυλώνα» που γνώριζε πως δεν θα καταρριφθεί ποτέ. Την οικογένειά του. Η μητέρα του, η κα Αναγνωστοπούλου, τον ακούει και χαμογελά γλυκά. Τον προτρέπει να σκέφτεται το μέλλον και όχι το παρελθόν. Αλήθεια,

ποιο θα είναι το μέλλον της Καρδιοχειρουργικής; *«Πιστεύω ότι πηγαίνουμε ολοταχώς στη δημιουργία μιας σύνθετης ειδικότητας του Καρδιο-αγγειο-αναπνευστικού συστήματος. Η Ιατρική και ειδικότερα οι ειδικότητες που ασχολούνται με την καρδιά θα ωφεληθούν πολύ από τις ανακαλύψεις που λαμβάνουν χώρα σε κάθε επιστημονικό κλάδο. Σε συνδυασμό μάλιστα με την Βιοχημεία και τη Γενετική, το μέλλον προδιαγράφεται λαμπρό. Αυτό που με χαροποιεί ιδιαίτερα είναι το γεγονός ότι στην Καρδιοχειρουργική επέστρεψαν οι έξυπνοι και προικισμένοι. Κάποτε στην ειδικότητα αυτή έμπαιναν μόνο οι καλύτεροι. Μετά από μια κάμψη, τώρα ήρθε πάλι η ώρα τους».*

Ο ιδιοφυής ερευνητής που με το πειραματικό του έργο έφερε την επιστήμη βήματα εμπρός, ο αφιερωμένος ιατρός που άσκησε το λειτουργημά του με τιμιότητα και περισσή σεμνότητα, ο εμπνευσμένος δάσκαλος που με την γνώση και την εμπειρία του «φώτισε» το πνεύμα νεότερων γενεών, ο πιστός υιός και πατέρας που μεγαλώνει με την πεποίθηση πως η οικογένεια εξανθρωπίζει το άτομο, ο κ. Κωνσταντίνος Αναγνωστόπουλος είναι αναμφισβήτητα ένας *Homo Universalis*, ένας οικουμενικός άνθρωπος. Από εκείνους που σπάνια έχει την ευκαιρία κανείς να γνωρίσει στη ζωή του. Γιατί απλά, τέτοιοι άνθρωποι υπάρχουν μόνο στον αθέατο, φανταστικό κόσμο των ιδεών...



## Σταθμοί Ζωής...

**1940:** Γεννιέται εν μέσω βομβαρδισμών στη Θεσσαλονίκη. Η οικογένειά του βρίσκεται εκεί κατόπιν μετάθεσης του πατέρα του, ο οποίος υπηρετούσε ως Υπάλληλος του Υπουργείου Οικονομίας.

**1953:** Η οικογένεια μετακομίζει στην Αμερική, καθώς ο πατέρας αναλαμβάνει θέση εμπορικού συμβούλου στην Ελληνική πρεσβεία. Εισάγεται, κατόπιν ειδικών εξετάσεων, στο τρίτο έτος του Πανεπιστημίου «Georgetown» στη Washington των ΗΠΑ. Ολοκληρώνει τον κύκλο σπουδών του σε 11 μήνες.

**1954:** Εισάγεται στην Ιατρική Σχολή του Πανεπιστημίου «Georgetown», από όπου και αποφοιτά το 1960.

**1963:** Ειδικεύεται για μια διετία στη Γενική Χειρουργική στο Νοσοκομείο «Columbia Presbyterian Medical Center», του «Columbia University» στη Νέα Υόρκη.

**1964:** Επιδίδεται σε Καρδιοχειρουργική έρευνα ως Fellow στην Ιατρική Σχολή του Πανεπιστημίου «Yale».

**1967:** Ανακηρύσσεται Διδάκτωρ Ιατρικής από το Πανεπιστήμιο Αθηνών. Την ίδια χρονιά, ανακηρύσσεται Λέκτορας Χειρουργικής της Ιατρικής Σχολής του «Yale University».



*Ο Καθηγητής Κ. Αναγνωστόπουλος με το μαθητή του Σ. Πράπα σε χαλαρό στιγμιότυπο του 2012, «απολαμβάνοντας» την ιδιότητά του ως συνταξιούχος!*



*Με τον Δημήτρη Αβραμόπουλο, υπουργό Υγείας και τον Στέφανο Γερούλανο στο Παγκόσμιο Συνέδριο της Κω (2008).*

**1969:** Ανακηρύσσεται Επίκουρος Καθηγητής Χειρουργικής Θώρακος, Καρδιάς και Αγγείων στο «University of Chicago».

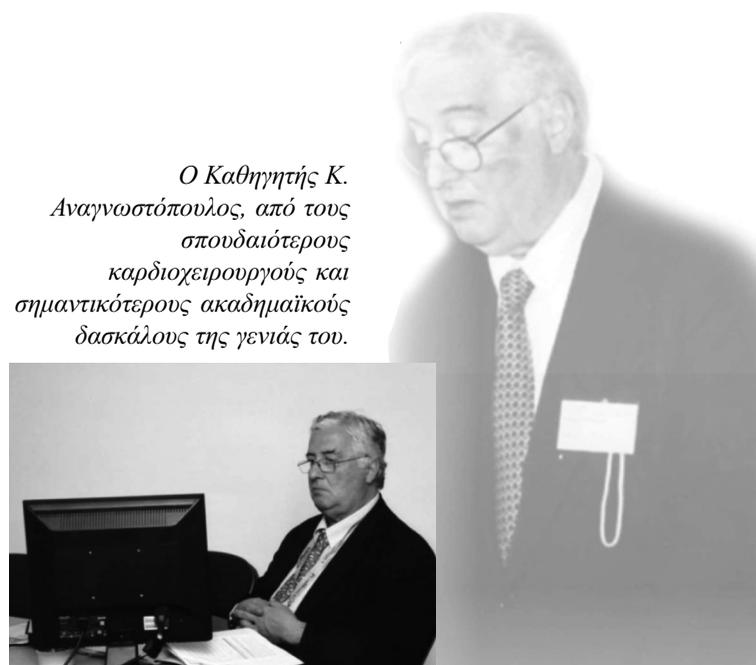
**Ιούλιος-Αύγουστος 1973:** Επισκέπτεται την Καρδιοχειρουργική Κλινική του «Massachusetts General Hospital» του Πανεπιστημίου «Harvard».

**1973:** Ανακηρύσσεται Αναπληρωτής Καθηγητής Χειρουργικής στο «University of Chicago».

**1979:** Ανακηρύσσεται Τακτικός Καθηγητής Χειρουργικής στο «University of Chicago».

**1982:** Ανακηρύσσεται Καθηγητής Χειρουργικής και Διευθυντής Τμήματος Καρδιοθωρακικής Χειρουργικής στο «State University of New York at Stony Brook».

**1983:** Παντρεύεται την Madelaine Low Reese. Από τον πρώτο του γάμο έχει αποκτήσει μια κόρη.



*Ο Καθηγητής Κ. Αναγνωστόπουλος, από τους σπουδαιότερους καρδιοχειρουργούς και σημαντικότερους ακαδημαϊκούς δασκάλους της γενιάς του.*

**1991:** Ανακηρύσσεται Καθηγητής Χειρουργικής και Διευθυντής του Τμήματος Καρδιοθωρακικής Χειρουργικής στο «St Luke's / Roosevelt Hospital Center» της Νέας Υόρκης.

**1993:** Εκλέγεται Επίτιμος Καθηγητής Καρδιοχειρουργικής και Παιδοκαρδιοχειρουργικής στο «Ωνάσειο Καρδιοχειρουργικό Κέντρο».

**1997:** Εκλέγεται Καθηγητής και Διευθυντής της Καρδιοχειρουργικής στην Ιατρική Σχολή του Πανεπιστημίου Ιωαννίνων.

**1998:** Ανακηρύσσεται Καθηγητής Χειρουργικής και Επίτιμο Μέλος στο «St Luke's / Roosevelt Hospital Center» της Νέας Υόρκης.

**2004:** Εκλέγεται Καθηγητής στην Ιατρική Σχολή του Καποδιστριακού Πανεπιστημίου Αθηνών και Διευθυντής στην ΚΡΧ Κλινική του «Αττικού» Νοσοκομείου Αθηνών.

**Christidi Nancy (transl. by CE Anagnostopoulos)**

*Translated. Reprinted from the book «Νίκες Καρδιάς» (Victories of the Heart), period six «Recognitron» 1993-1991: The leading figures «Κωνσταντίνος Αναγνωστόπουλος» (Constantine Anagnostopoulos), with permission of the Publisher S. Prapas-Papandreopoulou and the Greek Society of Thoracic Cardiac and Vascular Surgeons, Editors 2105;6:414-419*

# Constantine Anagnostopoulos

## *A Homo Universalis...*

### *in a society of medical ideas*

The definition «Homo Universalis» was used in Renaissance to describe the characteristics of a «catholic», universal human. One who works in real environments, addressing real problems, approaching situations in a deterministic way, combining logic and a «best alternative» mood that does not lead to simplistic truths, one who is not eager to integrate himself with instances without fully understanding himself; of a Scientist characterized by responsibility, of the Teacher characterized by restless spirit of the Man characterized by curiosity. Lonely, genius, inquisitive and erudite he is for modern society in which the matrix of ecumenism never matured enough, a rare and hard to find person. Dr. Constantine Anagnostopoulos is such a person. As a true Homo Universalis he is not just another celebrity, he is a brilliant scientist.

**1944, Thessaloniki.** The city was bombed mercilessly by Allied troops in a battle that will result in the departure of the German occupying forces from the country. The frightened citizens seek protection in shelters. But it is not only the bombing that stigmatizes the memories of those in whom fate records these events in the log-books of their lives. A terrible cataclysm occurs, endangering the lives of people hiding in shelters

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*Papandreopoulou Stella, Henry Dunant Hospital Cardiac Surgery, Athens Greece EU*

in rock holes, the debris ... The voice of a young mother who temporarily loses control of her four-year son within the muddy waters of the flood which even blocks the sound of bombers. There is panic ... Fortunately, the little boy that once born, learned to survive the vicissitudes of war,



is well. Fate mocked the odds ... The Creator has other plans for him ... At some point, people will call him Dr Constantine Anagnostopoulos...

### 1958 AUGUST

#### Georgetown College, Washington DC, USA

The father's transfer leads the Anagnostopoulos family to the capital of America. Young Constantine is asked to choose what course of study to follow. He dreams of nuclear energy laboratories and applications that will change the world tomorrow. His father, however, distinguishing a rare intelligence in his son pushes Medicine. *«I was frightened by the number years that had to pass until one begins to practice medicine. You see, as a Greek in the US, I had to first complete 4 years of courses in College and then go on to 4 more years in medical school vs. 6 total in Europe. And I do not hide from you that Nuclear Physics excites. I saw myself in a white, sterile laboratory, with dozens of buttons in front of me, experimenting in innovative applications. But my father insisted. So we visited the Georgetown College, the dean of which agreed to give me special tests and to join depending on my level of knowledge. I entered the third year and with summer school I finished college at 11 months, which was unprecedented for that time.»* In September 1959 Dr. Anagnostopoulos is a freshman student of the Georgetown University Medical School, 14 months after highschool!

### 1962 Medical Laboratories

#### Georgetown University Washington, USA

World renowned in his era, Heart Surgeon Professor Charles Hufnagel invites students of the Medical School, where he teaches, to voluntarily participate in his Laboratories and Operating Theaters. Professor C. Hufnagel has established himself worldwide as the man who created the first plastic implantable heart valve. *«All students, I remember, wanted to join in the Hufnagel operating rooms and laboratories. I originally started there for two weeks, but a lifetime relationship was developed with him and later with the specialty of cardiac surgery. This is how I found myself in Cardiac Surgery while Hufnagel was my*

*mentor in this decision.»* Under the guidance of this great scientist with diplomas and parchments that many would envy, a year later, Columbia University opens its doors to accept Dr. Anagnostopoulos as a first-year «intern» in General Surgery. But even this important institution seems to be unable to «accommodate» his genius. Very soon, Dr. Anagnostopoulos ventures forth for the famous **Yale University**.

### 1969 Cardiac Surgery,

#### University Hospital « Chicago », USA

A great poet wrote «it is no good to brawl with the inevitable», adding «the only possible argument you can bring against a strong wind is to wear your **coat**». The «inevitable» leads Dr. Anagnostopoulos to the position of Assistant Professor of Cardiac Surgery at The University of Chicago Hospitals, as successor to Dr Magdi Yacoub, who is leaving to take over the management of the new Cardiac Surgery Department of Harefield Hospital, London.

The **coat** becomes necessary ... *«it was so cold there, people had no choice but to work day and night indoors. So did I!! The University of Chicago was then known worldwide as an production “machine” of more than 50 Nobel prizes. It was in the new hospital that the trustees wanted someone who worked hard to ensure the further development of clinical excellence. “The first operation performed in the Clinical Cardiac center was transmitted as “influential news” by the international television channel NBC.»* Dr. Anagnostopoulos, even though he enjoys international acceptance, remains dedicated to experimental laboratories. *«Every afternoon, when I finished operating, I expected the students in order*



*to start some pilot project. We had equipped a huge space beside my office and there experimented on various animal protocols. Many of them have been presented at conferences as a work which established our lab as an important producer of research science».*

### **1974 World Cardiology Congress, Buenos Aires, Argentina.**

Dr. Anagnostopoulos arrives in the capital of Argentina ready to amaze the medical community. The experimental studies on transposition of great vessels and aortic aneurysms will show that his recognition is not accidental. At the end of a presentation he receives a controversial proposal. *«After I presented my study on experimental model of transposition of great vessels, I was approached by the Argentine Heart Surgeon Professor A. Jatene, suggesting that we apply these experimental protocols in children. At that time, Argentina had a high incidence of this congenital heart disease, with mortality rate of 95%. Had I accepted, the future procedure would possibly be known as the “Anagnostopoulos” operation and I would have stayed in history as having first applied the method in clinical practice ...».* (Dr. Anagnostopoulos vacillates and ultimately denies the sentence...)

A year later, Professor A. Jatene, based on the experiments and referencing the protocols of Dr. Anagnostopoulos, presents at a global conference the results of successful large vessel transfer cases. The method goes on History of Cardiovascular Surgery as the «“Jatene” procedure»...

### **1991 World Congress of Diabetes, Budapest, Hungary.**

Some believe that there are random incidents in a perfectly synchronized universe. But events like the «accidental» phone call between Mr. Anagnostopoulos with Professors Rapti and Bartsoka from the capital of Hungary, show that the universe, at times, simply whistles casually ... *“ My call with two beloved colleagues sowed the Onassis germ and my possible return to Greece and the prospect of a purely Cardiac Center at home, (since I knew the problems faced by colleagues*

*here in convincing patients who left abroad for surgery). Until then, I had never thought of this perspective. Following this meeting, the phones started from the trustees of “Onassis” to sign a contract. At the same time I received a proposal from the Columbia University which I seriously thought about. Eventually, I did both.»*

### **1993 Onassis Cardiac Surgery Center Athens.**

Cooperation of Dr. Anagnostopoulos with Onassis Cardiac Surgery Center started in the form of periodic presence as a Visiting Scientist and had a five year horizon. *«In the years I was at the Onassis, the most important part of my work concerned the Pediatric program. Not that we did not operate on adults (sometimes as many as 15 during my week there!) but just because there was no independent congenital heart surgery clinic it was an exciting opportunity to be able to help children who had congenital heart disease. In those years before the official creation of a pure Pediatric Clinic, we conducted ~400 procedures in children. During my presence there, I worked closely with Drs Azariades and Prapas (the first later returned there as Director with Dr. Mitropoulos whom I chose for the staff at Athens University). We had the full support of amazing Pediatric Cardiologists such as Professor Rammos who had come from Germany, so our results were excellent. I think that in number of procedures we had surpassed the clinic of Children’s Hospital “St. Sophia”»*



### 1996, New York, USA

For the second time in life Dr. Anagnostopoulos, the universe casually whistles ... On a return trip to New York, he «accidentally» meets Dr. P. Soucacos, Professor of Orthopedics at the University Ioannina, good friend and old Anavyryta classmate, who brings him face to face with an unexpected dilemma ... «*Dr. Soucacos began to describe his administrative efforts made to organize a Cardiac Surgery Clinic in Ioannina Greece. He told me about a group that had come from Thessaloniki to operate there once, then about ICU bed shortages and other problems that should be addressed. – If it would become successful, I'll come, I said. – You will succeed he replied. If you do not do this, no one ever will he added with characteristic emphasis! My wife, who saw positively my return to Greece also insisted. So, I decided to accept.*

The positive response from Dr. Anagnostopoulos and the involvement of Mr. Soucacos in hospital management issues «oiled» the slow-moving «gears» of the Greek health system. Within a short time, the government orders a significant amount of money to purchase equipment to be used in the Cardiac Surgery Clinic of the University Hospital of Ioannina.

### 1998 Cardiac Surgery Clinic, University Hospital of Ioannina, Ioannina.

The equipment has been purchased, the staff is trained, the Ioannina society is excited and eagerly awaiting the start of the University Heart Surgery Clinic activity. Cardiac Surgeons Drs G. Drosos, S. Syminelakis, O. Galanos hired already hired and sworn in the Public University System as associates of Dr. Anagnostopoulos. But the delayed onset of clinical function and obstruction is not due this time to «exogenous» factors, but reactions from the «inside»!!... «*We had it all ready but we did not have operating theater assigned time to operate in. None of our colleagues, you see, was willing to give "space" of his own to allow us in the surgical program. Some might even envy the "new" and "impressive" program that we would start. Then, once again, his friend Professor P. Soucacos, brokered a deal "by lending"*

*us orthopedic surgery time, once or twice a week. And so we started...».*

Although we had started thoracic surgery in September 1998, finally by May 1999 the Cardiac Surgery Clinic of the University Hospital of Ioannina officially starts its operations, realizing on the same day two open-heart operations. On December 31 of that year, the clinic already completes 26 procedures and exceeds 1.000 in 5 years.

### 1998 Private Hospital "Euroclinic", Athens.

The presence of Dr. Anagnostopoulos in Greece and his undoubted abilities, not only surgical but at the organizational level, make his coveted «transition» desirable to the largest private cardiac surgery centers of the capital. Proposals come from almost everyone, but he, as a great "teacher" chooses to "build" a new "bridge" ... «*Having the opportunity by law to perform operations as University Professor in private hospitals I started to think this possibility. Besides, I was approached by almost all boards of major centers. Why did I choose "Euroclinic" one would reasonably ask? I learned in the U.S. to always do my own. To express, to require, to claim, that which can ensure the best for my patients. With the administration of "Euroclinic" I had this luxury. We started a clinic of excellent quality and very quickly.*» But patients do not seem ready to trust this new venture ... Dr. Anagnostopoulos saw for the second time that he faced the "status quo". «*It had been a month and not a patient had appeared. In Athens there operated a "system", into which we had not been introduced. I had, therefore, to think of something different. We decided, therefore, to accept the most "challenging" problem patients that others on call would turn down, in order to gain the trust of the world. So it happened.*»

The first such patient operated by Dr. Anagnostopoulos in "Euroclinic" is a patient who is intubated with double valve endocarditis in the ICU of the University Hospital of Ioannina, awaiting the start of Cardiac Surgery Clinic operation. A few days after his successful emergency double valve operation at Euroclinic of Athens



the patient is flown back home to Ioannina and the second patient comes to Athens on the same day.

### 2003. Cardiac Clinic, “ΕΚΠΑ” University Hospital “Attikon”, Athens.

Visions, even if unattainable, are endlessly creative. To become a reality, they need people who can translate thoughts into actions. The vision of creating a Cardiac Surgery University Clinic at the Medical School of Athens “plagued” the State and the University for years, but no solution was given. Professor P. Soucacos plays once again the role of «catalyst». *«Following his “descent” from Ioannina to Athens, Dr. P. Soucacos started talking about my own potential “descent”. He insisted that I was the most suitable candidate to complete what for years lived “forgotten on the shelf”. In the end I was convinced. I initiated my candidacy and received the unanimous professorship vote for the position of the outgoing Professor P. Assimakopoulos. At first the proposal was for creating a University clinical cardiac surgery unit at the “Red Cross” Hospital but finally the Secretary of Health decided to develop the University Cardiac Surgery Clinic at “Attikon” Hospital. Even there, however, I encountered many difficulties. Had not Professors Soucacos and Raptis insisted to accelerate the process, we might even now in 2015 be struggling to start! “Make it while Anagnostopoulos is here”, they told the ministers. “If he does not start it, no one else will”».*

Two years later, in June 2006, the then Secretary of Health Mr. D. Avramopoulos and the Assistant Secretary of Health Mr. A. Yiannopoulos (covered on the TV evening news) visited during

the procedure on the first patient –with an aortic aneurysm–, operated by Dr. Anagnostopoulos and the Cardiac Surgery Team of the Clinic of Athens University Medical School at “Attikon” Hospital.

### July 2010, Plaka, Athens.

From the balcony of his apartment, the ritual nature requires silence. We are located just before sundown and persistently delay the start of the debate so that we can enjoy a Polaroid magic that many times though it has seen in his life, always fascinated him as to the faces for the first time. The spectacle raises philosophical issues. The finite existence, the «incurable» Destiny, the subjectivity of happiness. The soul of «blackened» with his birth. *«When you are born, Thessaloniki bombed by the Germans. My father had to lock the door of the clinic not to leave the doctors and let my mother and me helpless, time of birth. On the first day of my life I learned to exist and be fed in shelters. During the great flood, four years later, I was almost drowned in the mud. Such snapshots blacken your soul and bring an invisible bar for the degree of difficulty. In the years that followed, whatever difficulty you are facing, I say with humor: If a bomb and not drown, then problem no».* He has been described as «child prodigy», «gre-





at teacher», «controversial figure». Remember the saying of a philosopher who said that luck is unexplored, colossal. Raises human top reputation, but also alters the ash. «*My life had it all. In my 37 already I measured 1,500 surgeries and 13 years clinical practice and research work. In Greece, my colleagues did not have such capabilities. I remember we were in conference with Mr. Andri-tsaki, Mr. Lazaridis and Mr. Toli and I described the difficult conditions faced to establish the specificity of the country. I had the luck to be in mature environments that promoted the development of new methods. Even my return to Greece was smooth. Was already developed great centers, confidence had won and I was asked to put my own pebble. Whichever institution they worked, I remember good times. From “Onassis”, University Hospital of Ioannina, the “Euroclinic”, the “Atticon” and “Errikos Ntynan” with which I worked for some time. This does not mean that I experienced and the “ashes”*». The timbre of his voice changed. The emotion left over. Fate was not always good towards him. But he always made sure to return the unique «pillar» that he knew would never refuted. His family. His mother, Ms. Anagnostopoulos heard and smiling sweetly. Urges him to think about the future and not the past. True, what will be the future of Cardiovascular Surgery? «*I believe that going ahead*



*in creating a complex specialty of cardiovascular-respiratory system. Medical and particular specialties involved in heart will benefit greatly from the discoveries taking place in each discipli-*

*ne. Coupled with the fact Biochemistry and Genetics, the future is bright. What is particularly pleasing is the fact that in Cardiac returned smart and talented. Once entered in this specialty only the best. After a slump, now again it's time.»* The genius researcher with experimental work brought science steps forward, the dedicated doctor brought his office with honesty and abundant modesty, the inspired teacher with the knowledge and experience of the «enlightened» spirit younger generations, the faithful son and father growing up with the belief that the family humanizes man, Mr. Konstantinos Anagnostopoulos is decidedly a *Homo Universalis*, a universal man. Of those who rarely have the opportunity to meet anyone in his life. Why simply, such people exist only in the invisible, imaginary world of ideas...



**Stations life ...****1940**

Born amid bombings in Thessaloniki. His family is there then swap his father, who served as Clerk of the Economy Ministry.

**1953**

The family moves to America, and his father undertakes commercial adviser to the Greek embassy. Introduced, following special examination, in the third year of the University «Georgetown» in Washington, USA... complete the studies in 11 months.

**1954**

Enter the Medical School of the University «Georgetown», from where he graduated in 1960.

**1963**

Specialized for two years in General Surgery at the Hospital «Columbia Presbyterian Medical Center», the «Columbia University» in New York.

**1964**

Indulging in Cardiac investigation Fellow at the Medical School of the University «Yale».

**1967**

The designation Doctor of Medicine from the University of Athens. That same year, declared Professor of Surgery Medical School «Yale University».

**1969**

The designation Assistant Professor of Thoracic Surgery, Heart and Vascular in «University of Chicago».

**July-August 1973:** Visits Cardiac Surgery Clinic «Massachusetts General Hospital» University «Harvard».

**1973**

The designation Associate Professor of Surgery at the «University of Chicago».

**1979**

The designation Ordinary Professor of Surgery at the «University of Chicago».

**1982**

The designation Professor of Surgery and Director of Cardiothoracic Surgery Department at «State University of New York at Stony Brook».

**1983**

He marries Madelaine Low Reese. From his first marriage he has gained a daughter.

**1991**

The designation Professor of Surgery and Director of Cardiothoracic Surgery Department at «St. Luke's / Roosevelt Hospital Center» New York.

**1993**

Elected Honorary Professor of Pediatric Cardiovascular Surgery and the «Onassis Cardiac Surgery Center».

**1997**

Elected Professor and Chairman of Cardiac Surgery at the Medical University of Ioannina.

**1998**

The designation Surgery Professor and Honorary Member of the «St. Luke's / Roosevelt Hospital Center» New York.

**2003-2007**

Professor of Cardiac Surgery University of Athens and Clinic Director «Attikon» Hospital Center



# Hybrid Coronary Revascularization has Improved Short Term Outcomes but Worse Midterm Reintervention rates Compared to CABG: A Propensity Matched Analysis

Yu Xia, MD and Joseph J. DeRose, MD

## SUMMARY

**Objective:** We evaluated short term outcomes and midterm survival and reintervention of hybrid coronary revascularization versus conventional coronary artery bypass grafting using a propensity score matched cohort.

**Methods:** We conducted a retrospective review of patients undergoing surgery for multivessel coronary artery disease from 2007-2015 at a single institution. Patients were propensity matched 1:1 to receiving hybrid coronary revascularization or conventional bypass grafting by multivariate logistic regression on preoperative characteristics. Short-term outcomes were compared. Freedom from reintervention and death were assessed by Kaplan-Meier analysis, log-rank test, and Cox proportional hazards regression.

**Results:** Propensity score matching selected 91 patients per group from 91 hybrid and 2601 conventionally revascularized patients. Hybrid revascularization occurred with surgery first in 56(62%), percutaneous intervention first in 32(35%), and simultaneously in 3(3%) patients. Median interval between interventions were 3 and 36 days for surgery first and percutaneous intervention first, respectively. Preoperative characteristics were similar. Patients undergoing hybrid revascularization had shorter post-operative length of stay [median 4vs5 days,  $p<0.001$ ] and less post-operative transfusion (13.2%vs34.1%,  $p=0.001$ ) and respiratory failure (0% vs 6.6%,  $p=0.03$ ). They were more likely to be discharged home (93.4%vs71.4%,  $p<0.001$ ), with no difference in 30-day mortality( $p=0.99$ ), readmission( $p=0.23$ ), or midterm survival ( $p=0.79$ ). Hybrid revascularization was associated with earlier reintervention ( $p=0.02$ ). Hazard ratios for reintervention and patient mortality of hybrid coronary

revascularization versus conventional revascularization were 3.60(95% confidence interval 1.16-11.20) and 1.17(95% confidence interval 0.37-3.72), respectively.

**Conclusions:** Despite having favorable short term outcomes and similar survival, hybrid coronary revascularization may be associated with earlier reintervention compared to conventional techniques.

**Key Words:** hybrid coronary revascularization, CABG, reintervention, survival, short-term outcomes

## INTRODUCTION

Conventional coronary artery bypass grafting (CABG) remains the gold standard treatment for multivessel coronary artery disease, largely due to the superior patency of the left internal mammary artery (LIMA) when used to revascularize the left anterior descending (LAD) artery.<sup>1,2</sup> For non-LAD targets, however, newer drug eluting stents may be superior to saphenous vein grafts with regard to long term patency.<sup>3,4</sup> Moreover, percutaneous coronary interventions (PCI) have the added advantage of being less invasive, have a quicker recovery time, and reduced short-term complications compared to surgical revascularization.<sup>5</sup> Hybrid coronary revascularization (HCR), which combines the advantages of a minimally invasive LIMA-LAD grafting and PCI to non-LAD targets, represents an attractive alternative to conventional CABG, particularly in treating multivessel disease in high-risk patients and as economic feasibility improves with robotic technology.<sup>6,7</sup> Several groups have reported short term benefits of HCR including decreased need for blood transfusion, decreased intubation time, shorter length of intensive care and overall hospital stay, and faster recovery and return to work while maintaining similar major adverse cardiac and cerebrovascular event (MACCE) rates compared to on-pump and off-pump CABG.<sup>4,8,9</sup> The durability of HCR is not well studied, however, with several centers reporting increased rates of revascularization despite similar MACCE outcomes on midterm follow-up.<sup>8</sup> The goal of our study was to assess the short-term and midterm outcomes of HCR compared to conventional CABG using a propensity-score matched cohort at our institution.

## METHODS

This study was approved by the institutional review board of the Albert Einstein College of Medicine/Montefiore Medical Center.

We conducted retrospective review of all patients who underwent isolated conventional CABG and HCR from January 1, 2007 and March 31, 2015 by querying our institutional database. This database is a combination of all the data fields from both the Society of Thoracic Surgery database and the New York State database. It also includes data fields specific for robotic CABG and hybrid revascularization. All conventional CABG's were performed on-pump. The minimally invasive LIMA-LAD operation performed in all cases was a robotic minimally invasive direct coronary artery bypass (MIDCAB) and assessed with intraoperative duplex and transit time flow measurements with calculation of pulsatility index and diastolic and systolic flow. HCR was defined as planned revascularization of the LIMA-LAD and PCI of non-LAD vessels occurring within 90 days of each other. Patients were excluded if they underwent other cardiac procedures, emergency or urgent surgery, had previous cardiac surgery, or had complete revascularization occurring more than 90 days apart.

Following collection of baseline characteristics, propensity scores were generated for HCR versus conventional CABG by multivariable logistic regression on age, gender, ejection fraction, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, dialysis, cerebrovascular disease, and number of vessels revascularized. Patients were then matched 1:1 by propensity score.

Short-term outcomes were determined by review of electronic medical records and included

Table 1. Patient Characteristics Used in Propensity Score Matching

	Unmatched				Matched			
	CABG (n=2601)	HCR (n=91)	SD  (%)	P-value	CABG (n=91)	HCR (n=91)	SD  (%)	P-value
Male	1768 (68.0%)	71 (78.0%)	22.7%	0.04	69 (75.8%)	71 (78.0%)	5.0%	0.73
Age, years	63.3 ± 10.5	64.6 ± 10.8	12.2%	0.25	63.9 ± 11.0	64.6 ± 10.8	6.0%	0.69
EF	50.2 ± 13.6	55.7 ± 11.4	44.4%	<0.001	56.1 ± 12.3	55.7 ± 11.4	2.5%	0.86
PAD	348 (13.4%)	10 (11.0%)	7.3%	0.51	12 (13.2%)	10 (11.0%)	6.7%	0.65
CVD/CVA	352 (13.5%)	18 (19.8%)	16.8%	0.09	16 (17.6%)	18 (19.8%)	5.9%	0.71
COPD	253 (9.7%)	11 (12.1%)	7.5%	0.46	13 (14.3%)	11 (12.1%)	7.0%	0.66
Dialysis	131 (5.0%)	3 (3.3%)	8.7%	0.63	2 (2.2%)	3 (3.3%)	5.5%	0.99
Diabetes	1415 (54.4%)	44 (48.4%)	12.1%	0.26	49 (53.9%)	44 (48.4%)	11.0%	0.46
#Vessels Revascularized	3.1 ± 0.8	2.4 ± 0.6	101.8%	<0.001	2.4 ± 0.7	2.4 ± 0.6	3.0%	0.82

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVD/CVA = cerebrovascular disease/cerebrovascular accident; EF = ejection fraction; HCR = hybrid coronary revascularization; PAD = peripheral arterial disease; SD = standardized difference

30-day mortality and readmission, post-operative length of stay, discharge location (home versus other), post-operative blood transfusion, reoperation for bleeding, infection/sepsis/endocarditis, renal failure requiring dialysis, respiratory failure, and stroke or transient ischemic attack.

The primary mid-term outcome was freedom from re-intervention, defined as balloon angioplasty, stenting, or repeat bypass of a target or non-target vessel. The secondary outcome was overall survival. Outcomes were assessed by review of electronic medical records and attempted telephone contact with the patient and/or next of kin. Patient mortality data was additionally supplemented by querying the Social Security Death Index as of August 25, 2015.

### Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared using t-test for those meeting normality criteria. Otherwise, they were expressed as median and interquartile range (IQR) and compared with Wilcoxon rank-sum test when assumptions were violated. Categorical variables were expressed as proportions and compared by Chi-Square test. Fisher's exact test was used when more than 25% of the expected frequencies were <5.

Propensity score matching was conducted using the nearest neighbor method without replacement and a caliper width of 0.01. Standardized differences of covariates were compared in the unmatched and matched cohorts, with differences <15% considered acceptable for achieving adequate balance. Time-to-event analysis for re-in-

tervention and death was conducted using the Kaplan-Meier method and compared with log-rank test. Hazard ratios for re-intervention or death of HCR vs CABG were calculated by univariate Cox-proportional hazards regression. The proportional hazards assumption was evaluated and no important deviations were found. Two-sided p-values <0.05 were considered significant.

All data analysis was conducted using Stata version 13.1, and propensity analysis was conducted using psmatch2.<sup>10</sup>

## RESULTS

### *Patient Characteristics*

Of 2,601 conventional CABG and 91 HCR patients identified in the initial cohort, 91 each of HCR and conventional CABG patients were selected after propensity score matching. Comparisons of covariates in the unmatched and matched cohorts are depicted in Table 1 and demonstrate reduction in standardized difference among all covariates. In addition, patients were not significantly different with regard to variables not used for propensity score matching (Table 2).

Of the HCR patients, 56 (61.5%) received CABG first, 32 (35.2%) received PCI first, and 3 (3.3%) were completed as a one-stage procedure. Median time between interventions was 3 (IQR 3-6) days for those who received CABG first and 36 (IQR 30-50) days for those who received PCI first. The vast majority of patients who underwent PCI first had acute coronary syndrome with non-LAD vessels as the culprit vessel, including 14(41%) with NSTEMI, 12(38%) with STEMI, and 3(9%) with unstable angina. Three patients had PCI electively after a positive stress test.

PCI was accomplished with drug eluting stents in 74(81%), bare metal stents in 13 (14%), and balloon angioplasty in 4 (5%) of patients. In total, 116 non-LAD target vessels underwent PCI. These included 40 (34%) right coronary, 40 (34%) left circumflex, 2 (2%) left main, 23 (20%) obtuse marginal, 3 (3%) diagonal, 5 (4%) posterior descending, and 3(3%) ramus intermedius arteries. A total of 154 stents were placed, or 1.3 stents

per vessel. At time of discharge following completion of revascularization, patients in the HCR group had a significantly higher proportion of clopidogrel or prasugrel use compared to conventional CABG (100% vs 24%,  $p<0.01$ ). Other discharge medications were not significantly different (Table 3).

### *Short-Term Outcomes*

Thirty day and in-hospital outcomes are depicted in Table 4. There was no significant difference in 30 day mortality (0% vs 0%,  $p=0.99$ ) and readmissions within 30 days (13.2% vs 7.7%,  $p=0.23$ ). HCR patients had a shorter post-operative length of stay [median(IQR) 4<sup>3-6</sup> vs 5<sup>4-8</sup>,  $p<0.001$ ], with a lower incidence of post-operative transfusion (13.2% vs 34.1%,  $p=0.001$ ) and respiratory failure (0% vs 6.6%,  $p=0.03$ ). HCR patients were also more likely to be discharged home (93.4% vs 71.4%,  $p<0.001$ ) as opposed to an extended care or rehabilitation facility.

### *Mid-TERM Outcomes*

Median follow-up time was 2.4 (IQR 1.0-4.3) years for CABG patients and 2.7 years (IQR 1.3-4.0) years for HCR patients ( $p=0.59$ ). Twelve (13.2%) CABG and 6 (6.6%) HCR patients had follow-up less than 6 months ( $p=0.14$ ).

Of the CABG patients, 4 required re-intervention and 7 patients died. Two patients required stenting of both their LAD and a non-LAD target, 104 and 258 days after CABG. One patient received a bare metal stent to the LAD on post-operative day 46, and another patient received a drug eluting stent to a target obtuse marginal artery 1763 days after CABG.

Of the HCR patients, 13 required re-intervention and 6 patients died. No patients required intervention on their LIMA-LAD graft when followed by PCI as part of their HCR strategy. Median time to repeat revascularization was 242 (IQR 113-784) days. Of the vessels re-vascularized, 5 were LAD lesions, 9 were non-LAD target lesions, and 1 was a non-target non-LAD lesion. One patient had an acute left main coronary dissection during the PCI portion of his HCR and underwent emergent CABG.

Table 2. Patient Characteristics Not Used in Propensity Score Matching

	CABG (n=91)	HCR (n=91)	P-value
<b>Race*, n(%)</b>			
White	32 (40.0%)	31 (37.4%)	
Black	15 (18.8%)	18 (21.7%)	0.92
Multiracial	25 (31.3%)	24 (28.9%)	
Other	8 (10.0%)	10 (12.1%)	
BMI (kg/m <sup>2</sup> )	28.9 ± 4.8	28.1 ± 5.3	0.28
Creatinine†(mg/dl)	1.1 ± 0.9	1.0 ± 0.3	0.41
STS Predicted Mortality	1.7 ± 2.0%	1.6 ± 1.9%	0.08
Year After 2011	41 (51.3%)	49 (59.0%)	0.32
Single-Vessel Disease	2 (2.2%)	0 (0%)	
Double-Vessel Disease	28 (30.8%)	31 (34.1%)	0.45
Triple-Vessel Disease	61 (67.0%)	60 (65.9%)	

\*Race unknown or declined in 11 CABG and 8 HCR patients

†Creatinine compared for patients not on dialysis, Wilcoxon rank sum test used for non-normality  
 BMI = body mass index; CABG = coronary artery bypass grafting; HCR = hybrid coronary revascularization;  
 STS = Society of Thoracic Surgeons

Actuarial survival for the CABG group was 100% at one year and 95% at three years compared to 99% at one year and 95% at three years in the HCR group. Actuarial freedom from re-intervention was 96% at both one and three years for the CABG group compared to 92% at one year and 85% at three years for the HCR group. Freedom from re-intervention was significantly lower in the HCR group (Fig 1, log-rank  $p = 0.02$ ), while overall survival was similar (Fig 2, log-rank  $p=0.79$ ). The haz-

ard ratios for re-intervention and patient mortality of HCR compared to CABG were 3.60 (95% CI 1.16-11.20) and 1.17 (95% CI 0.37-3.72), respectively.

## DISCUSSION

Although multiple prospective randomized studies comparing multi-vessel PCI and CABG have re-

Table 3. Discharge medications of patients after completion of HCR and CABG

	HCR (n=91)	CABG (n=91)	P-value
Aspirin	89 (98%)	90 (99%)	0.99
Clopidogrel or Prasugrel	91 (100%)	22 (24%)	<0.01
Warfarin	3 (3%)	3 (3%)	0.99
Antiarrhythmic	16 (18%)	16 (18%)	0.99
ACE Inhibitor	29 (32%)	26 (29%)	0.63
Statin	88 (97%)	84 (92%)	0.33
Beta Blocker	84 (92%)	85 (93%)	0.77

HCR = hybrid coronary revascularization, CABG = coronary artery bypass grafting, ACE = angiotensin converting enzyme

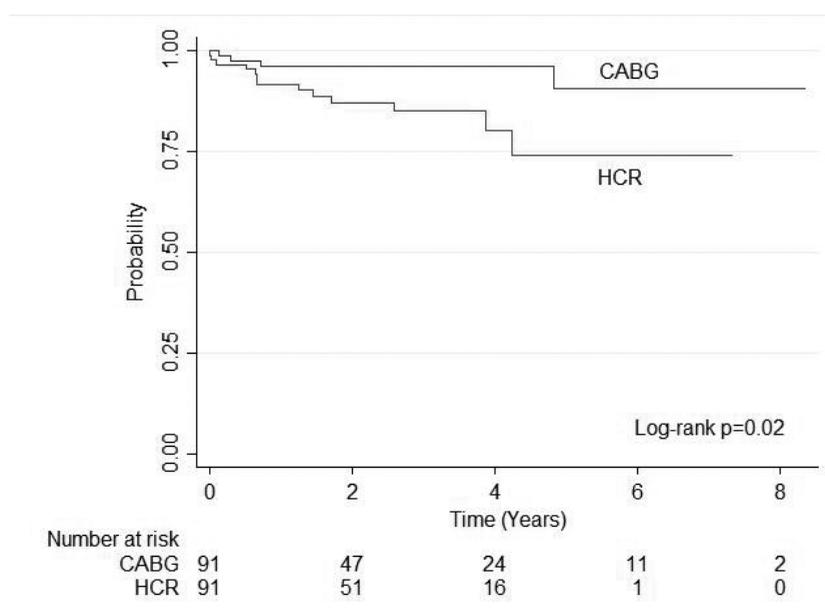


Figure 1. Freedom from Reintervention of HCR and CABG Patients  
CABG = coronary artery bypass grafting; HCR = hybrid coronary revascularization

Table 4. Short Term Outcomes of HCR and Conventional CABG

Outcome	HCR (n=91)	Conventional CABG (n=91)	P-value
30 Day Mortality*	0 (0%)	0 (0%)	0.99
Readmission <30 Days	12 (13.2%)	7 (7.7%)	0.23
Post-op Length of Stay, days	4(3-6)	5 (4-8)	<0.001
Discharged Home	85 (93.4%)	65 (71.4%)	<0.001
Postoperative Transfusion	12 (13.2%)	31 (34.1%)	0.001
Reoperation for Bleeding*	1 (1.1%)	0(0%)	0.32
Infection/Sepsis/Endocarditis*	0 (0%)	3 (3.3%)	0.25
Renal Failure/Dialysis*	0 (0%)	0 (0%)	0.99
Respiratory Failure*	0 (0%)	6(6.6%)	0.03
Stroke/TIA*	0 (0%)	2 (2.2%)	0.50

CABG = coronary artery bypass grafting; HCR = hybrid coronary revascularization; TIA = transient ischemic attack \*Compared with Fisher's exact test due to low expected frequencies

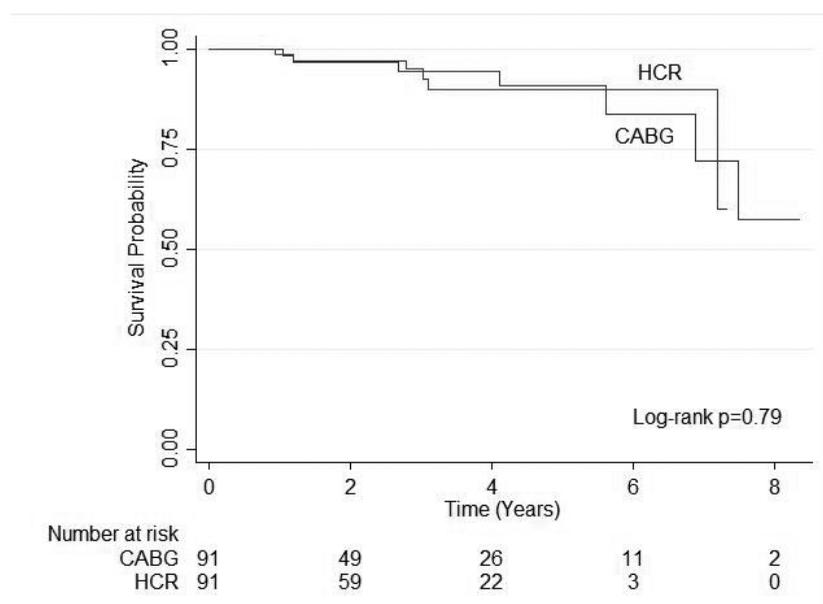


Figure 2. Overall Survival of HCR and CABG Patients

CABG = coronary artery bypass grafting; HCR = hybrid coronary revascularization

vealed a decreased incidence of repeat revascularization with CABG,<sup>11-16</sup> controversy still exists about the most suitable revascularization option for each particular patient with multivessel disease in real world practice. However, there has been no controversy that CABG can improve survival when compared to PCI in particular subsets of patients including diabetic patients with triple vessel disease, patients with multi-vessel disease and a decreased LVEF and patients with left main coronary artery disease<sup>17-21</sup>. The most powerful factor which confers this survival advantage is a patent LIMA-LAD anastomosis.

The SYNTAX trial was designed to compare MACCE in real world patients with multivessel coronary artery disease undergoing CABG or multivessel PCI with DES.<sup>16</sup> In both short and medium term follow-up repeat revascularization was significantly higher in the PCI group when compared to the CABG group in all SYNTAX score tertiles. Furthermore, in patients with intermediate or high risk SYNTAX scores, MACCE, death, MI and repeat revascularization were all statistically improved with CABG compared to PCI. It is this very data which has continued to give encouragement to a hybrid revascularization approach in the treatment of selected patients with multivessel disease.

In the present study, hybrid revascularization again was shown to be superior to conventional CABG in terms of recovery, length of stay, transfusion requirement and respiratory complications. While overall infections did not reach statistical significance, HCR is likely to cause fewer infections than conventional CABG by eliminating the risk of mediastinitis. This lends credence to the ongoing assertion that sternal sparing incisions and off-pump surgery can have benefits related to short term recovery as compared to conventional CABG.<sup>22</sup> This can be especially useful in patients who are higher risk for sternotomy and bypass including those patients at risk for stroke, and those patients with limited ability to rehabilitate. For patients who are felt to be good candidates for conventional CABG, the present study also sheds light on the role of HCR within the spectrum of revascularization options available to the treating physician. In medium term follow-up we found an in-

creased incidence of repeat revascularization in patients undergoing HCR (14.2%) versus patients undergoing CABG (4.4%) despite greater antiplatelet therapy. The rate of LAD repeat revascularization was not significantly different between the two groups with most of the repeat revascularization coming in either target or non-target non-LAD vessels. As with multiple prior studies which have incorporated routine post-operative angiography, LIMA-LAD patency in the robotic CABG group remains excellent at approximately 95% at 3 to 5-year follow-up.<sup>23-25</sup>

The increased incidence of repeat revascularization in non-LAD targets maybe the result of a number of different factors. First, in-stent restenosis much more frequently results in a symptomatic coronary syndrome than coronary bypass graft occlusion which can frequently be asymptomatic. Another complicating factor is that the HCR patients underwent many more angiograms as part of scheduled revascularization and subclinical lesions may have been more readily detected. Nonetheless, the repeat revascularization rate of our HCR patients (14.2%) falls between the incidence of repeat revascularization reported in the SYNTAX study at a similar time point (3-year follow-up) for conventional CABG (10.7%) and for multivessel PCI (19.7%)<sup>13</sup>. A prospective randomized comparison of HCR and CABG (85% off-pump) demonstrated similar LAD arterial graft patency on angiographic follow-up at one year (94% vs 93%,  $p=0.74$ ). These authors found that the HYBRID patency score, defined as the proportion of grafts/stents free of stenosis or occlusion out of the total number of grafted or stented vessels, was higher in HCR patients (90% vs 81%,  $p=0.01$ ), mostly attributable to a high rate of stenosis or occlusion in vein grafts.<sup>26</sup> However, not all vein graft occlusions or stenoses are clinically relevant, as the native diseased vessel remain patent and collateralizes while an occluded stent has more serious implications. Our study, based on symptomatic treatment, suggest that stented non-LAD vessels are more likely to be the culprit when patients undergoing HCR require re-intervention.

The comparable medium-term mortality in our study between HCR and CABG does support the

hypothesis that the two revascularization techniques provide equal survival advantage in the treatment of multivessel CAD. The results of our paper are similar to the propensity matched groups of off-pump CABG and HCR compared by Halkos, et al.<sup>27</sup> In that study, an increased incidence of repeat revascularization for HCR (12.2%) was found at 3-year follow-up compared to patients undergoing off pump CABG (3.7%) yet no difference in 5-year mortality was found. More recent analyses of data from the same institution demonstrated no difference in long term all-cause mortality using not only a 1:3 HCR:CABG propensity-score matched cohort (HR 0.91, 95% CI 0.55-1.52), but also a 1:1 HCR vs open bilateral IMA revascularization propensity-score matched cohort (HR 1.05, 95% CI 0.48-2.29).<sup>26,28,29</sup>

HCR is a revascularization strategy which should be in the tool box of all coronary heart teams when assessing each particular patient with multivessel CAD. Retrospective and propensity matched studies suggest that the survival advantage of HCR is equivalent to that conferred by conventional CABG but that the incidence of repeat revascularization exists somewhere between conventional CABG and multivessel PCI. Depending upon patient risk factors as well as particular patient concerns, the advantages and disadvantages of each strategy should be discussed with each patient and a tailored plan designed. A large scale prospective randomized study comparing multi-vessel PCI, conventional CABG and HCR will be necessary in order to more clearly define the role of each therapy in more granular clinical situations.

There are several limitations to this study with the most notable being that the data is retrospective. While propensity score matching may adjust for measured covariates associated with treatment and outcomes, unmeasured confounders may be present. In particular, patients undergoing HCR were a highly-selected group of patients after review of coronary anatomy by the cardiac surgeon and interventional cardiologist. These patients typically had a large distal LAD with good anterior wall viability along with short focal proximal lesions in the RCA or left circumflex amenable to PCI. Long term follow-up was also not complete with 13.6% of pa-

tients in the CABG group and 6.6% of patient in the HCR group having less than 6 months follow-up. This limitation was exacerbated by the unreliability of the SSDI after 2011. Finally, it should be noted that the HCR patients all underwent robotic CABG by a single surgeon (JD) with a total experience of over 500 robotic cases. As such, this study does not include the well described learning curve which occurs over the first 50 robotic CABG cases in a surgeon's experience.

## CONCLUSIONS

Retrospective review of our institutional experience of a propensity matched cohort of HCR and conventional CABG patients demonstrated that while HCR had improved short term outcomes and similar mid-term survival, it is associated with increased risk for repeat revascularization. Prospective studies to confirm these findings are warranted as HCR may be an important alternative to PCI and conventional CABG, particularly in high risk patients.

## ACKNOWLEDGEMENTS

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## ABBREVIATIONS

CABG = coronary artery bypass grafting  
 LIMA = left internal mammary artery  
 LAD = left anterior descending  
 PCI = percutaneous coronary intervention  
 HCR = hybrid coronary revascularization  
 MACCE = major adverse cardiac and cerebrovascular events  
 IQR = interquartile range  
 LVEF = left ventricular ejection fraction  
 DES = drug eluting stent  
 SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery

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# Επιπλοκές Καρδιοχειρουργικών Επεμβάσεων από το Ήπαρ

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## ΠΕΡΙΛΗΨΗ

Η λειτουργία ήπατος και καρδιάς παρουσιάζει στενή αλληλεπίδραση και αναγνωρίζεται πληθώρα οξέων αλλά και χρόνιων καταστάσεων με εκδηλώσεις και από τα δύο όργανα. Σε αυτές υπάγονται και οι καρδιοχειρουργικές επεμβάσεις, μετά τις οποίες παρατηρείται διαταραχή της ηπατικής βιοχημείας ως και στο 10% των ασθενών. Η ηπατική προσβολή κυμαίνεται από την ασυμπτωματική τρανσαμινασαιμία ή υπερχολερυθριναιμία ως την απειλητική για τη ζωή οξεία ηπατική ανεπάρκεια. Οι μηχανισμοί της ηπατικής βλάβης είναι ποικίλοι και περιλαμβάνουν τις επιπλοκές της ίδιας της επέμβασης όπως η ισχαιμική ηπατίτιδα και ο μετεγχειρητικός ίκτερος, τη φαρμακευτική τοξικότητα και άλλες παθολογικές καταστάσεις με υψηλή επίπτωση στους βαρέως πάσχοντες. Η διάγνωση είναι κατά κύριο λόγο κλινική. Απαιτεί γνώση των σχετιζόμενων με την επέμβαση ηπατικών επιπλοκών, εκτενή κλινική εξέταση και λεπτομερή λήψη του ιστορικού ιδίως αναφορικά με τροποποιήσεις της φαρμακευτικής αγωγής. Ο έλεγχος για ιογενή λοίμωξη είναι συχνά απαραίτητος και θέτει σε κάποιες περιπτώσεις τη διάγνωση. Ο απεικονιστικός έλεγχος σπάνια είναι βοηθητικός, ιδίως στις περιπτώσεις αλιθιασικής χολοκυστίτιδας και στην ανάδειξη διάτασης των ηπατικών φλεβών στις περιπτώσεις συμφορητικής ηπατοπάθειας. Η λήψη βιοψίας του ήπατος σπάνια έχει ένδειξη. Η θεραπεία είναι στοχευμένη, ανάλογα με την υποκείμενη αιτία. Στις περιπτώσεις καρδιακής ή κυκλοφορικής ανεπάρκειας, η άρση της υποκείμενης αιτίας οδηγεί σε ταχεία αποκατάσταση της ηπατικής βιοχημείας. Η πρόγνωση εξαρτάται από το υποκείμενο αίτιο και τη βαρύτητα της ηπατικής βλάβης. Όμως, η εμφάνιση ηπατικών επιπλοκών μετά την καρδιοχειρουργική επέμβαση σχετίζεται με αυξημένη νοσηρότητα και θνητότητα.

## ΕΙΣΑΓΩΓΗ

Η αιμάτωση του ήπατος (δέχεται 1500 ml αίματος/ min, το 25% της καρδιακής παροχής) είναι διμερής, από την ηπατική αρτηρία και την πυλαία φλέβα, ενώ η απαγωγός κυκλοφορία γίνεται με τις ηπατικές φλέβες.<sup>1</sup> Η ηπατική αρτηρία αποτελεί τη κύρια πηγή οξυγόνωσης του ήπατος, ενώ η πυλαία φλέβα παρέχει το 80% της αιμάτωσης αλλά μόνο το 40% της οξυγόνωσης. Σε σημαντική μείωση της ηπατικής αρτηριακής αιμάτωσης (πχ λόγω καταπληξίας), το ήπαρ ανταποκρίνεται με αγγειοκινητικούς μηχανισμούς (αυτορρύθμιση) που προκαλούν αύξηση της αιμάτωσης από το πυλαίο σύστημα και αύξηση (μέχρι 95%) της απορρόφησης οξυγόνου. Στο μηχανισμό αυτορρύθμισης, κεντρικό ρόλο έχει η αδενοσίνη που παράγεται τοπικώς από τα ηπατικά αγγεία.<sup>1</sup>

Ηπατικές εκδηλώσεις διαπιστώνονται συχνά σε ασθενείς με καρδιακές παθήσεις και η κλινική βαρύτητά τους κυμαίνεται από τις ασυμπτωματικές αυξήσεις των ηπατικών ενζύμων μέχρι την οξεία/κεραυνοβόλο ηπατική ανεπάρκεια. Για τις υψηλού κινδύνου καρδιοχειρουργικές επεμβάσεις, εκτιμάται ότι το 10% των ασθενών θα εμφανίσει κάποιου βαθμού ηπατική βλάβη, η οποία σχετίζεται με αυξημένη νοσηρότητα και θνητότητα.<sup>2</sup> Συνηθέστερα, η ηπατική βλάβη αποδίδεται σε μειωμένη αρτηριακή αιμάτωση που οδηγεί σε ισχαιμία, αυξημένο οξειδωτικό stress και εμφάνιση συνδρόμου ισχαιμίας/επαναιμάτωσης.<sup>3,4</sup> Έτερος μηχανισμός είναι η εμφάνιση συνδρόμου συστηματικής φλεγμονώδους αντίδρασης που επάγεται από τη εφαρμογή καρδιοπνευμονικής παράκαμψης.<sup>2</sup> Επίσης, η φλεβική συμφόρηση του ήπατος ως αποτέλεσμα της καρδιακής ανεπάρκειας οδηγεί σε διαταραχή της ηπατικής λειτουργίας στην οξεία και στη χρόνια δεξιά καρδιακή ανεπάρκεια.<sup>5</sup> Επιπλέον, μερικά καρδιολογικά φάρμακα (πχ αμιωδαρόνη, αντιπηκτικά) έχουν την δυνατότητα εκδήλωσης ηπατοτοξικότητας.<sup>6</sup> Τέλος, κλινικές οντότητες όπως η αλιθιασική χολοκυστίτιδα και η οξεία λοίμωξη ή αναζωπύρωση του κυτταρομεγαλοϊού έχουν υψηλή επίπτωση στους βαρέως πάσχοντες, συμπεριλαμβανομένων των καρδιοχειρουργικών ασθενών.

## ΣΥΜΦΟΡΗΤΙΚΗ ΗΠΑΤΟΠΑΘΕΙΑ

Οι εκδηλώσεις από το ήπαρ στη δεξιά καρδιακή ανεπάρκεια (συχνότερα λόγω συμφορητικής καρδιακής ανεπάρκειας και σπανιότερα λόγω πνευμονικής καρδιάς ή πρωτοπαθούς πνευμονικής υπέρτασης) και στη συμφυτική περικαρδίτιδα είναι συχνές. Σε αυτή την κατηγορία υπάγεται και η ηπατική προσβολή μετά από επέμβαση Fontan.<sup>7</sup> Στους ασθενείς αυτούς διαπιστώνεται αύξηση της ηπατικής φλεβικής πίεσης που συνοδεύεται από διάταση των κολποειδών (συμφορητική ηπατοπάθεια) και υποξία των ηπατοκυττάρων, η οποία γίνεται μεγαλύτερη όταν μειωθεί επιπρόσθετα η καρδιακή παροχή (ισχαιμική ηπατίτιδα). Σε πολλές περιπτώσεις συμφορητικής καρδιακής ανεπάρκειας οι 2 αυτοί παθοφυσιολογικοί μηχανισμοί συνυπάρχουν.<sup>8,9</sup> Εξάλλου, η συμφυτική περικαρδίτιδα (λόγω φυματώσης, ιογενούς λοίμωξης, νεοπλασίας κλπ) συχνά παρουσιάζει άτυπες κλινικές εκδηλώσεις και μιμείται ηπατικές παθήσεις (κίρρωση ή σύνδρομο θρόμβωσης των ηπατικών φλεβών/ σύνδρομο Budd-Chiari).<sup>10,11</sup>

Το συμπεφορημένο ήπαρ είναι διογκωμένο, πορφυρού χρώματος (μοσχοκαρυοειδές -nutmeg) που αποδίδεται σε εναλλαγές φυσιολογικών περιοχών με συμπεφορημένες –αιμορραγικές.<sup>12</sup> Μικροσκοπικώς, η κεντρική φλέβα των ηπατικών λοβίων (ζώνη 3) και τα κολποειδή είναι διατεταμένα. Σε σοβαρότερες περιπτώσεις, παρατηρείται αιμορραγία στη ζώνη 3, εναλλαγές ωχρών και αιμορραγικών περιοχών και τοπική νέκρωση των ηπατικών κυττάρων, όταν συνυπάρχει ισχαιμική βλάβη.<sup>13</sup> Χαρακτηριστικώς, απουσιάζει η φλεγμονώδης διήθηση. Επίσης, το πυλαίο διάστημα (ζώνη 1) δεν παρουσιάζει αλλοιώσεις και περιτριγυρίζεται από υγιή ηπατικά κύτταρα. Σε προχωρημένα στάδια καρδιακής ανεπάρκειας παρουσιάζονται ίνωση γύρω από την κεντρική φλέβα του ηπατικού λοβίου και γεφυρώσεις μεταξύ των κεντρικών φλεβών με αποτέλεσμα τα μη προσβαλλόμενα πυλαία διαστήματα να περιτριγυρίζονται από ινώδη ιστό (καρδιογενές κίρρωτικό ήπαρ).<sup>8,9,12</sup>

Ο ασθενής με ηπατική συμφόρηση παραπονείται κυρίως για πόνο στο δεξιό υποχόνδριο που μπορεί να εμφανίζεται μετά από κόπωση και καλείται ηπατική στηθάγχη.

Στην αντικειμενική εξέταση διαπιστώνεται συχνά (>90 %) ευαίσθητη ηπατομεγαλία, που οφείλεται σε διάταση των νευρικών απολήξεων της κάψας του Glisson, και σπληνομεγαλία (20%).<sup>14</sup> Το ήπαρ είναι μεγάλο, σκληρό και μπορεί να σφύζει. Έτσι, σε ανεπάρκεια της τριγλώχινας μπορεί να γίνονται αντιληπτές συστολικές σφύξεις του ήπατος (“σφύζων ήπαρ”), ενώ σε στένωση της τριγλώχινας προσυστολικές σφύξεις.<sup>15,16</sup> Επίσης, οι ασθενείς παρουσιάζουν διάταση των φλεβών του τραχήλου και ηπατοσφαγιτιδική παλινδρόμηση.<sup>17,18</sup> Σε ασθενείς με περικαρδίτιδα μπορεί να διαπιστωθούν σημεία καρδιακού επιποματισμού (παράδοξος σφυγμός, σημείο Kussmaul).

Οι ασθενείς δεν έχουν στίγματα χρόνιας ηπατικής νόσου (αγγειοματώδεις σπίλους κλπ) ή πυλαιοσυστηματικές αναστομώσεις (πχ κισσούς οισοφάγου). Συνυπάρχουν, συχνά, περιφερικά οιδήματα, πλευρίτιδα (συνήθως δεξιά) και ασκίτης (25% των ασθενών,<sup>3</sup> συχνότερα σε χρόνιες καταστάσεις παρά σε οξεία δεξιά καρδιακή ανεπάρκεια ή συμπίεστική περικαρδίτιδα). Ο ασκίτης μπορεί να είναι δυσανάλογα μεγάλος σε σχέση με τα περιφερικά οιδήματα και την βαρύτητα των υπολοίπων συμπτωμάτων της καρδιακής ανεπάρκειας ή της περικαρδίτιδας. Το λεύκωμα του ασκίτικού υγρού είναι μεγαλύτερο από το συνήθως παρατηρούμενο στην κίρρωση του ήπατος (>2,5 g/dl), με κλίση λευκοματίνης ασκίτικού υγρού και αίματος >1,1 g/dl και προσομοιάζει με το παρατηρούμενο σε σύνδρομο απόφραξης των ηπατικών φλεβών (Budd-Chiari).<sup>19,20</sup> Επίσης, το ασκίτικό υγρό περιέχει περισσότερα ερυθρά αιμοσφαίρια απ’ότι παρατηρείται σε άλλης αιτιολογίας κίρρωση του ήπατος. Σπανιότερα, μπορεί να διαπιστωθεί χυλώδης ασκίτης (τριγλυκερίδια >150mg/dl, ή τριγλυκερίδια υγρού>τριγλυκερίδια αίματος) που αποδίδεται σε αυξημένη πίεση στα λεμφικά αγγεία του μεσεντερίου που είναι δυνατόν να ραγούν.<sup>21,22,23</sup>

Εργαστηριακά, διαπιστώνονται αύξηση της χολερυθρίνης στο 25-80% (άμεση < έμμεση), των τρανσαμινασών (alanine aminotransferase-ALT, aspartate aminotransferase-AST), της γαλακτικής αφυδρογονάσης (Lactate Dehydrogenase, LDH) και της γ-γλουτάμυλ-τρανσπεπτιδάσης (Gamma-glutamyl transferase, γ-GT) στο 30-60%, παρά-

ταση του χρόνου προθρομβίνης (Χρ. Quick) στο 80-90%, υπολευκωματιναίμια στο 30-50% και ελαφρά υπεργαμμασφαιριναιμία στο 50% των ασθενών.<sup>24</sup> Η αλκαλική φωσφατάση (alkaline phosphatase, ALP) είναι φυσιολογική ή λίγο αυξημένη. Οι βιοχημικές αυτές διαταραχές υποχωρούν με τη βελτίωση της καρδιακής λειτουργίας.

Η χολερυθρίνη στο 1/3 των ασθενών υπερβαίνει τα 2mg/dl, αλλά παραμένει συνήθως σε επίπεδα <3mg/dl. Η συμφόρηση του ηπατικού παρεγχύματος προκαλεί αύξηση της πίεσης στα ηπατικά κολποειδή, η οποία συνεπάγεται καταστροφή του ενδοθηλίου τους, αύξηση της πίεσης άμεσα στα ηπατικά κύτταρα και ακολούθως στα χοληφόρα τριχοειδή με αποτέλεσμα την αύξηση της χολερυθρίνης. Ο ίκτερος βαθιάίνει όσο τα επεισόδια της καρδιακής ανεπάρκειας επιτείνονται.<sup>5</sup> Η διαφορική διάγνωση του ικτέρου σε ασθενή με καρδιακή ανεπάρκεια περιλαμβάνει την συμφόρηση του ήπατος, την πνευμονική εμβολή (αυξημένη παραγωγή έμμεσης χολερυθρίνης από αποδόμηση των ερυθρών αιμοσφαιρίων), τη χοληδοχολιθίαση, τη σηψαιμία, την αιμόλυση και τη φαρμακευτική ηπατοτοξικότητα. Οι τρανσαμινάσες είναι λίγο (2-3 φορές η ανώτερη φυσιολογική τιμή - 2-3XΦΤ) αυξημένες αλλά μπορεί να αυξηθούν πολύ σε παροξύνσεις της νόσου (σε συνδυασμό με μείωση της καρδιακής παροχής –ισχαιμική ηπατίτιδα).<sup>5</sup>

Στο υπερηχογράφημα κοιλίας παρατηρείται συχνά διάταση της κάτω κοίλης φλέβας και των ηπατικών φλεβών.<sup>25</sup> Οι περισσότεροι ασθενείς παρουσιάζουν παθολογικά ευρήματα στο υπερηχογράφημα καρδιάς, που οφείλονται σε διατατική μυοκαρδιοπάθεια, στεφανιαία νόσο, υπερτροφική μυοκαρδιοπάθεια, οξεία μυοκαρδίτιδα κ.ά. Οι αποτιτανώσεις στο περικάρδιο στην απλή ακτινογραφία ή στην αξονική τομογραφία βοηθούν στη διάγνωση της συμφυτικής περικαρδίτιδας. Η βιοψία ήπατος συχνά δεν είναι εφικτή λόγω του ασκίτη και των διαταραχών της πήξεως. Η ιστολογική εικόνα (με διάταση των κολποειδών και αιμορραγικές νεκρώσεις) μπορεί να ομοιάζει με την παρατηρούμενη στο σύνδρομο Budd-Chiari.<sup>26,27</sup> Όταν υπάρχει αμφιβολία για τη διάγνωση, διενεργείται δεξιός καρδιακός καθετηριασμός με προσδιορισμό των πιέσεων της πνευμονικής κυκλοφορίας.

Η πρόγνωση της ηπατικής νόσου εξαρτάται από την υποκείμενη καρδιοπάθεια. Αν ο ασθενής ανταποκριθεί στην θεραπεία για την καρδιακή ανεπάρκεια, η κίρρωση αντιρροπείται. Ωστόσο, ο ίκτερος αποτελεί κακό προγνωστικό σημείο. Οι ηπατικές εκδηλώσεις σε ασθενείς με συμφυτική περικαρδίτιδα υποστρέφουν μετά την χειρουργική περικαρδιοεκτομή.<sup>28</sup> Σε ασθενείς με καρδιακή ανεπάρκεια, η χρήση των διουρητικών δεν πρέπει να επιπλακεί από μείωση του ενδαγγειακού όγκου με πιθανή συνέπεια τη μείωση της αρτηριακής αιμάτωσης του ήπατος και την πρόκληση ισχαιμικής ηπατίτιδας.

### ΙΣΧΑΙΜΙΚΗ ΗΠΑΤΙΤΙΔΑ

Η ισχαιμική ηπατίτιδα αναφέρεται ιστολογικός στην κεντρολοβιακή (ζώνη 3) ηπατοκυτταρική νέκρωση σε συνθήκες μειωμένης ηπατικής άρδευσης.<sup>29</sup> Πρόκειται για λανθασμένο όρο, αφού δεν συνοδεύεται από φλεγμονή. Η νέκρωση αποδίδεται στη δομή του ηπατικού λόβιου που οδηγεί στην άρδευση της ζώνης 3 με λιγότερο οξυγονωμένο αίμα, καθώς αυτό κυλά στα ηπατικά κολποειδή με κατεύθυνση από το πυλαίο διάστημα (ζώνη 1) προ το κέντρο.<sup>1</sup>

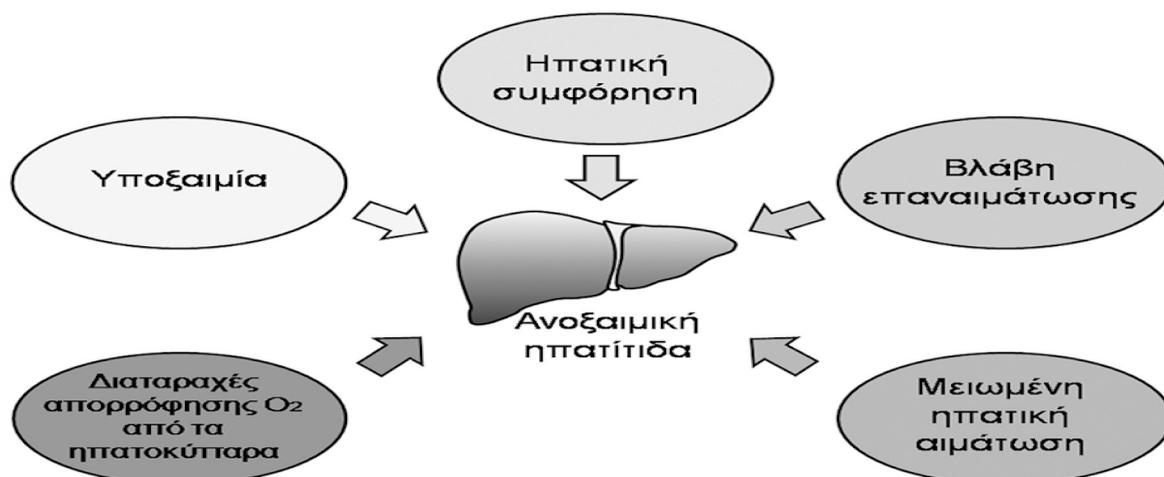
Παθοφυσιολογικά, αναφέρεται στη βλάβη που προκαλείται από μειωμένη προσφορά οξυγόνου στα ηπατικά κύτταρα. Η προσφορά οξυγόνου εξαρτάται από την καρδιακή παροχή, την τιμή της αιμοσφαιρίνης, τον κορεσμό της σε οξυγόνο και τη δυνατότητα απελευθέρωσης του οξυγόνου στους ιστούς. Οποιαδήποτε κατάσταση προκαλεί μεταβολή των ανωτέρω παραμέτρων, αποτελεί δυναμικά αιτία ισχαιμικής ηπατίτιδας. Έτσι, οι υποκείμενες αιτίες μπορούν αδρά να χωριστούν σε 3 βασικές κατηγορίες: καρδιογενής καταπληξία (shock), κυκλοφορική ανεπάρκεια (πχ υποογκαιμία, σηπτική καταπληξία) και υποξαιμία αρτηριακού αίματος. Ο όρος ισχαιμική ηπατίτιδα είναι συνυφασμένος με την ηπατική βλάβη ως απόρροια των 2 πρώτων αιτίων, ενώ η ηπατίτιδα ως αποτέλεσμα υποξαιμίας συχνά χαρακτηρίζεται ως ανοξαιμική. Πάντως, πολλοί συγγραφείς πλέον προτιμούν τον όρο ανοξαιμική και για τις 3 καταστάσεις, καθώς αντανακλά την βασική πα-

θοφυσιολογική διαταραχή της ανεπαρκούς οξυγόνωσης του ηπατοκυττάρου (Εικόνα 1).<sup>30</sup>

Η καρδιακή ανεπάρκεια αποτελεί την υποκείμενη αιτία έως και στις μισές περιπτώσεις.<sup>30</sup> Συγκεκριμένα, ισχαιμική ηπατίτιδα αναπτύσσεται συχνότερα σε έδαφος αριστερής καρδιακής ανεπάρκειας, στεφανιαίας νόσου ή μυοκαρδιοπάθειας όταν, λόγω ενός οξέος συμβάντος (πχ καρδιογενής καταπληξία από έμφραγμα μυοκαρδίου ή αρρυθμία), μειωθεί οξέως η καρδιακή παροχή προς το ήδη συμπεφορημένο ήπαρ. Το εκάστοτε οξύ σύμβαμα μπορεί να αναγνωρισθεί έως και στο 80% των περιπτώσεων.<sup>31</sup> Η συνύπαρξη φλεβικής συμφόρησης του ήπατος είναι ιδιαίτερα σημαντική στην παθογένεια του συνδρόμου, καθώς αναγνωρίζεται στο 90% των περιπτώσεων.<sup>31</sup> Αντίθετα, καταστάσεις με εκσεσημασμένη υπόταση χωρίς συνύπαρξη καρδιακής νόσου δεν επιπλέκονται συχνά από ισχαιμική ηπατίτιδα (shock liver). Χαρακτηριστικά, παρατηρείται σαφώς σπανιότερα σε έδαφος υποογκαιμικής ή σηπτικής καταπληξίας, θερμοπληξίας, λήψης υπερδοσολογίας εργοταμίνης και παρατεταμένων επιληπτικών σπασμών σε παιδιά.<sup>30</sup>

Η επίπτωση της ισχαιμικής ηπατίτιδας μετά από καρδιοχειρουργική επέμβαση υπολογίζεται στο 1.1%.<sup>32</sup> Πιθανοί παράγοντες κινδύνου είναι η υπέρταση, ο σακχαρώδης διαβήτης, το χαμηλότερο κλάσμα εξωθήσεως μετεγχειρητικά και το γυναικείο φύλο.<sup>32</sup>

Αναφορικά με την κλινική εικόνα, ο ασθενής είναι συχνά βαρέως πάσχων, παρουσιάζοντας χαμηλή αρτηριακή πίεση και ταχυκαρδία. Όμως, σε πολλές περιπτώσεις, η μείωση της αρτηριακής πίεσης είναι πολύ μικρής διάρκειας και δεν γίνεται αντιληπτή ως και στο 50% των ασθενών.<sup>31,33</sup> Οι ασθενείς μπορεί να παρουσιάζουν ναυτία, εμετό και πόνο στο δεξιό υποχόνδριο όταν συνυπάρχει ηπατική συμφόρηση, οπότε ανευρίσκονται στην αντικειμενική εξέταση ηπατομεγάλια και θετικό ηπατοσφαγιτιδικό σημείο.<sup>31</sup> Η κλινική εικόνα μπορεί να μοιάζει με αυτήν της ιογενούς ηπατίτιδας ή άλλης αιτιολογίας οξεία ηπατική βλάβη (από φάρμακα ή αυτοάνοση). Ο ασθενής μπορεί να είναι συγχυτικός, ληθαργικός και ενίοτε σε κώμα λόγω της εγκεφαλικής ανοξίας και όχι λόγω ηπατικής εγκεφαλοπάθειας.<sup>31</sup> Σπανίως, οι εκδηλώ-



**Εικόνα 1.** Παθοφυσιολογικοί μηχανισμοί εκδήλωσης ισχαιμικής/ανοξαιμικής ηπατίτιδας (από Wassem et al, τροποποιημένο).<sup>33</sup>

σεις από τον εγκέφαλο οφείλονται σε συνυπάρχουσα υπογλυκαιμία.

Από τον εργαστηριακό έλεγχο, διαπιστώνονται εκσεσημασμένη (>500 IU/l, μπορεί και >200XΦΤ) και ταχεία (σε 1-3 ημέρες) αύξηση των τρανσαμινασών, με συνοδό μεγάλη αύξηση της LDH (πηλίκο ALT/LDH <1,5), ενώ η χολερυθρίνη και η αλκαλική φωσφατάση είναι φυσιολογικές ή ελαφρώς αυξημένες (<4X και <2XΦΤ αντιστοίχως). Τα ηπατικά ένζυμα μειώνονται ταχέως (εντός 7-10 ημερών) εφόσον ο ασθενής αναταχθεί αιμοδυναμικά. Όταν παρατηρείται αύξηση της χολερυθρίνης, αυτό συμβαίνει συνήθως μετά από την αρχόμενη μείωση των τρανσαμινασών.<sup>31</sup> Η παράταση της αύξησης των ηπατικών ενζύμων εκφράζει κακή πρόγνωση λόγω της συνοδού μεγάλης μείωσης της καρδιακής παροχής. Αν το ήπαρ είναι ήδη επηρεασμένο από χρόνια φλεβική συμφόρηση, τότε η οξεία καρδιακή ανεπάρκεια μπορεί να οδηγήσει σε ηπατική ανεπάρκεια που χαρακτηρίζεται από πολύ παρατεταμένο χρόνο προθρομβίνης. Έτσι, απαιτείται ιδιαίτερη προσοχή σε όσους λαμβάνουν αντιπηκτικά φάρμακα. Η αποκατάσταση του χρόνου προθρομβίνης συμβαίνει σε περίπου 1 εβδομάδα μετά την άρση της υποκείμενης αιτίας.<sup>31</sup> Συχνά, συνυπάρχουν αυξήσεις της ουρίας και της κρεατινίνης λόγω της νεφρικής συμμετοχής στη συστηματική μείωση της αιμάτωσης ή/και διαταραχές της γλυκαιμίας (υπερ- ή υπογλυκαιμία). Χαρακτηριστική είναι και η παρουσία θρομβοπενίας.<sup>34</sup>

Η διαφορική διάγνωση της ισχαιμικής ηπατίτιδας γίνεται από την οξεία ιογενή και τη φαρμακευτική ηπατίτιδα στις οποίες οι αμινοτρασφεράσες αυξάνονται και μειώνονται σταδιακά σε 1-2 εβδομάδες. Στις ιογενείς ηπατίτιδες, η αύξηση της LDH δεν είναι σημαντική, ενώ στη διάγνωση βοηθά το επιδημιολογικό ιστορικό και οι ορολογικές εξετάσεις.<sup>31</sup> Σε φαρμακευτική ηπατοτοξικότητα (π.χ. από παρακεταμόλη), οι αυξήσεις της LDH μπορεί να είναι πολύ μεγάλες, ενώ μπορεί να συνυπάρχει νεφρική ανεπάρκεια. Άλλα αίτια μεγάλης αύξησης των τρανσαμινασών είναι η ραβδομύολυση, το οξύ έμφραγμα του μυοκαρδίου, η οξεία χολαγγειίτιδα, το ηπατικό τραύμα ή το έμφρακτο.

Το υπερηχογράφημα της καρδιάς μπορεί να αναδείξει την συνυπάρχουσα καρδιοπάθεια. Η βιοψία ήπατος συνήθως δεν είναι εφικτή λόγω της γενικής κατάστασης του ασθενούς και της συνυπάρχουσας διαταραχής της πήκτικότητας.<sup>31</sup>

Η γρήγορη και έγκαιρη διάγνωση της ισχαιμικής ηπατίτιδας διαδραματίζει ιδιαίτερο ρόλο στη πρόγνωση. Η διάγνωση στην καθημερινή κλινική πράξη βασίζεται στην αύξηση των τρανσαμινασών και της LDH σε ασθενή που παρουσίασε υποτασικό επεισόδιο και χρειάστηκε τη χορήγηση αγγειοσυσπαστικών φαρμάκων. Παρ' όλα αυτά, η οξεία ισχαιμική ηπατίτιδα μπορεί να αποτελέσει διαγνωστικό πρόβλημα (κυρίως από φαρμακευτική ηπατίτιδα πχ από αμιωδαρόνη).<sup>30</sup>

Η θνησιμότητα της ισχαιμικής ηπατίτιδας εί-

ναι υψηλή (περίπου 50%) και αποδίδεται στην υποκείμενη καρδιοπάθεια και όχι στην ηπατική βλάβη που είναι συνήθως καλοήθους πορείας. Συγκεκριμένα, η μηνιαία και ετήσια επιβίωση βρέθηκε 47% και 28%, αντιστοίχως,<sup>31</sup> ενώ σε ασθενείς με κίρρωση, η θνητότητα είναι ακόμη υψηλότερη, υπολογιζόμενη σε 60-100%.<sup>31</sup> Προγνωστικοί παράγοντες της θνητότητας στις 30 ημέρες είναι οι τιμές της AST, της κρεατινίνης και του γαλακτικού οξέος, το INR>2 και η σηπτική καταπληξία.<sup>31,33</sup> Ο βαθμός αύξησης των τρανσαμινασών δεν έχει προγνωστική σημασία, όπως έχει η ταχύτητα αποκατάστασης των τιμών τους.

Η αιμοδυναμική αποκατάσταση του ασθενούς οδηγεί σε αναγέννηση του ηπατικού παρεγχύματος και πλήρη επάνοδο του ηπατικού λοβίου στη φυσιολογική κατάσταση.<sup>31</sup> Έτσι, η θεραπεία στοχεύει στην υποκείμενη καρδιακή νόσο και στην αποκατάσταση της αιμάτωσης του ήπατος με τη χρήση ινοτρόπων φαρμάκων (κυρίως ντοπαμίνη και δοβουταμίνη) σε συνδυασμό με την υποχώρηση της φλεβικής συμφόρησης. Η επιλογή του ινότροπου φαρμάκου εξαρτάται από την αιμοδυναμική κατάσταση και όχι από την ηπατική επιπλοκή. Σε καταστάσεις υποογκαιμικής ή σηπτικής καταπληξίας, χορηγούνται κολλοειδή και κρυσταλλοειδή διαλύματα για την αποκατάσταση του ενδαγγειακού όγκου. Έχουν επίσης δοκιμαστεί σε πειραματικά μοντέλα παράγοντες που μειώνουν το οξειδωτικό stress όπως η resveratrol ή τη βλάβη από το σύνδρομο ισχαιμίας/επαναιμάτωσης όπως η δοξορουβικίνη και η αιμο-οξυγονάση -1 (heme oxygenase-1, HO-1), όμως τα δεδομένα είναι ελάχιστα και οι εν λόγω παράγοντες δεν εφαρμόζονται στην κλινική πράξη.<sup>30</sup> Χρειάζεται ιδιαίτερη προσοχή στη χρήση φαρμάκων (π.χ. ξυλοκαΐνη, αναστολείς των δίαυλων ασβεστίου κλπ.) τα οποία μεταβολίζονται στο ήπαρ. Ελεγχόμενη πρέπει να είναι και η χορήγηση αναλγητικών, ιδιαίτερα των οπιούχων, καθώς η μειωμένη ηπατική τους κάθαρση μπορεί να οδηγήσει σε νευρολογικές εκδηλώσεις ή καταστολή του αναπνευστικού κέντρου. Τέλος, αξίζει να σημειωθεί ότι η παρακεταμόλη μπορεί να παρουσιάζει τοξικότητα σε ασθενείς με συμφορητική καρδιακή ανεπάρκεια, ακόμα και χωρίς συνύπαρξη παραγόντων κινδύνου όπως η κατάχρηση αιθυλικής αλκοόλης.

## ΑΝΟΞΑΙΜΙΚΗ ΗΠΑΤΙΤΙΔΑ

Η ανοξαιμική ηπατίτιδα (Hypoxic hepatitis) αποτελεί ουσιαστικά υποσύνολο της ισχαιμικής ηπατίτιδας με βασικό παθογενετικό μηχανισμό την ανεπαρκή προσφορά οξυγόνου στο ήπαρ που δεν οφείλεται όμως σε διαταραχές της αιμάτωσης του.<sup>35</sup> Σε αυτή την περίπτωση, σε αντίθεση με την ισχαιμική ηπατίτιδα καρδιογενούς αιτιολογίας, η εκσεσημασμένη υποξυγοναιμία συνοδεύεται από αυξημένη καρδιακή παροχή και μείωση των περιφερικών αγγειακών αντιστάσεων, στα πλαίσια προσπάθειας διατήρησης επαρκούς οξυγόνωσης των ιστών.

Πιο αναλυτικά, η αναπνευστική ανεπάρκεια αναγνωρίζεται ως αιτία της ισχαιμικής ηπατίτιδας στο 15% των περιπτώσεων.<sup>31</sup> Συνήθως, παρατηρείται στα πλαίσια οξείας επιδείνωσης προϋπάρχουσας πνευμονοπάθειας και σε καταστάσεις όπως η αποφρακτική υπνική άπνοια με υποξυγοναιμία (PaO<sub>2</sub><50 mmHg). Συχνά, συνυπάρχει ηπατική φλεβική συμφόρηση, χωρίς έκδηλη καρδιακή επιβάρυνση.<sup>36,37,38,39</sup>

Η διαταραχή της ισορροπίας προσφοράς-ζήτησης οξυγόνου, φαινόμενο που συχνά χαρακτηρίζεται ως «δυσοξία» είναι η παθοφυσιολογική βάση και για την ανοξαιμική ηπατίτιδα στα πλαίσια σήψης, χωρίς καταπληξία.<sup>31</sup> Σε αυτή την περίπτωση, η ανάγκη των ηπατοκυττάρων για οξυγόνο είναι αυξημένη. Παράλληλα, η απελευθέρωση οξυγόνου στα ηπατοκύτταρα αναστέλλεται από τη δράση φλεγμονωδών κυτταροκινών και ενδοτοξινών.<sup>34,40</sup> Με τον ίδιο μηχανισμό της μη επαρκούς απελευθέρωσης του κυκλοφορούντος οξυγόνου στο ήπαρ προκαλείται ηπατική βλάβη σε δηλητηρίαση από τοξίνες όπως το μονοξείδιο του αζώτου (NO) και στη μεθαιμοσφαιριναιμία.<sup>34</sup> Σε αυτές τις περιπτώσεις, η ηπατική βλάβη υποχωρεί με την αντιμετώπιση της υποξαιμίας με τη χορήγηση O<sub>2</sub> με ταυτόχρονη αντιμετώπιση της εκάστοτε εκλυτικής αιτίας.<sup>31,41</sup>

## ΙΚΤΕΡΟΣ ΜΕΤΑ

### ΑΠΟ ΚΑΡΔΙΟΧΕΙΡΟΥΡΓΙΚΗ ΕΠΕΜΒΑΣΗ

Κατά την πρώτη εβδομάδα μετά από καρδιοχειρουργική επέμβαση, ίκτερος εμφανίζεται στο 3-

40% των ασθενών ενώ σε περιπτώσεις αντικατάστασης της μιτροειδούς βαλβίδας το ποσοστό αυξάνεται περαιτέρω και αγγίζει το 55%.<sup>42</sup> Εμφανίζεται συνήθως την 2η μετεγχειρητική ημέρα, κορυφώνεται την 8-12η ημέρα (χολερυθρίνη ορού 24-40 mg/dl) και εξαφανίζεται σε 14-18 ημέρες.<sup>42</sup> Η υπερχολερυθριναιμία είναι συνήθως αμέσου τύπου (80%), λόγω ενδοηπατικής χολόστασης. Η εμμέσου τύπου υπερχολερυθριναιμία παρατηρείται σπανιότερα, αποδίδεται σε αιμόλυση σε έδαφος των πολλαπλών μεταγγίσεων και της χρήσης συσκευών καρδιοπνευμονικής παράκαμψης, κορυφώνεται την 2-3 μετεγχειρητική ημέρα και δε σχετίζεται με αυξημένη νοσηρότητα και θνητότητα.<sup>43</sup> Οι τρανσαμινάσες είναι συχνά πολύ αυξημένες, ενώ η αλκαλική φωσφατάση μπορεί να είναι αυξημένη ή φυσιολογική.<sup>44</sup>

Παράγοντες που συμμετέχουν στην ηπατική βλάβη είναι η χρονία ηπατική συμφόρηση λόγω καρδιακής νόσου, η χαμηλή παροχή, η εγχειρητική υποθερμία, η σήψη, το μηχάνημα εξωσωματικής κυκλοφορίας, η αιμόλυση, η νεφρική ανεπάρκεια και η απορρόφηση των αιματωμάτων.<sup>42,45</sup> Η διαφορική διάγνωση οφείλει να γίνει από οξεία ηπατική βλάβη ιογενούς ή φαρμακευτικής αιτιολογίας (αναισθητικά κ.ά).<sup>42</sup>

Όταν ο ίκτερος εκδηλώνεται 2-3 εβδομάδες μετά από καρδιοχειρουργική επέμβαση, οφείλεται συνήθως σε οξεία ηπατίτιδα από μεγαλοκυτταροϊό (cytomegalovirus-CMV) και σπανίως, στις μέρες μας, από τους ιούς ηπατίτιδας Β και C. Συννοδεύεται από μεγάλη αύξηση των τρανσαμινασών (>10 ΧΦΤ). Διαφορική διάγνωση γίνεται και σε αυτή την περίπτωση από την φαρμακευτική ηπατίτιδα και την ηπατική βλάβη στα πλαίσια καρδιακής ανεπάρκειας.

Οι ηλικιωμένοι βρίσκονται σε μεγαλύτερο κίνδυνο εμφάνισης ικτέρου τις πρώτες μετεγχειρητικές ημέρες, που αυξάνεται αναλόγως του χρόνου επέμβασης, των μονάδων αίματος που χορηγούνται και του αριθμού των βαλβίδων που αντικαθίστανται.<sup>43</sup> Άλλοι παράγοντες κινδύνου είναι οι υψηλές πιέσεις στο δεξιό κόλπο προεγχειρητικά και η προϋπάρχουσα ηπατική νόσος.<sup>42,43</sup>

Ο ίκτερος συχνά έχει κακή πρόγνωση, σχετιζόμενος με παράταση της μηχανικού αερισμού και της παραμονής σε ομάδα εντατικής νοσηλεί-

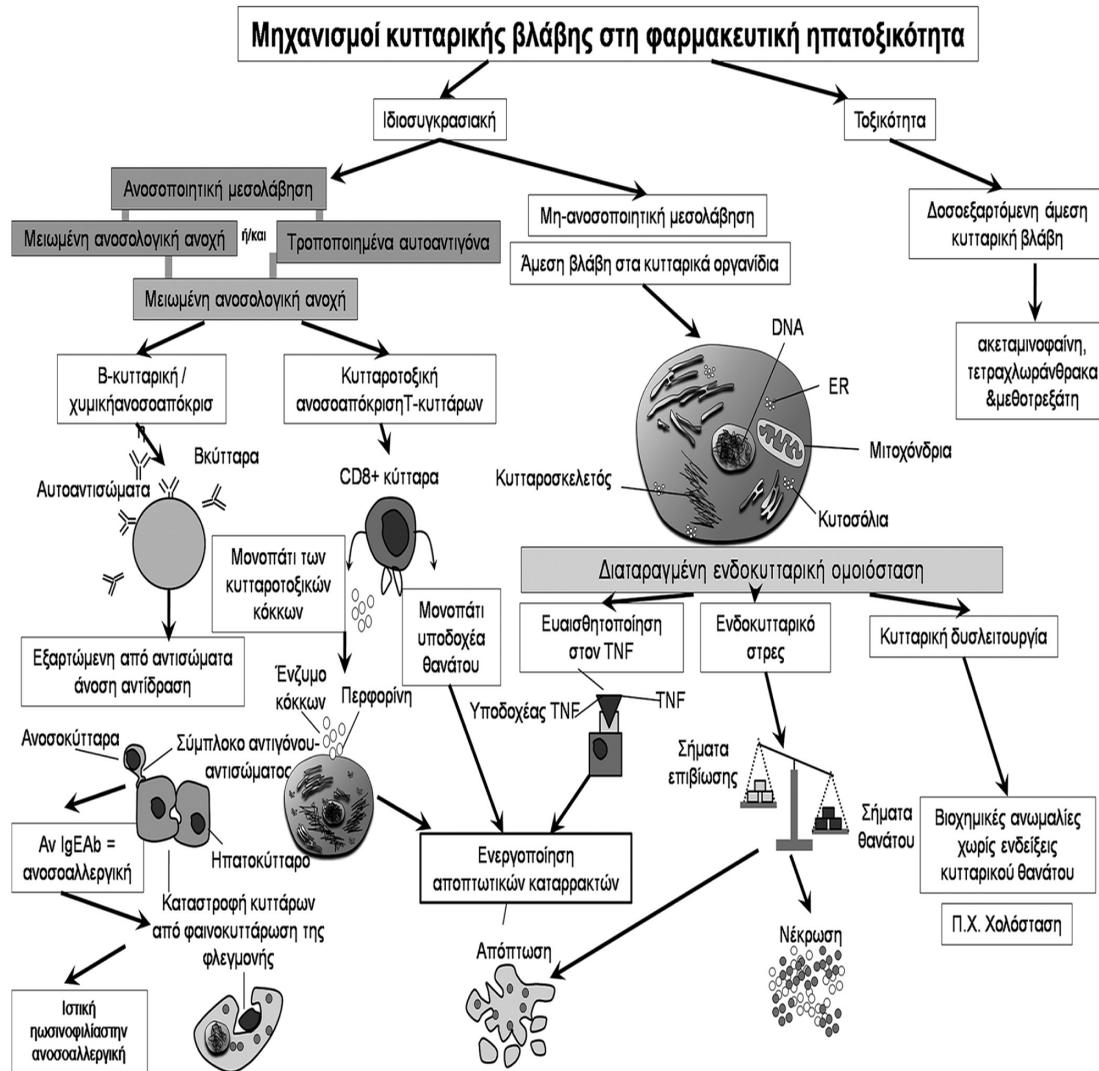
ας, με αυξημένη συχνότητα σήψης, οξείας νεφρικής βλάβης και αναπνευστικών επιπλοκών.<sup>42,43,46</sup>

## ΦΑΡΜΑΚΕΥΤΙΚΗ ΗΠΑΤΟΤΟΞΙΚΟΤΗΤΑ ΚΑΡΔΙΟΛΟΓΙΚΩΝ ΦΑΡΜΑΚΩΝ

Η επαγόμενη από φάρμακα ηπατική βλάβη (drug induced liver injury – DILI) είναι υπεύθυνη έως και για το 30% των περιπτώσεων οξείας διαταραχής της ηπατικής βιοχημείας,<sup>47</sup> αποτελώντας αναγνωρισμένη επιπλοκή περισσότερων από 670 φαρμακευτικών ουσιών σύμφωνα με τις διεθνείς βάσεις δεδομένων (LiverTox database).<sup>48</sup> Στους παράγοντες που ενοχοποιούνται περιλαμβάνονται πλήθος ουσιών με εφαρμογή στην καρδιολογία όπως οι αναστολείς των υποδοχέων της αγγειοτενσίνης II,<sup>49,50,51</sup> οι β-αναστολείς,<sup>52</sup> τα αντιαιμοπεταλιακά,<sup>53</sup> και τα αντιπηκτικά<sup>54</sup> (Πίνακας 1). Η θνητότητα αγγίζει έως και το 6%<sup>47</sup> και τα υψηλότερα ποσοστά αφορούν τους πάσχοντες από υποκείμενη ηπατική βλάβη.<sup>48</sup>

Η βλάβη προκαλείται με πληθώρα μηχανισμών. Ελάχιστες ουσίες όπως η μεθοτρεξάτη και η ακεταμινοφαίνη παρουσιάζουν άμεση ηπατοτοξική δράση η οποία είναι εξαρτώμενη από τη δόση και τη διάρκεια χορήγησης.<sup>47</sup> Στην πλειονότητα των περιπτώσεων, η αντίδραση είναι ιδιοσυστασιακή. Εκδηλώνεται σε λίγα σχετικούς άτομα που παρουσιάζουν απροσδιόριστη, γενετικώς καθορισμένη, ευαισθησία σε κάποιον από τους μεταβολίτες του φαρμάκου.<sup>47</sup> Η ηπατοτοξικότητα αυτή είναι απρόβλεπτη, δεν εξαρτάται από τη δόση του φαρμάκου, ενώ είναι αδύνατος ο έλεγχος ή η αναπαραγωγή της σε ζώα-μοντέλα. Ο βασικός παθογενετικός μηχανισμός είναι η διαταραχή στο μεταβολισμό του κυττάρου, η ανοσολογικά επαγόμενη κυτταρική καταστροφή ή ο συνδυασμός τους (Εικόνα 2).<sup>47</sup> Οι ανωτέρω μηχανισμοί μπορεί να επηρεάσουν έναν ή περισσότερους τύπους ηπατικών κυττάρων όπως τα ηπατοκύτταρα, τα κύτταρα των χοληφόρων, τα επιθηλιακά κύτταρα των κολποειδών και τα αστεροειδή κύτταρα.<sup>47</sup>

Οι παράγοντες κινδύνου για την ανάπτυξη ιδιοσυστασιακού DILI δεν έχουν αποσαφηνιστεί. Υπάρχουν ενδείξεις ότι η γενετική προδιάθεση δια-



Εικόνα 2. Παθοφυσιολογικοί μηχανισμοί της επαγόμενης από φάρμακα ηπατικής βλάβης (από Bleibel et al, τροποποιημένο).<sup>47</sup>

IgEAb : Immunoglobulin E Antibody = Ανοσοσφαιρίνη E, DNA : Deoxyribonucleic acid = Δεοξυριβονουκλεϊ(νι)κό οξύ, ER : Endoplasmic Reticulum = Ενδοπλασματικό δίκτυο, TNF : Tumor Necrosis Factor = Παράγοντας νέκρωσης όγκου

δραματίζει σημαντικό ρόλο καθώς συγκεκριμένα αλληλία των HLA γονιδίων έχουν συσχετιστεί με DILI από συγκεκριμένες φαρμακευτικές ουσίες (πχ φλουκλοζακιλλίνη, αμοξυκιλλίνη-κλαβουλανικό).<sup>48</sup> Επίσης, πιθανό παθογενετικό μηχανισμό αποτελεί η ετερογένεια στην έκφραση αλλά και τη δραστηριότητα ηπατικών ενζύμων που εμπλέκονται στον μεταβολισμό των φαρμάκων όπως το σύστημα του κυτοχρώματος P450.<sup>47</sup> Αν και η γενετική προδιάθεση αποτελεί το βασικότερο παράγοντα, δεν ερμηνεύει επαρκώς όλο το φάσμα του DILI. Άλλοι παράγοντες κινδύνου που

έχουν προταθεί είναι η ηλικία άνω των 55, το γυναικείο φύλο, η πολυφαρμακία, το ιστορικό προηγούμενων φαρμακευτικών αντιδράσεων, η διατροφική κατάσταση, η εγκυμοσύνη, το πρόσφατο χειρουργείο και η κατανάλωση αλκοόλ.<sup>47</sup>

Η εργαστηριακή εικόνα του DILI είναι ποικιλόμορφη, με πρότυπο ηπατοκυτταρικής καταστροφής, χολόστασης ή συνδυασμού τους. Η DILI ορίζεται ως η άνοδος της ALT > 5 X ΑΦΤ, ή ως άνοδος της ALP > 2 XΑΦΤ με ταυτόχρονη άνοδο της γ-γλουταμυλτρανσφεράσης ή ως άνοδος της ALT > 3XΑΦΤ και της χολερυθρίνης

**Πίνακας 1.** Φαρμακευτικές ουσίες που προκαλούν ηπατοτοξικότητα και τύποι ηπατικής βλάβης (από Rosellini SR et al, Larrey D et al, Chang CY et al)<sup>49,50,53</sup>

Κοκκιώματα	<ul style="list-style-type: none"> <li>• Κινιδίνη</li> <li>• Μεθυλντόπα</li> <li>• Υδραλαζίνη</li> </ul>
Φωσφολιπίδωση και ίνωση	<ul style="list-style-type: none"> <li>• Αμιωδαρόνη</li> </ul>
Οξεία ηπατίτιδα	<ul style="list-style-type: none"> <li>• Αμιωδαρόνη</li> <li>• Βεραπαμίλη</li> <li>• Δελτιαζέμη</li> <li>• Λαβεταλόλη</li> <li>• Ατενολόλη</li> <li>• Προπρανολόλη</li> <li>• Λισινοπρίλη</li> <li>• Εναλαπρίλη</li> <li>• Καπτοπρίλη</li> <li>• Κινιδίνη</li> <li>• Υδραλαζίνη</li> <li>• Κλοπιδογρέλη</li> <li>• Νεότερα από του στόματος αντιπηκτικά</li> </ul>
Χρονία ηπατίτιδα	<ul style="list-style-type: none"> <li>• Μεθυλντόπα</li> <li>• Στατίνες</li> </ul>
Χολόσταση	<ul style="list-style-type: none"> <li>• Δισοπυραμίδη</li> <li>• Ουαρφαρίνη</li> <li>• Νιφεδιπίνη</li> <li>• Χλωροθαλιδόνη</li> </ul>
Μικτή	<ul style="list-style-type: none"> <li>• Τικλοπιδίνη</li> <li>• Προκαϊναμίδη</li> </ul>

> 2ΧΑΦΤ.<sup>55</sup> Το πρότυπο της βλάβης καθορίζεται από το λόγο (ALT/ΑΦΤ)/(ALP/ΑΦΤ) ως ηπατοκυτταρικό όταν ο λόγος είναι = 5, χολοστατικό όταν είναι = 2 και μεικτό όταν είναι >2 και < 5.<sup>55</sup>

Λόγω της μη ειδικής κλινικής και εργαστηριακής εικόνας, η τεκμηρίωση της διάγνωσης αποτελεί πρόκληση. Βασίζεται στη λήψη εκτενούς φαρμακευτικού ιστορικού, τη χρονική συσχέτιση της ηπατικής βλάβης με την αλλαγή της φαρμακευτικής αγωγής και την ομαλοποίηση των ηπατικών παραμέτρων με την απόσυρση του φαρμάκου.<sup>47</sup> Απαραίτητος είναι επίσης ο αποκλεισμός άλλων αιτιών ηπατικής βλάβης όπως ιογενούς ηπατίτιδας, αυτοάνοσων παθήσεων του ήπατος, αιμοχρωμάτωσης και νόσου Wilson. Συ-

χνά, η DILI συνοδεύεται από θετικά αυτοαντισώματα (ANA, SMA, AMA, LKM<sup>2</sup>), καθιστώντας δυσχερέστερη τη διαφορική διάγνωση. Η παθογενετική σημασία των αυτοαντισωμάτων για την πρόκληση ηπατικής βλάβης δεν έχει αποσαφηνιστεί, συχνά όμως παραμένουν θετικά και μετά τη διακοπή του φαρμάκου και την αποδρομή της DILI.<sup>56</sup> Μπορεί, για τον αποκλεισμό άλλης αιτίας ηπατικής νόσου, να απαιτηθεί η διενέργεια ηπατικής βιοψίας. Η ιστολογική εικόνα της DILI δεν είναι συγκεκριμένη, όμως ευρήματα που συνηγορούν υπέρ της διάγνωσης είναι η διήθηση από ηωσινόφιλα και η παρουσία κοκκιωμάτων. Συγκεκριμένα φάρμακα έχουν σχετιστεί με ένας ή περισσότερους τύπους ιστολογικών αλλοιώσεων γεγονός που μπορεί να χρησιμοποιηθεί για τον αποκλεισμό ή την ένταξη στη διαφορική διάγνωση φαρμακευτικών ουσιών.<sup>57</sup>

Από τα καρδιολογικά φάρμακα, ο παράγοντας με τη σαφέστερη συσχέτιση με ηπατική βλάβη είναι η αμιωδαρόνη. Στο 15-50% των περιπτώσεων θεραπείας με αμιωδαρόνη, όταν χορηγείται από το στόμα στις συνηθισμένες δόσεις, παρατηρείται ελαφρά αύξηση των τρανσαμινασών χωρίς ιδιαίτερη κλινική σημασία. Σπανιότερα παρουσιάζονται, συνήθως ασυμπτωματικώς, οξεία ηπατίτιδα, χολόσταση, κοκκιώματα και χρονία ηπατίτιδα.<sup>58,59,60</sup> Επίσης, αναφέρονται σπάνιες περιπτώσεις χολοστατικού ικτέρου, ακόμα και 4 μήνες μετά τη διακοπή του φαρμάκου.<sup>61</sup> Σε μεγάλες δόσεις, η αμιωδαρόνη προκαλεί αύξηση των ηπατικών ενζύμων στο 10 – 20 % των ασθενών (υποχωρούν με την ελάττωση της δόσης) και σπανιότερα οξεία ηπατίτιδα με ή χωρίς ηπατική ανεπάρκεια.<sup>62-65</sup> Όμως, ως γενική αρχή, η ηπατοτοξικότητα της αμιωδαρόνης δε συνοδεύεται από σημαντικό ίκτερο και οι αυξήσεις των τρανσαμινασών είναι χαμηλότερες από τις παρατηρούμενες σε νεκρωτικές ηπατοκυτταρικές βλάβες. Μετά τη διακοπή του φαρμάκου, η ηπατική βλάβη υποχωρεί βραδύτατα. Σπανίως, μπορεί να έχουμε κλινικές εκδηλώσεις χρονίας ηπατικής νόσου με εμφάνιση ικτέρου, ηπατομεγαλίας, ασκίτη ή/και εγκεφαλοπάθειας. Στις περιπτώσεις αυτές, η ιστολογική εξέταση στο κοινό μικροσκόπιο αναδεικνύει ψευδοαλκοολικές βλάβες (σωμάτια Mallory, λίπωση, διήθηση από πολυμορ-

φοπύρηνα, ίνωση ή/και κίρρωση). Η διαφορική διάγνωση από την αλκοολική ηπατοπάθεια μπορεί να είναι δύσκολη.<sup>66</sup>

Ενίοτε, μπορεί να συνυπάρχουν και άλλες φαρμακευτικές τοξικές εκδηλώσεις όπως θυρεοειδοπάθεια (υπέρ- ή υπο-θυρεοειδισμός), νευρίτιδα, πνευμονική ίνωση ή εναποθέσεις της αμιωδαρόνης στον κερατοειδή χιτώνα του οφθαλμού.

Η παθογένεια της ηπατικής βλάβης είναι ασαφής αν και μελετάται εκτενώς τα τελευταία χρόνια. Η αμιωδαρόνη εισέρχεται στα λυσοσωμάτια των ηπατοκυττάρων, συνδέεται με φωσφολιπίδια και αναστέλλει τη δράση φωσφολιπασών. Η παραπάνω φωσφολιπίδωση είναι συχνή και ίσως υποχρεωτική. Η άθροιση των φωσφολιπιδίων στα λυσοσώματα επιβεβαιώνεται ιστοχημικώς και αποτελεί το αίτιο της διόγκωσης και μικροφυσσαλιδώδους εμφάνισής τους στο κοινό μικροσκόπιο. Καθώς η αμιωδαρόνη απελευθερώνεται από τα λυσοσωμάτια μπορεί και ανιχνεύεται στο πλάσμα μήνες μετά από την διακοπή της. Το πώς όμως προκαλείται η φαρμακευτική ηπατοτοξικότητα είναι ακόμη άγνωστο.

Αναφορικά με την αντιπηκτική αγωγή, τα νεότερα από του στόματος αντιπηκτικά (novel oral anticoagulants, NOACs) σχετίζονται με ηπατοτοξικότητα στο 1,8-3,9%<sup>67</sup> των ασθενών, η οποία μπορεί να είναι απειλητική για τη ζωή στο 3-12% των περιπτώσεων.<sup>67</sup> Η συσχέτιση είναι σαφέστερη για το rivaroxaban,<sup>68</sup> ενώ, με τα μέχρι τώρα δεδομένα, το apixaban και το dabigatran σχετίζονται σπανιότερα με ηπατική βλάβη, η οποία μάλιστα είναι και ηπιότερη.<sup>48</sup> Μέχρι στιγμής, ο μηχανισμό πρόκλησης της ηπατικής βλάβης παραμένει άγνωστος.<sup>67</sup> Από τις λοιπές κατηγορίες, η ενοξαπαρίνη αλλά και άλλες χαμηλού μοριακού βάρους ηπαρίνες σχετίζονται με αυτοπεριοριζόμενη, ασυμπτωματική άνοδο των τρανσαμινασών > 3 ΧΑΦΤ στο 4-13% των ασθενών.<sup>54</sup> Λόγω της έλλειψης αναφορών για πρόκληση σοβαρής ηπατικής βλάβης, η τρανσαμινασαιμία πιθανολογείται ότι είναι απότοκος εξωηπατικής παραγωγής, μεταβολής της κάθαρσης τους από το ήπαρ ή αναδιαμόρφωσης της μεμβράνης των ηπατοκυττάρων χωρίς κυτταρική βλάβη.<sup>54</sup> Τέλος, από την κατηγορία των αντιαιμοπεταλιακών, η τικλοπιδίνη και η ευρύτερα χρησιμοποιούμενη κλοπιδογρέλη, σχετίζονται με η-

πατική βλάβη μέσω άμεσης κυτταρικής καταστροφής που προκαλείται από τους δραστικούς μεταβολίτες τους.<sup>53</sup> Ειδικά για την κλοπιδογρέλη, η τοξικότητα της έχει συσχετιστεί με την αυξημένη δραστηριότητα συγκεκριμένων κυτοχρωμάτων, όπως το CYP3A4, CYP2C19 και CYP2B6.<sup>53,69</sup>

## ΟΞΕΙΑ ΧΟΛΟΚΥΣΤΙΤΙΔΑ

Η οξεία χολοκυστίτιδα είναι σπάνια επιπλοκή των καρδιοχειρουργικών επεμβάσεων καθώς αποτελεί το 6-18% του συνόλου των γαστρεντερολογικών τους επιπλοκών.<sup>70</sup> Χαρακτηριστικά, σε μελέτη με 16.576 ασθενείς μετά από καρδιοχειρουργική επέμβαση, χολοκυστίτιδα διαγνώστηκε στο 0.11%, με το 0.03% να αφορά τον λιθιασικό τύπο και το 0.08% τον αλιθιασικό.<sup>70</sup>

Η αλιθιασική χολοκυστίτιδα είναι ο επικρατέστερος τύπος χολοκυστίτιδας σε όλες τις κατηγορίες βαρέως πασχόντων ασθενών,<sup>70</sup> με συχνότητα 0.5-18%.<sup>71</sup> Υψηλότερη επίπτωση παρατηρείται στις περιπτώσεις μειζόνων χειρουργικών επεμβάσεων, μειζόνων τραυμάτων και σε σοβαρού βαθμού εγκαύματα. Συσχετίζεται επίσης με τη συμφορητική καρδιακή ανεπάρκεια, την άνηψη μετά από καρδιακή ανακοπή και το σακχαρώδη διαβήτη.<sup>72</sup> Επίσης, το ανδρικό φύλο αποτελεί παράγοντα κινδύνου, καθώς μετά από μη σχετιζόμενα με τραύμα χειρουργεία, το 80% των περιπτώσεων που διαγιγνώσκονται είναι άνδρες.<sup>72</sup>

Ο παθοφυσιολογικός μηχανισμός ανάπτυξης της είναι πολυπαραγοντικός.<sup>73</sup> Το φαινόμενο ισχαιμίας/επαναιμάτωσης είναι καθοριστικής σημασίας για την εκδήλωσή της, ενώ ακολουθεί η επινέμηση του ισχαιμου ιστού από βακτήρια.<sup>72</sup> Έτερος βασικός παθογενετικός μηχανισμός είναι η χολική στάση, η οποία είναι συνέπεια πληθώρας παραγόντων. Πιο αναλυτικά, η υποογκαιμία οδηγεί σε συμπίκνωση της χολής, συνεπώς σε αυξημένο ιξώδες. Επιπλέον, η φυσιολογική παροχέτευση της χολής καθίσταται δυσχερής από τον επαγόμενο από την αναλγησία με οπιοειδή σπασμό του σφιγκτήρα του Oddi.<sup>72</sup> Εξάλλου, με χολική στάση έχει συσχετιστεί και ο μηχανικός αερισμός με θετική πίεση,<sup>74</sup> και η μακροχρόνια χορήγηση ολικής παρεντερικής διατροφής που ο-

δηγεί σε αλιθιασική χολοκυστίτιδα σε ποσοστό έως και 30%.<sup>75</sup> Η χολική στάση οδηγεί σε αυξημένη πίεση στα τοιχώματα της χοληδόχου κύστης και σε μεταβολή της φυσιολογικής σύστασης της χολής. Η αύξηση της συγκέντρωσης παραγόντων όπως η λυσοφωσφατιδυλο-χολίνη και η βήτα-γλυκουρονιδάση, έχουν συσχετιστεί με βλάβη του βλεννογόνου της κύστεως και εμφάνιση αλιθιασικής χολοκυστίτιδος.<sup>72</sup>

Η διάγνωση αποτελεί πρόκληση καθώς η νόσος συχνότερα εμφανίζεται με μη ειδική κλινική εικόνα, ως σύνδρομο συστηματικής φλεγμονώδους αντίδρασης (systematic inflammatory response syndrome, SIRS), σήψης ή σηπτικής καταπληξίας. Στους βαρέως πάσχοντες, η διαφορική διάγνωση των ανωτέρω κλινικών συνδρομών είναι ευρύτατη. Το υπερηχογράφημα ήπατος-χοληφόρων παρουσιάζει τη μεγαλύτερη ειδικότητα και ευαισθησία, με χαρακτηριστικότερο εύρημα την πάχυνση του τοιχώματος της χοληδόχου κύστεως.<sup>72</sup> Το όριο των 3.5 mm έχει ευαισθησία 100% και ειδικότητα 98.5% στην τεκμηρίωση της διάγνωσης.<sup>76</sup> Άλλα ευρήματα αποτελούν το περιχολοκυστικό οίδημα και η παρουσία ενδοτοιχωματικού αέρα. Ψευδώς θετικά αποτελέσματα παρατηρούνται σε περιπτώσεις ύπαρξης χολικής λάσπης, μη ακτινοσκοπιών χολόλιθων καθώς και ασκίτικης συλλογής.<sup>72</sup> Η αξονική τομογραφία θέτει εξίσου αξιόπιστα τη διάγνωση, όμως λόγω υψηλότερου κόστους και δυσχερέστερης πρόσβασης, αποτελεί εξέταση δεύτερης γραμμής.<sup>77</sup> Τέλος, η λαπαροσκοπική εξέταση προσφέρει τη δυνατότητα τεκμηρίωσης της διάγνωσης και ταυτόχρονης θεραπευτικής αντιμετώπισης, όμως τα δεδομένα για την ασφάλεια και αποτελεσματικότητα της δεν έχουν επιβεβαιωθεί ακόμα σε μελέτες με μεγάλο αριθμό ασθενών.<sup>72</sup>

Η θεραπεία εκλογής είναι η χολοκυστεκτομή, ανοιχτή ή λαπαροσκοπική. Η ανοιχτή χολοκυστεκτομή παρουσιάζει θνητότητα της τάξης του 44-55% και πλέον επιλέγεται στις περιπτώσεις σοβαρής νέκρωσης της χοληδόχου κύστης.<sup>71</sup> Η λαπαροσκοπική χολοκυστεκτομή συνοδεύεται από σαφώς χαμηλότερη νοσηρότητα και θνητότητα, όμως τα ποσοστά διεγχειρητικής μετατροπής της σε ανοιχτή επέμβαση είναι της τάξης του 20-35%.<sup>71</sup> Τέλος, η διαδερμική χολοκυστοστομία α-

ποτελεί αποδεκτή εναλλακτική θεραπευτική μέθοδο. Πραγματοποιείται με τοπική αναισθησία και έχει ποσοστό επιτυχίας 85% στη λύση της χολοκυστίτιδας και την αντιμετώπιση της συστηματικής φλεγμονής.<sup>72</sup> Μείζονες επιπλοκές παρατηρούνται στο 8.7% των ασθενών και περιλαμβάνουν αιμορραγία, βακτηραιμία, χολοπεριτόναιο και σύνδρομο οξείας αναπνευστικής δυσχέρειας των ενηλίκων (acute respiratory distress syndrome).<sup>72</sup> Η τεχνική αυτή προτιμάται στους ασθενείς υψηλού εγχειρητικού κινδύνου. Μετά τη διενέργειά της, αφού ο ασθενής ανανήψει, ακολουθεί χολαγγειογραφία και σε περίπτωση απουσίας χολολίθων (αληθής αλιθιασική χολοκυστίτιδα) η διενέργεια χολοκυστεκτομής δεν είναι απαραίτητη και ο καθετήρας αφαιρείται με ασφάλεια.<sup>78</sup> Επί μη βελτίωσης εντός 24 ωρών, κρίνεται απαραίτητη η διενέργεια ανοιχτής χολοκυστεκτομής.

Η αντιβιοτική αγωγή ως μονοθεραπεία δεν αρκεί, όμως είναι απαραίτητη συμπληρωματικά της χειρουργικής αντιμετώπισης. Τα συχνότερα απομονωμένα παθογόνα από τις καλλιέργειες χολής των ασθενών είναι *E. coli*, *Klebsiella*, and *Enterococcus faecalis*, οπότε η εμπειρική αντιβιοτική αγωγή πρέπει να στοχεύει στην αντιμετώπιση αυτών. Εντούτοις, η προηγηθείσα αντιβιοτική αγωγή, η σοβαρή κλινική κατάσταση και η μακρά παραμονή σε μονάδες εντατικής θεραπείας, σχετίζονται με την απομόνωση ανθεκτικών ή ευκαιριακών παθογόνων όπως *Pseudomonas*, *staphylococci* (συμπεριλαμβανόμενων στελεχών ανθεκτικών στη μεθυκυλλίνη), *Enterobacter*, αναερόβιων (*Clostridium*, *Bacteroides*), και μυκήτων.<sup>72</sup>

Η νοσηρότητα της αλιθιασικής χολοκυστίτιδας είναι υψηλή καθώς επιπλέκεται με γάγγραινα στο 50% των περιπτώσεων και διάτρηση στο 30%.<sup>72</sup> Επίσης υψηλή είναι η θνητότητα που εκτιμάται στο 50%.<sup>71</sup>

## ΛΟΙΜΩΞΗ ΑΠΟ ΚΥΤΤΑΡΟΜΕΓΑΛΟΪΟ

Ο κυτταρομεγαλοϊός (cytomegalovirus, CMV) είναι μέλος της οικογένειας των ερπητοϊών. Η λοίμωξη είναι κοινή στον γενικό πληθυσμό. Χαρακτηριστικά, το 65% του πληθυσμού 40-45 ετών

και το 91% αυτών άνω των 80 ετών, έχει έρθει σε επαφή με τον ιό.<sup>79</sup>

Ο CMV προκαλεί νόσο είτε με άμεση βλαπτική δράση στα όργανα-στόχους (π.χ ήπαρ, πνεύμονες), είτε εμμέσως, επάγοντας συστηματική φλεγμονώδη αντίδραση ή προκαλώντας ανοσοκαταστολή και αυξάνοντας την ευπάθεια σε δευτερογενείς λοιμώξεις από βακτήρια και μύκητες.<sup>79</sup>

Η οξεία λοίμωξη σε ανοσοεπαρκείς ασθενείς ακολουθεί συνήθως καλοήγη, αυτοπεριοριζόμενη πορεία. Τυπικά, εκδηλώνεται ως μη ειδική ιογενής λοίμωξη ή ως σύνδρομο μονοπυρήνωσης. Στην κλινική εικόνα τυπικά προεξάρχουν ο πυρετός και η κακουχία.<sup>80</sup> Ηπατική συμμετοχή παρατηρείται ως και στο 90% των ασθενών και μπορεί να περιλαμβάνει ηπατομεγαλία, ίκτερο ή/και αύξηση των τρανσαμινασών.<sup>81</sup> Σε αρκετές περιπτώσεις, η λοίμωξη είναι ασυμπτωματική. Σπανίως, ο ιός οδηγεί σε σοβαρή, απειλητική για τη ζωή νόσο, προκαλώντας πνευμονίτιδα, κολίτιδα, προσβολή του κεντρικού νευρικού συστήματος (μηνιγγίτιδα, εγκεφαλίτιδα, μυελίτιδα, πάρεση νεύρων), προσβολή των οφθαλμών (ραγοειδίτιδα, αμφιβληστροειδίτιδα), αρτηριακές και φλεβικές θρομβώσεις ή αιματολογικές διαταραχές όπως θρομβοπενία και αυτοάνοση αιμολυτική αναιμία.

Όπως και άλλοι ερπητοϊοί, μετά την αρχική λοίμωξη, ο CMV παραμένει στον οργανισμό σε λανθάνουσα κατάσταση, ιδίως εντός των μονοπύρηνων λευκοκυττάρων.<sup>82</sup> Στους ανοσοεπαρκείς, συχνά ανιχνεύεται στα ούρα ή στο σίελο χωρίς όμως λοιπά συμπτώματα.<sup>80</sup> Η αναζωπύρωση της λοίμωξης, οριζόμενη ως ανίχνευση του ιού στο αίμα, σχετίζεται με καταστάσεις ανοσοανεπάρκειας όπως οι αιματολογικές κακοήθειες, το σύνδρομο επίκτητης ανοσοανεπάρκειας (Acquired Immune Deficiency Syndrome, AIDS) και η ισχυρή ανοσοκαταστολή μετά από μεταμόσχευση. Στους εν λόγω ασθενείς, η αναζωπύρωση οδηγεί σε αυξημένη νοσηρότητα και θνητότητα.<sup>83</sup>

Όμως, ακόμα και σε ασθενείς χωρίς υποκείμενη ανοσοανεπάρκεια, καταστάσεις που σχετίζονται με παροδική διαταραχή της ανοσίας μπορούν να οδηγήσουν σε αναζωπύρωση του ιού. Σε αυτή την κατηγορία υπάγονται οι βαρέως πάσχοντες, στους οποίους τα ποσοστά υπολογίζονται στο 36-71%.<sup>80,84</sup> Για τις μείζονες καρδιοχειρουργικές ε-

πεμβάσεις, το αντίστοιχο ποσοστό είναι 16.5%.<sup>83</sup> Ως ανεξάρτητοι παράγοντες κινδύνου αναγνωρίζονται ο σακχαρώδης διαβήτης και η ανάγκη για πολλαπλές μεταγγίσεις.<sup>83</sup> Άλλες καταστάσεις που πιθανώς σχετίζονται είναι ο μηχανικός αερισμός, η βακτηριακή πνευμονία και η σήψη.<sup>80,85</sup>

Στην εν λόγω κατηγορία ασθενών, η αιμία από CMV σχετίζεται με παράταση της νοσηλείας, παράταση του μηχανικού αερισμού, αύξηση της επίπτωσης βακτηριακών και μυκητιασικών λοιμώξεων, αύξηση της συχνότητας νεφρικής βλάβης και ηπατικής δυσλειτουργίας<sup>80,86</sup> και τέλος αύξηση της θνητότητας μέχρι και 2 φορές σε σχέση με τους βαρέως πάσχοντες χωρίς CMV λοίμωξη, ανεξάρτητα από την απόλυτη τιμή του ιικού φορτίου.<sup>83,87</sup> Παρά τη σαφή συσχέτιση της αιμίας με αύξηση των δυσμενών συμβαμάτων, η παθογονικότητα του ιού παραμένει αντικείμενο διχογνωμίας, με αρκετούς να υποστηρίζουν ότι η αναζωπύρωση αποτελεί ακόμα μια από τις εκδηλώσεις της εκάστοτε σοβαρής υποκείμενης νόσου.<sup>79,84</sup>

Για τη διάγνωση της αιμίας, χρησιμοποιούνται 3 μέθοδοι : καλλιέργειες, ανίχνευση του αντιγόνου στο αίμα και η αλυσιδωτή αντίδραση πολυμεράσης (polymerase chain reaction, PCR). Οι καλλιέργειες (συμβατικές και σε κυτταρικό πληθυσμό) δεν χρησιμοποιούνται πλέον λόγω της χαμηλής ευαισθησίας αλλά και του χρόνου που απαιτείται μέχρι το αποτέλεσμα.<sup>88</sup> Η ανίχνευση του αντιγόνου πραγματοποιείται με τον εντοπισμό της πρωτεΐνης pp65 στην επιφάνεια των λευκοκυττάρων με τη χρήση μονοκλωνικών αντισωμάτων. Είναι ευαίσθητη και αξιόπιστη μέθοδος, με περιορισμό την ανάγκη για επαρκή αριθμό λευκοκυττάρων στο περιφερικό αίμα. Έτσι, μέθοδος εκλογής θεωρείται η PCR λόγω της υψηλής ευαισθησίας της αλλά και του σύντομου χρονικού διαστήματος έως τα αποτελέσματα καθώς και της δυνατότητας διενέργειας σε απόλυτα ουδετεροπενικούς ασθενείς. Πρέπει πάντως να επισημανθεί ότι αν και η ευαισθησία της αγγίζει το 100%, η ειδικότητα της είναι χαμηλή, υπολογιζόμενη μόνο στο 54% για τη διάγνωση CMV λοίμωξης.<sup>88</sup>

Για τη θεραπεία της CMV λοίμωξης, οι ευρύτερα χρησιμοποιούμενοι παράγοντες είναι η γανκυκλοβίρη, η ακυκλοβίρη, η σιδοφοβίρη και η φוסκαρνέτη, που όμως δε στερούνται παρενε-

γειών. Η φοσκαρνέτη σχετίζεται με νεφρική βλάβη και σπανιότερα με ηλεκτρολυτικές διαταραχές, η ακυκλοβίρη κυρίως με νεφρική βλάβη, η σιδοφοβίρη επίσης με νεφρική βλάβη αλλά και αιματολογική τοξικότητα (ουδετεροπενία) ενώ η γανκυκλοβίρη με αιματολογική τοξικότητα, ιδίως θρομβοπενία και ουδετεροπενία και σπανιότερα αναιμία.<sup>79</sup> Θεραπεία εκλογής, ως λιγότερο τοξική, είναι η γανκυκλοβίρη.<sup>79</sup>

Για την αναζωπύρωση του CMV στους βαρέως πάσχοντες, δεν υπάρχουν κατευθυντήριες οδηγίες για χορήγηση αγωγής είτε ως προφύλαξη είτε ως θεραπεία, καθώς ελλείπουν μεγάλες τυχαίοι-ημένες μελέτες.<sup>79</sup> Η απόφαση θεραπείας είναι εξατομικευμένη για κάθε ασθενή, σύμφωνα με την κρίση του θεράποντος. Μια προτεινόμενη από τη βιβλιογραφία προσέγγιση είναι η χορήγηση αγωγής επί τεκμηρίωσης της ιαιμίας και ταυτόχρονα ενδείξεων λοίμωξης συμβατών με βλάβες από CMV πχ κολίτιδα και πνευμονίτιδα, τρανσαμινασαιμία ή ίκτερος, αιμοφαγοκυττάρωση και μη απομόνωση άλλου παθογόνου από τις συμβατικές καλλιέργειες. Επί μη σαφών ενδείξεων λοίμωξης, η ιαιμία ενδεχομένως να χρήζει αντιμετώπισης σε ασθενείς με συνοδούς παράγοντες κινδύνου όπως γνωστή διαταραχή της ανοσιακής απάντησης.<sup>79</sup> Η χορήγηση προφυλακτικής αγωγής στους βαρέως πάσχοντες στις μονάδες εντατικής θεραπείας δεν έχει ένδειξη. Στους ανοσοκατεσταλμένους ασθενείς, όπου οι μελέτες είναι περισσότερες, η προφυλακτική χορήγηση γανκυκλοβίρης έχει ένδειξη όταν δεν είναι εφικτός ο τακτικός έλεγχος για αντίχνευση ιαιμίας. Πάντως, σε αυτή την ομάδα ασθενών, η προφυλακτική αγωγή αν και μειώνει την επίπτωση CMV λοίμωξης, δεν οδηγεί σε βελτίωση της ολικής επιβίωσης.<sup>81</sup> Μελέτες ήδη σε εξέλιξη, αναμένεται να δώσουν περισσότερα στοιχεία για την παθογονικότητα του ιού αλλά και τις ενδείξεις αντιμετώπισης της ιαιμίας.<sup>79</sup>

#### ΚΑΡΔΙΟΧΕΙΡΟΥΡΓΙΚΕΣ ΕΠΕΜΒΑΣΕΙΣ ΣΕ ΧΡΟΝΙΑ ΗΠΑΤΙΚΗ ΝΟΣΟ

Στις επεμβάσεις γενικής χειρουργικής, συνήθως για αντιμετώπιση ενδοκοιλιακών παθήσεων, η κίρρωση αποτελεί βασικό προεγχειρητικό πα-

ράγοντα κινδύνου για σοβαρές επιπλοκές και αυξημένη θνητότητα. Μάλιστα, υπάρχει άμεση συσχέτιση μεταξύ της βαρύτητας της ηπατικής νόσου και της έκβασης της επέμβασης. Το ίδιο ισχύει και για τις καρδιοχειρουργικές επεμβάσεις.<sup>89</sup> Χαρακτηριστικά, για score Child-Turcotte-Pugh A, B και C η ενδονοσοκομιακή θνητότητα είναι 0-10%, 18-50% και 67-100% αντιστοίχως και οι μείζονες επιπλοκές 22-60%, 56-100% και 100% αντιστοίχως.<sup>6,89</sup> Χαμηλότερη είναι η επιβίωση και στα 1, 5 (50% αντί 68% των μη κίρρωτικών) και 10 έτη (41% αντί 62%) μετά την επέμβαση, σε σχέση με το γενικό πληθυσμό.<sup>89,90</sup> Μεταξύ των κίρρωτικών ασθενών, δυσμενέστερη είναι η πρόγνωση για όσους υποβλήθηκαν σε χειρουργεία βαλβίδος σε σύγκριση με τις επεμβάσεις αορτοστεφανιαίας παράκαμψης. Μια πιθανή εξήγηση είναι η ανάγκη μακρόχρονης λήψης κουμαρινικών αντιπηκτικών που σε αυτή την ομάδα ασθενών σχετίζεται με 2 έως 9 φορές πιο υψηλό κίνδυνο αιμορραγίας σε σχέση με το γενικό πληθυσμό.<sup>90,91</sup>

Δεν υπάρχει ομοφωνία ως προς τον βέλτιστο προγνωστικό παράγοντα θνητότητας στους εν λόγω ασθενείς μετά από καρδιοχειρουργική επέμβαση. Η χρήση του score Child-Pugh χρησιμοποιείται ευρέως, όμως ο υπολογισμός του ενέχει τον κίνδυνο της υποκειμενικής εκτίμησης του βαθμού της ασκτικής συλλογής και της εγκεφαλοπάθειας. Σύμφωνα με τα μέχρι τώρα δεδομένα, τιμή > 7 προβλέπει τη θνητότητα με ευαισθησία 86% και ειδικότητα 92% ενώ η αρνητική προγνωστική αξία εκτιμάται στο 97%.<sup>92</sup> Για το Model for End-Stage Liver Disease (MELD) score που προκύπτει από τον υπολογισμό εργαστηριακών παραμέτρων, τα δεδομένα για την ακρίβεια του στην πρόβλεψη θανάτου είναι ιδιαίτερα αντιφατικά, καθώς έχει υψηλή ειδικότητα αλλά χαμηλή ευαισθησία.<sup>6,89,93</sup> Μια πιθανή εξήγηση είναι ότι στον υπολογισμό του συμπεριλαμβάνεται το διεθνούς κανονικοποιημένου ηπικό (international normalized ratio, INR), δείκτης που επηρεάζεται από τα από του στόματος κουμαρινικά αντιπηκτικά. Έτσι, ορισμένοι συγγραφείς προτείνουν τη χρήση του Model for End-stage Liver Disease excluding INR score (MELD-XI) για τους ασθενείς υπό αντιπηκτική αγωγή, με τα

μέχρι τώρα αποτελέσματα να είναι ικανοποιητικά.<sup>94</sup> Η χρήση του Ευρωπαϊκού συστήματος εκτίμησης του κινδύνου καρδιοχειρουργικής επέμβασης (European system for cardiac operative risk evaluation, EuroSCORE), αν και δε λαμβάνει υπόψη την ηπατική λειτουργία, δίνει επίσης καλά αποτελέσματα στην πρόβλεψη του μετεγχειρητικού αποτελέσματος.<sup>94</sup> Έχει επίσης προταθεί η χρήση εργαστηριακών παραμέτρων όπως ο αριθμός των αιμοπεταλίων προεγχειρητικά αλλά και η τιμή της χολινεστεράσης. Η τελευταία, είναι ένζυμο με ηπατική παραγωγή που αντανάκλα τη συνθετική εφεδρεία του ήπατος.<sup>6</sup> Τα χαμηλά προεγχειρητικά της επίπεδα έχουν συσχετιστεί με δυσμενέστερη πρόγνωση σε ασθενείς που υποβάλλονται σε καρδιοχειρουργική επέμβαση.<sup>6</sup>

Οι συχνότερες μετεγχειρητικές επιπλοκές περιλαμβάνουν ρήξη της αντιρρόπησης, οξεία νεφρική βλάβη που συχνά απαιτεί υποστήριξη με συνεδρίες τεχνητού νεφρού, αναπνευστική ανεπάρκεια, γαστρεντερική αιμορραγία και σήψη.<sup>89,90</sup>

Θεραπευτικές προσεγγίσεις που έχουν δοκιμαστεί έως τώρα για τη βελτίωση της έκβασης στο στάδιο Child-Turcotte-Pugh C, περιλαμβάνουν το συνδυασμό καρδιοχειρουργικής επέμβασης με ορθοτοπική μεταμόσχευση ήπατος.<sup>89</sup> Υπάρχουν επίσης ενδείξεις η αποφυγή χρήσης καρδιοπνευμονικής παράκαμψης στις επεμβάσεις επαναγγείωσης, οδηγεί σε καλύτερα αποτελέσματα σε αυτή την κατηγορία ασθενών.<sup>6,89</sup>

## ΣΥΜΠΕΡΑΣΜΑΤΑ

Μετά τις καρδιοχειρουργικές επεμβάσεις, η διαταραχή της ηπατικής βιοχημείας είναι συχνό φαινόμενο. Οι υποκείμενες διαταραχές μπορεί να είναι συνέπεια της ίδιας της επέμβασης, της φαρμακευτικής αγωγής που χρησιμοποιείται πχ αντιπηκτικά, αντιβιοτικά ή παθολογικών καταστάσεων όπως ιογενείς λοιμώξεις, σήψη ή χολοκυστίτιδα. Η διαφορική διάγνωση βασίζεται πρωτίστως στην κλινική αξιολόγηση του ασθενούς, την αναγνώριση του μοντέλου της ηπατικής βλάβης (ηπατοκυτταρικό, χολοστατικό, μεικτό) και τη χρονολογική συσχέτιση της ηπατικής βλάβης με μεταβολές της κλινικής εικόνας όπως η εμφάνιση καταπληξίας ή πυρετού και με ιατρογενείς παρεμβάσεις όπως η τροποποίηση της θεραπευτικής αγωγής. Ο απεικονιστικός έλεγχος σε ελάχιστες περιπτώσεις (πχ χολοκυστίτιδα) μπορεί να βοηθήσει στην τεκμηρίωση της διάγνωσης. Η θεραπεία εξαρτάται από την υποκείμενη πάθηση. Σε περιπτώσεις ισχαιμικής ηπατίτιδας ή συμφορητικής ηπατοπάθειας, η άρση της εκλυτικής αιτίας οδηγεί σε ταχεία αποκατάσταση της ηπατικής βιοχημείας και λειτουργίας. Η πρόγνωση εξαρτάται από την υποκείμενη αιτία αλλά και το βαθμό της ηπατικής προσβολής. Ως γενική αρχή όμως, η ηπατική προσβολή μετεγχειρητικά σχετίζεται με αυξημένη νοσηρότητα και θνητότητα. Η έγκαιρη και εξατομικευμένη αντιμετώπιση είναι καθοριστικής σημασίας για τη βελτιστοποίηση της έκβασης.

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**Dougenis Dimitrios**

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# Repair of acute type A aortic dissection: moving towards a more aggressive approach but keeping the old gold standards

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**Keywords:** Aortic dissection • Brain protection • Hemiarch and aortic arch replacement • Hypothermia • Circulatory arrest  
• Hybrid aortic arch replacement

In this issue of the *European Journal of Cardiothoracic Surgery*, Russo et al. [1] report the early and long-term results after surgery for type A acute aortic dissection (TA-AAD) in a retrospective multicentre study from seven different Italian referral centres. They included 1.148 consecutive patients surgically treated between 1981 and 2013. Their objective was to evaluate whether surgical treatment of TA-AAD has shown different clinical outcomes in the last decades in terms of in-hospital mortality, long-term survival and freedom from reoperation. The overall 30-day mortality rate was 25.7% and neurological impairment rate at discharge was 23% of the cases. In general terms, hospital mortality and stroke after TA-AAD repair, although reduced in the last two decades, still remain relatively high despite improvements in surgical approach, cerebral protection, and early and detailed diagnosis [2].

The authors identified that severe aortic regurgitation at the time of surgery was a significant risk factor for reintervention during the long (median 70 months) follow-up of hospital survi-

vors. Cumulative survival rates from cardiac death were 95.3% at 5 years, 92.8% at 10 years and 52.8% at 20 years, respectively.

The study is valuable for several reasons:

(i) It presents the recent surgical history of treating AAD and amplifies our practice and factors that have changed over the years.

(ii) It showed that severe aortic regurgitation at the time of surgery is a significant risk factor for reintervention.

(iii) It outlines detailed demographic table presentations, predisposing conditions and long-term surgical outcomes with a notable cumulative survival rate from cardiac death of 52.8% at 20 years.

(iv) It clearly demonstrates that over the years, and particularly after 2000, the surgical outcome has improved despite the increased proportion of elderly patients being operated.

The latter has been shown by other studies as well. Rylski et al. [3] analysed the perioperative and intraoperative conditions of 2137 patients prospectively reported to the multicentre German

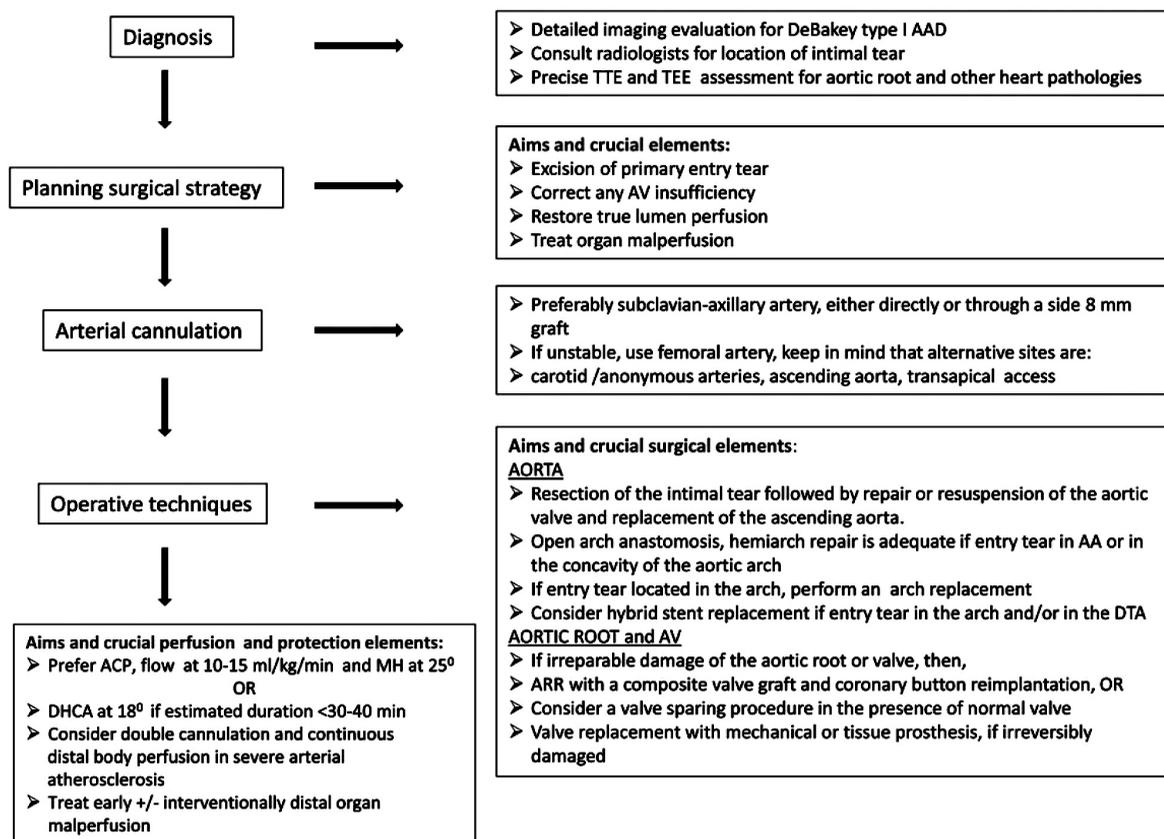


Figure 1: A proposed rational brief approach to type A acute aortic dissection (AAD) management. AV: aortic valve; AA: ascending aorta; DTA: descending thoracic aorta; ACP: antegrade cerebral perfusion; DHCA: deep hypothermic circulatory arrest; MH: moderate hypothermia; ARR: aortic root replacement.

Registry for TA-AAD in relation to age. The lowest probability of 30-day mortality was noted in the youngest patients (11–14%); however, it rose progressively with age, peaking at 25% in octogenarians. The authors concluded that current survival rates are acceptable, even in very elderly patients.

Similarly, the group from St Louis [4] evaluated early and late survival between patients who underwent repair of TA-AAD between 2000–2005 and 2006–2010. The operative mortality rate decreased from 24 to 12% in the later period, indicating improved clinical outcomes and survival in the current surgical era.

Russo *et al.* [1] reported different levels of hypothermia (18–25°C) for organ protection during circulatory arrest. Cerebral protection was accomplished with retrograde cerebral perfusion (RCP) in 300 patients, with moderate hypothermia and selective direct antegrade cerebral perfusion (ACP) of supra-aortic vessels in 502 patients,

and the remaining 346 patients were treated with straight deep hypothermic circulatory arrest (DHCA). Since its introduction in the 1970s, the clinical effectiveness of DHCA has been proven and repeatedly documented, and thus 'DHCA remains the gold standard for brain protection'. Ziganshin *et al.* [5], using mainly the femoral artery as the preferred cannulation site, reported a low incidence of stroke in aortic arch surgery with DHCA at a mean bladder temperature of 18.7°C. However, profound hypothermia alone may not be enough for brain protection as it predisposes to enzyme and organ dysfunction, exacerbates bleeding, lengthens the duration of bypass and aggravates systemic inflammatory responses. In a recent study, Algarni *et al.* [6] found that moderate hypothermia (22–28°C) was independently associated with a lower risk of mortality, and major adverse cardiac and cerebrovascular events during repair of TA-AAA. Although for circulatory arrest periods <30 min no difference can be

clinically documented among ACP, RCP and DHCA, the issue of the best method for brain protection remains debatable. However, ACP through the subclavian–axillary artery with moderate hypothermia is becoming popularized and currently being used by 40–60% of surgeons as the preferred method for brain protection [7]. In contrast RCP is increasingly less commonly used.

Finally, regarding operative techniques, *Russo et al.* [1] treated their patients with a variety of different surgical procedures. There is an increasing tendency for more aggressive surgery including a frozen elephant trunk (FET) repair in all acute aortic dissections involving the arch and the descending aorta [5, 7–10]. Tsagakis et al. [8], in a multicentre trial, showed that extended thoracic aortic repair of TA-AAD with a hybrid stent graft is feasible with acceptable early mortality and promotes false lumen thrombosis around the stent graft and below. They noted an early complete or partial false lumen thrombosis in 61%. Similarly, others advocate that, compared with conventional surgery, the

FET provides a high rate of false lumen thrombosis of the thoracic aorta [9, 10]. FET, however, should only be performed in experienced centres

and it must be underlined that it has not yet been proven to be the procedure of choice in TA-AAD repair, even if a tear exists in the arch or the descending aorta. Nevertheless, the concepts of hybrid operating theatre and heart team approach to TA-AAD management will become increasingly important issues during the next years.

In summary, surgery for TA-AAD has progressed and outcomes have improved. Yet, many debatable issues still exist, mainly due to confounding data provided in many studies. The recent establishment of the international aortic arch surgery study group (ARCH projects) will undoubtedly help in properly collecting and analysing data, and thus, further define neuroprotection and surgical strategies in arch pathology repair.

*Russo et al.* [1] are to be congratulated for sharing with us these valuable data. Nonetheless, there are several limitations, which the authors themselves acknowledge and state in the manuscript, and, therefore, are not mentioned in detail here. A proposed rational brief approach to TA-AAD that readers might find useful is depicted in Fig. 1.

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# Pericardial Fat is Strongly Associated With Atrial Fibrillation After Coronary Artery Bypass Graft Surgery<sup>†</sup>

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Fotini Ampatzidou, Athanasios Madesis, Kalliopi Bimpa, Panagiotis Palladas, Labros Karagounis*

## **Abstract**

### **OBJECTIVES**

Recent evidence suggests that pericardial fat may represent an important risk factor for cardiovascular disease because of its unique properties and its proximity to cardiac structures. It has been reported that pericardial fat volume (PFV) is associated with atrial fibrillation (AF). The purpose of this study was to investigate the association between PFV and new-onset AF following coronary artery bypass graft surgery (CABG).

### **METHODS**

PFV was measured using computed tomography in 83 patients with coronary artery disease scheduled to undergo elective isolated on-pump CABG. Patient characteristics, medical history and perioperative variables were prospectively collected. Any documented episode of new-onset postoperative AF until discharge was defined as the study end point.

### **RESULTS**

Twenty-eight patients (33.7%) developed postoperatively AF during hospital stay. There was no significant difference in demographics and

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comorbidities among patients that maintained sinus rhythm (SR) and their AF counterparts. In univariate analysis, patients with postoperative AF had significantly more pericardial fat compared with SR patients ( $195 \pm 80$  ml vs  $126 \pm 47$  ml,  $P = 0.0001$ ). Larger left atrial diameter was also associated with postoperative AF ( $42.4 \pm 6.9$  mm vs  $39.3 \pm 4.8$  mm,  $P = 0.017$ ). Additionally, the prebypass use of calcium channel-blocking agents was independently associated with a lower incidence of postoperative AF, confirmed also by multivariate analysis ( $P = 0.035$ ). In multivariate logistic regression analysis, PFV was the strongest independent variable associated with the development of postoperative AF (odds ratio: 1.018, 95% confidence interval: 1.009–1.027,  $P = 0.0001$ ). The best discriminant value assessed by receiver operating characteristic analysis was 129.5 ml (sensitivity 86% and specificity 56%).

### CONCLUSIONS

PFV is strongly associated with AF following CABG, independently of many traditional risk factors. Our findings suggest that PFV may represent a novel risk factor for postoperative AF. However, the role of pericardial fat in AF mechanism needs to be further delineated.

### INTRODUCTION

Atrial fibrillation (AF) occurs in 20–40% of patients after coronary artery bypass grafting (CABG) requiring cardiopulmonary bypass (CPB) and it may be a marker of postoperative complications, including stroke, congestive heart failure (CHF) and increased mortality [1, 2]. Postoperative AF is likely related to a combination of factors. These include pre-existing degenerative myocardial changes and pre- and perioperative conditions that result in abnormalities of electrophysiological parameters that promote the development of AF. Clinical variables, such as advanced age, hypertension (HTN), male gender, right coronary artery (RCA) stenosis, depressed left ventricular function and a remote history of previous AF may predispose to postoperative AF; intraoperative surgical variables, including combined valve replacement/CABG procedures and prolonged aortic cross-clamp and bypass times, are similarly associated with a more frequent AF incidence [3–5]. Therefore, identifying high-risk patients and facilitating preventive measures is of utmost importance.

Recently, attention has been focused on heart

adiposity because of its inflammatory and endocrine properties. The theory of a local toxic effect of excess adipose tissue is supported by evidence from basic science, translational science and epidemiology [6–8]. A significant contribution was made by the rapid development in the field of non-invasive imaging, which has made it possible to quantify fat masses with accuracy [9, 10]. Adipose tissue surrounding the heart, within the pericardial sac, is called epicardial or pericardial fat and given its direct apposition to myocardium and coronary arteries, it may play a central role in the pathogenesis of cardiovascular disease, mediated by its inflammatory properties [11]. Several studies have shown a relationship of increased pericardial fat volume (PFV) with coronary artery disease, atherosclerosis and the progression of coronary plaque burden [12–14], major adverse cardiovascular events [15] and AF [16–19]. Adipose tissue secretes both proinflammatory cytokines such as interleukin-6 and anti-inflammatory mediators such as adiponectin [6–8, 11]. In a recent study, Kourliouros *et al.* [20] have reported that epicardial adiponectin is associated with maintenance of sinus rhythm (SR) following cardiac surgery. This paper reinforces the in-

flammatory hypothesis in the pathogenesis of postoperative AF, which may be result of a balance of pro- and anti-inflammatory markers.

In the context of cardiac surgery, inflammation due to CPB, ischaemia and oxidative stress has been implicated in the development of postoperative AF [1, 4, 5]. To the best of our knowledge, the relationship of PFV with post-CABG AF has not been explored. In view of evidence suggesting the modulatory role of epicardial adipose tissue in arrhythmogenesis and its association with a nearly 40% higher odds of AF, we conducted a study to evaluate the impact of pericardial fat on the development of postoperative AF.

The aim of the present study was thus to characterize the relationship between PFV, as measured by multidetector computed tomography (MDCT), and the occurrence of new-onset postoperative AF, in a CABG cohort.

## MATERIALS AND METHODS

### Patient population and data collection

A total of 83 patients undergoing elective first time coronary revascularization for single-, double-, triple- or more vessel disease, were recruited in our study over a 12-month period (January 2012 to December 2012), following approval from the institutional review board. Patients were selected at the Clinic of Cardiac Surgery by surgeon decision. All subjects were acceptable candidates for elective operation with CPB. They all provided written informed consent and underwent preoperative MDCT for pericardial fat measurement and echocardiography.

Patient characteristics, medical history, intraoperative variables and postoperative outcomes were prospectively collected. Potential predictors of AF were chosen based on a review of the literature. Data prospectively collected from patient medical records included age, sex, body mass index (BMI) ( $\text{kg}/\text{m}^2$ ), preoperative medication with beta-blockers, calcium channel blockers (CCBs) or angiotensin-converting enzyme inhibitors (ACEIs) and comorbidities (HTN, diabetes mellitus [DM], CHF-New York Heart Associa-

tion [NYHA] III–IV, chronic obstructive pulmonary disease [COPD], peripheral vascular disease [PVD], recent myocardial infarction [MI] and history of cerebrovascular accident [CVA]). Preoperative variables also recorded were: the presence of critical RCA stenosis (defined as narrowing of the proximal or mid-segment  $>90\%$  of lumen diameter and assessed on coronary angiogram), left ventricular hypertrophy and left ventricular ejection fraction (LVEF) (assessed on preoperative echocardiography). Procedural-related variables included aortic cross-clamp time, pump time, use of retrograde cardioplegia, number of bypass grafts and the perioperative use of intra-aortic balloon pump (IABP). Postoperative levels of potassium and magnesium were daily recorded.

### Exclusions

Exclusion criteria were the presence of AF (persistent or paroxysmal) or past history suggestive of AF or any other arrhythmia atrial and concomitant valve surgery along with CABG. We also excluded patients in dialysis, use of antiarrhythmic medications (other than  $\beta$ -blockers), the presence of permanent pacemakers, systemic inflammatory or terminal illness, and patients under treatment with corticosteroids or non-steroidal anti-inflammatory drugs, other than aspirin.

### CT imaging protocol

CT studies were performed using a four slice MDCT scanner (Siemens Sensation 4, Siemens Medical Solutions, Erlangen, Germany). Continuous 2 mm slices of the heart with 1 mm overlap were acquired, from the level of the bifurcation of the pulmonary artery to the diaphragm. The images were analysed at a dedicated workstation (Siemens Leonardo, Siemens Medical Solutions, Erlangen, Germany), using a semiautomated technique. The operator was obliged to manually trace the pericardium in each of the slices, in order to create a three dimensional (3D) volume of interest. Pericardial fat was defined as the adipose tissue contained in this volume, within the pericardial sac (Fig. 1). A threshold between 200 and 300 Hounsfield units was used to identify the adipose

tissue within the volume of interest. The pericardial fat was measured by two independent readers with excellent intraobserver and interobserver reproducibility (0.95 and 0.97, respectively).

### Echocardiographic measurements

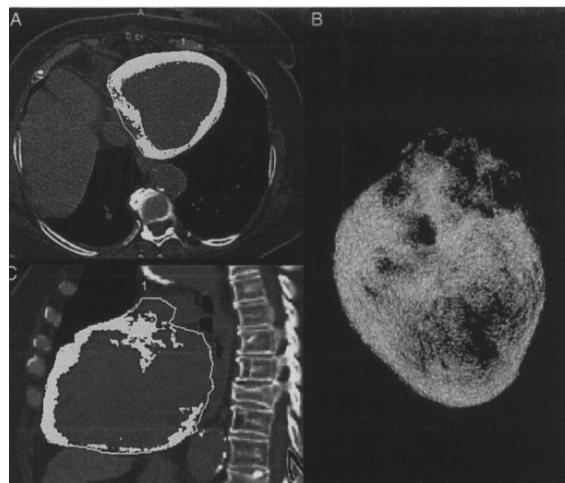
Transthoracic echocardiography was used to assess the structural and functional condition of the heart preoperatively. Left atrial diameter (LAD) was measured at end systole in the parasternal long-axis view. Left atrial enlargement was defined as diameter  $>4.2$  cm. We also evaluated the thickness of the interventricular septum and posterior left ventricular (LV) wall in diastole and the end-diastolic LV dimension using M-mode and two dimensional images from parasternal and apical projections. LVEF was measured by biplanar Simpson's method.

### Surgical protocol

All patients underwent standard median sternotomy CABG performed by a single consultant surgeon and were operated on CPB. All efforts were made to leave aortic fat pad intact but anterior fat pad in the aortopulmonary window was dissected before placing the aortic cross clamp. After initiation of CPB, myocardial protection was achieved with ice slush and cold blood cardioplegia, with a temperature drift to  $34^{\circ}\text{C}$ . Conduits for bypass included the internal mammary artery in all cases and saphenous vein grafts. The distal anastomoses were performed first. The left internal mammary artery was exclusively used to bypass left anterior descending artery stenosis and major saphenous vein grafts were used to bypass the diseased marginal, diagonal and/or RCA. The proximal anastomoses were constructed with the aorta clamped.

### Postoperative protocol

All patients were nursed initially in the cardiac surgery intensive care unit (ICU) and then on high dependency unit (HDU) and the cardiothoracic wards until discharge. Potassium supplementation was given as necessary to maintain electrolyte balance within the normal range. Patients were continuously monitored in cardiac surgery ICU



**Figure 1:** Images generated after the semiautomatic segmentation of the pericardial fat and calculation of its volume. Axial (A) and sagittal (B) CT images, in which the pericardial fat is highlighted in orange colour. 3D reconstruction (C) of the pericardial adipose tissue of the same subject, displayed with the volume rendering technique. For this subject, the pericardial fat volume was  $266\text{ cm}^3$ .

and HDU and monitoring was continued after being transferred to the ward with electrocardiographic (ECG) telemetry with a central monitor at the nursing station. All haemodynamically stable patients received beta-blockade on the first postoperative day and had routine daily 12-lead ECGs. Nursing observations were performed routinely every 4 h by measuring blood pressure, pulses, assessing the heart rhythm and carrying out 12-lead ECGs whenever a cardiac dysrhythmia was suspected. Postoperative AF was defined as new-onset AF, detected by continuous telemetry monitoring during the postoperative hospital stay. The analysis took into account any single episode of AF requiring treatment or lasting longer than 20 min, or for a cumulative total of more than 60 min within a 24-h period. Any documented episode of postoperative AF was defined as the study end point. Patients, who developed AF, were treated with amiodarone (intravenous and oral, following appropriate loading) while correcting electrolyte and acid–base imbalances.

### Statistical analysis

Univariate analysis was performed to examine the association of patient and operative variables on

postoperative AF, followed by multivariate logistic regression analysis to identify independent predictors of postoperative AF. Candidate variables with  $P < 0.2$  upon univariate analysis were entered into the logistic regression model. Dichotomous data were evaluated using Pearson's  $\chi^2$  test or Fisher's exact test, whereas unpaired  $t$ -test and Mann–Whitney  $U$ -test were used for continuous variables with normal or non-normal distribution, respectively. A  $P$ -value of  $< 0.05$  was considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for independent associates of AF. Statistical analysis was performed with the SPSS software package.

## RESULTS

Eighty-three patients undergoing their first elective on-pump CABG surgery were enrolled in our study. The mean age of the patients was  $64.6 \pm 8.9$  years (range, 38–82 years); 79.5% of patients were male. The mean BMI was  $29.6 \pm 4.5$  kg/m<sup>2</sup>. Comorbid conditions included HTN (81.9%), DM (47%), COPD (18%), PVD (24.1%), history of CVA (8.4%), recent MI (41%) and NYHA III–IV status (13.3%). Fifty (60.2%) patients had critical RCA stenosis, 69 (83.1%) were on preoperative medication with beta-blockers, only 20 (24.1%) on CCBs and 31 (37.3%) on ACEIs inhibitors.

In this study population, 28 (33.7%) patients developed postoperative AF and 55 (66.3%) maintained SR during hospitalization. Baseline characteristics and procedural differences between patients who developed postoperative AF and those who remained in SR are given in Table 1. As Table 1 demonstrates, patients with AF had significantly more pericardial fat compared with patients in SR ( $195 \pm 80$  ml vs  $126 \pm 47$  ml,  $P = 0.0001$ ). In addition, left atrial enlargement was also implicated, as patients who developed AF had higher atrial dimension than those who maintained SR ( $42.5 \pm 7$  vs  $29 \pm 4.6$  mm,  $P = 0.017$ ). Age and gender were not statistically associated with the development of AF upon univariate

analysis. The percentage of patients aged over 70 years old was the same and also BMI was not statistically different between SR and AF groups. Equally, differences in comorbid factors as DM, CVA, PVD, COPD, CHF and recent MI were not statistically significant. However, interesting enough, patients who remained in SR were more hypertensive, when compared with their AF counterparts, which almost reached statistical significance ( $P = 0.076$ ).

As for medication prior CABG, univariate analysis demonstrated that subjects that maintained SR had higher intake of CCBs ( $P = 0.042$ ). There was no difference in beta-blockers intake between groups (0.99). Procedure-related factors, as CPB and cross-clamp duration or the use of retrograde cardioplegia and number of bypass grafts, did not demonstrate any correlation with postoperative AF either. No episode of hypomagnesaemia (defined as Mg  $< 2$  mg/dl and measured once a day) was documented postoperatively. Also, there was no difference in episodes of documented hypokalaemia (defined as K  $< 3.5$  meq/l and measured every 2, 4, 6 and 8 h depended on the postoperative day) between patients that developed AF and those that maintained SR ( $P = 0.54$ ).

Variables with  $P < 0.2$  upon univariate analysis that entered into the regression model were PFV, preoperative LAD, HTN, PVD, CCBs and ACEIs intake. Multivariate logistic regression analysis identified PFV as a strong independent predictor of postoperative AF (OR: 1.018, 95% CI: 1.009–1.027,  $P = 0.0001$ ). This association was completely independent of LA size, HTN and PVD. Receiver operating characteristic (ROC) analysis showed that the best discriminatory level of PFV to predict new-onset post-CABG AF was 129.5 ml (sensitivity 86% and specificity 56%) (Fig. 2). The area under the curve was 0.757 with 95% CI: 0.651–0.845 and a  $P$ -value of  $< 0.0001$ . The second variable which was also associated with the development of postoperative AF was the absence of CCBs in patient's preoperative treatment (OR: 5.4, 95% CI: 1.13–25.5,  $P = 0.035$ ). When the PFV was dichotomized by the value 129.5, the logistic regression showed OR: 9.8, 95% CI: 2.85–33.41 and  $P = 0.0001$ . All vari-

Table 1:  
Patient characteristics and procedural variables according to postoperative rhythm

Variables <sup>a</sup>	Sinus rhythm	Atrial fibrillation	P-value
<i>n</i>	55	28	
Age (years)	64 ± 9	66 ± 8	0.31
Age >70 years old	16 (29)	7 (29)	0.96
Male	44 (80)	22 (79)	0.88
BMI (kg/m <sup>2</sup> )	30 ± 4.5	29 ± 4.6	0.49
Pericardial fat volume (ml)	126 ± 47	195 ± 80	0.0001 <sup>b</sup>
<i>Medical history</i>			
HTN	48 (87)	20 (71)	0.076 <sup>b</sup>
Diabetes	27 (49)	12 (43)	0.59
Chronic obstructive Pulmonary disease	8 (14.5)	7 (25)	0.24
Cerebrovascular			
Accident	4 (7.3)	3 (11)	0.59
PVD	16 (29)	4 (14)	0.13 <sup>b</sup>
Recent MI	25 (45)	9 (32)	0.24
NYHA III–IV	6 (11)	5 (18)	0.38
Beta-blockers	44 (80)	25 (89)	0.99
Angiotensin-converting-enzyme inhibitor intake		24 (44)	7 (25)
0.097 <sup>b</sup>			
CCBs	17 (31)	7 (11)	0.042 <sup>b</sup>
<i>Coronary angiography and echocardiography findings</i>			
RCA disease	31 (56)	19 (68)	0.31
Preoperative LVEF (%)	57 ± 10	54 ± 11	0.27
Preoperative LVH	7 (13)	5 (18)	0.53
Preoperative LAD (mm)	29 ± 4.6	42.5 ± 7	0.017 <sup>b</sup>
<i>Procedural variables</i>			
Number of bypass grafts	2.4 ± 0.6	2.3 ± 0.7	0.90
CPB time (min)	83.6 ± 26.4	77.4 ± 21.7	0.28
Cross-clamp time (min)	63.7 ± 21.5	59.5 ± 20.8	0.41
Use of retrograde cardioplegia	2 (40)	10 (36)	0.70
Perioperative use of IABP	3 (6)	2 (7)	0.76
<i>Postoperative variables</i>			
K < 3.5 meq/l	16 (29)	10 (36)	0.54
Age (years)	64 ± 9	66 ± 8	0.31
Age >70 years old	16 (29)	7 (29)	0.96
Male	44 (80)	22 (79)	0.88
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<i>Postoperative variables</i>			
K < 3.5 meq/l	16 (29)	10 (36)	0.54

BMI: body mass index; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LAD: left atrial diameter; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump.

<sup>a</sup>Categorical data are numbers (%); continuous data as means ± standard deviation.

<sup>b</sup>Variables examined in the multivariate regression analysis.

ables examined in multivariate regression analysis are given in Table 2.

## DISCUSSION

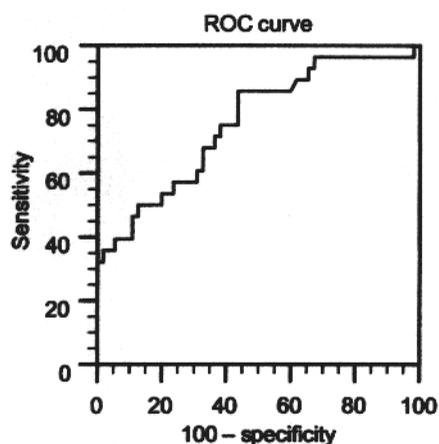
AF is one of the most common complications following CABG and the incidence has not changed in the last two decades, despite improvements in myocardial preservation and surgical techniques. The incidence of postoperative AF in

our study was 34%, corresponding to the data in the literature. The relatively high mean age of our patients, the gender and BMI did not have an impact on development of postoperative AF. Also, well-known risk factors and comorbidities did not reach statistical significance, mainly due to the small sample size. Previous reports suggest that beta-blockers suppress post-CABG AF; however, preoperative beta-blockers intake was not associated with lower incidence of AF. In contrast, preoperative use of CCBs afforded a significant

Table 2:  
Variables examined in the multivariate regression analysis

Variables	OR	95% CI	P-value
Pericardial fat volume (ml)	9.8	2.85–33.41	0.0001
Absence of CCBs intake	5.57	1.35–22.9	0.17
Preoperative LAD (mm)	1.09	0.97–1.24	0.15
HTN	1.86	0.44–8.02	0.40
PVD	2.92	0.7–12.14	0.14
Angiotensin-converting-enzyme inhibitor intake	2.6	0.77–8.73	0.12
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CCBs: calcium channel blockers; HTN: hypertension; LAD: left atrial diameter; PVD: peripheral vascular disease.



**Figure 2:** ROC curve illustrating sensitivity and false-positive rate (100 – specificity) at all possible cut-off levels to assess the performance of pericardial fat volume to predict post-CABG AF.

protective effect against arrhythmia in univariate analysis ( $P = 0.042$ ). Further multivariate logistic analysis showed that CCBs intake was also significantly correlated with reduced incidence of postoperative AF ( $P = 0.035$ ).

Structural changes of the heart, such as LA dilatation and LV hypertrophy, have been found to be other factors contributing to postoperative AF [4, 5]. One early report investigating the relationship between LA parameters and post-CABG

AF stated that only LA diameter was associated with postoperative AF [21]. In consistence with that finding, LA size was significantly larger in AF patients compared with SR patients ( $P = 0.017$ ). The higher mean of preoperative LA diameter in patients that developed post-CABG AF could have been a significant inherent risk of postoperative AF, but further analysis did not confirm LA diameter as an independent predictive factor for AF in our study. However, only one dimension of LA was assessed and volume of LA was not evaluated. Additionally, the two patient groups showed no differences in echocardiographic parameters of the left ventricle (LVH or LVEF).

To overcome some of the limitations of previous studies, including mixed coronary and valve cases, reoperations and off-pump cases, our population was homogeneous with patients undergoing first time, elective isolated CABG with the use of CPB. Although previous studies have shown a relationship between postoperative AF and CPB and cross-clamp duration, this study did not find significant difference between SR and AF patients [3, 5]. Electrolyte imbalance, especially hypokalaemia, is also considered to be a triggering factor of postoperative AF [1, 2]. In this study, there was no statistically significant rela-

tionship between serum potassium and the incidence of postoperative AF. This may be partly explained by normal serum potassium levels in the subgroups due to routine measurements and prompt supplementation of potassium in all patients after surgery.

The key measure of this study was PFV with the aid of non-invasive imaging. Based on the renewed interest on heart adiposity and on current evidence that PFV is associated with AF prevalence, we elected to evaluate the association with postoperative AF. This study, for the first time, showed that patients who developed AF following isolated on-pump CABG, had significantly higher PFV values than those who maintained SR. The association of pericardial fat with AF was further confirmed in multivariate logistic regression analysis, indicating increased PFV as a strong independent risk factor of postoperative AF. In particular, ROC analysis showed that the best discriminatory predictive level of PFV was 129.5 ml, with sensitivity of 86% and specificity of 56%. Although statistical analysis confirmed such an association, the role of the MDCT scan as a screening test remains uncertain. Further studies are required to evaluate the balance cost/benefit of this radiological examination as screening tool before cardiac operations.

Multiple studies have implicated the role of pericardial fat, quantified by cardiac CT, in the pathophysiology of coronary atherosclerosis. In the Framingham Heart Study and the Multi-Ethnic Study of Atherosclerosis, the volume of pericardial fat was found to be associated with coronary artery calcium and incident coronary artery disease [12–14]. In a community-based study of nearly 1000 participants undergoing MDCT examination, it was found that PFV was associated with LV mass, LVEDV and LA dimension in women and with LV mass and LA dimension in men [22]. In another report, PFV was found to be positively associated with LA size in men. Subsequent work supported these findings by demonstrating a positive association between pericardial adipose tissue and prevalent AF, which is known to be associated with LA size [16]. Al Chekakie *et al.* [19] demonstrated a significant

association of PFV with both paroxysmal and persistent AF that is completely independent of all major risk factors age, gender, HTN, valvular heart disease, left ventricular ejection fraction, DM and BMI, including also LA enlargement. Wong *et al.* [17] showed that PFV is associated with the presence and severity of AF, left atrial volumes and poorer outcomes after AF ablation, independent of systematic measures of adiposity.

Increasing evidence seems to point towards pericardial fat as a metabolically active tissue modulating the adjacent myocardial tissue, shedding further light on the idea of a local paracrine effect of epicardial tissue with findings of increased expression of numerous inflammatory markers [6, 7, 18]. Although AF pathophysiology is complex, increasing evidence supports mechanistic links between inflammation and AF. Surgical myocardial revascularization using CPB is still the therapeutic gold standard for multivessel coronary involvement. However, this procedure is associated with the occurrence of systemic inflammatory response syndrome of various possible causes, which may lead to postoperative AF. The intraoperative and postoperative periods are potentially stressful for the heart with extremes in response affecting reperfusion, inflammation, hemostasis and excitotoxicity. Inflammation is one of the risk factors of postoperative AF by affecting atrial conduction [1]. Inflammatory markers including IL-6, IL-8, C-reactive protein, tumour necrosis factor- $\alpha$  and indices of neutrophil and platelet activation are significantly increased in the systemic bloodstream after CABG [1, 4, 5]. In our study, patient population is limited to on-pump cases, not allowing definite conclusions to be made on association with the CPB effect. The interrelation though, of epicardial adiposity and CPB-related inflammatory response should be further delineated.

Although epicardial adipose tissue is considered to be proinflammatory and is associated with AF, not all epicardial fat pads are similar. The heart is reported to have mainly three epicardial fat pads with parasympathetic ganglia: a fat pad on the anterior surface of the atria located in the aortopulmonary window, a posterior fat pad be-

tween the inferior vena-cava and left atrium, and the one between the superior vena-cava and right atrium [6, 9, 18]. In an imaging analysis of 169 patients with cardiac CT, a significant, direct, relationship between AF burden and the thickness of the posterior periatrial fat pad between the oesophagus and LA was found, independent of BMI, age and LA area. It was hypothesized that local inflammatory mediators produced by the periatrial epicardial fat in the LA posterior wall promote the activation of ectopic foci in the pulmonary vein ostia [18]. Additionally, reports about the impact of surgical preservation of the anterior fat pad between the aorta and right pulmonary artery on postoperative AF have had conflicting results. It is considered usual practice to dissect it during CABG to clear the field of view and secure the aorta cross clamp. Canine studies demonstrated that this tissue contains vagal neurons and a small study in humans clearly demonstrated a paradoxical increased incidence of postoperative AF in patients with anterior FP dissection when compared with patients with preservation during CABG, probably due to imbalance of autonomic tone [23]. However, these data are not yet confirmed by similar studies and we proceeded accordingly with our routine operative practice of dissecting anterior fat pad.

Furthermore, current knowledge of cardiac lymphatics demonstrates their possible role in triggering arrhythmias in the postoperative period. Coronary bypass surgery requires removal from the ascending aorta of adventitial tissue and the aortic fat pad, which contains the sinoatrial node lymphatic collector. In addition, a cross clamp applied to aorta obstructs the entire lymphatic drainage from the heart and thus affects the conduction system of the heart [24]. During surgery, we tried to minimize aortic manipulations and right atrial damage and preserve the aortic fat pad to avoid negative effect on node function. Both distal and proximal anastomoses were performed under a single aortic cross-clamping period and duration was not different in the two subgroups.

In light of available data, our study further bolsters the association of increased PFV with AF. Our findings are consistent with the hypothesis

of a local pathogenic effect of pericardial fat promoting an arrhythmogenic substrate.

### Study limitations

Our study has a number of important limitations. In particular, the study design limits inferences of causality and the single-institution data limit generalizability. The current study was primarily designed to assess the association of PFV with postoperative AF. Patient population was narrowed to include only patients receiving standard median sternotomy on-pump bypass surgery. The role of statins in postoperative AF was not analysed. Other unmeasured factors also, may partially account for our findings. We also did not measure intrathoracic and visceral abdominal fat; these measures may have added incremental information on the effects of local vs systemic adiposity. Finally, because computed tomography (CT) scanning was performed without heart rate control, it is possible that measurements of pericardial fat may have been affected by motion artefacts. Our imaging protocol analysed the pericardial fat surrounding the entire heart and did not allow for focal fat quantification. Given the small sample size, we were unable to conduct many important analyses including the relation between AF and anatomic distribution of pericardial fat. Future software development may allow studies to include more sophisticated and detailed volumetric assessments of pericardial fat. Therefore, we believe that using imaging data gathered prospectively from an international multicentre population will confirm our findings and examine important subgroup analyses.

### CONCLUSIONS

To our knowledge, the present study provides the first report of an association between cardiac adiposity, as measured by pericardial fat, and postoperative AF. We have described the incidence of AF in a population undergoing elective isolated CABG, and identified PFV as a strong independent predictor of postoperative AF, thereby allow-

ing preoperative identification of vulnerable patients. However, the nature of the role that pericardial fat plays in cardiac surgery and postop-

erative AF pathogenesis requires further investigation.

**Conflict of interest:** none declared.

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*Elefteriades John A.*

# An Overview of Research at the Yale Aortic Institute

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## **Abstract**

This manuscript provides an overview of the major research milestones achieved at the Aortic Institute at Yale-New Haven Hospital and Yale University School of Medicine.

## **Introduction**

In the early 1990s, epidemiologist Dr. John Rizzo and cardiac surgeon Dr. John Elefteriades met at the bedside of Dr. Rizzo's wife, Carmella, who had just suffered a Type A aortic dissection with intra-pericardial rupture.

Carmella survived emergency aortic replacement and continues to do well to this day.

Since their meeting over 20 years ago at the time of Carmella's aortic dissection, Drs. Rizzo and Elefteriades pledged to combine their skills (epidemiology/surgery) to the study of thoracic aortic disease.

This chapter summarises investigations performed by Drs. Rizzo, Elefteriades, and their dedicated team (led in recent years by our Director of Research, Dr. Bulat Ziganshin).

We intend this summary of Yale research as an honour to Dr. Dino Anagnostopoulos, to whom this entire book is dedicated.

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### 1: Complication-specific approach for type B aortic dissections

For a number of years, there had been vigorous (heated) discussions between proponents of uniform surgical management of Type B (descending) aortic dissections and proponents of uniform medical management. In the early 1990s our group conducted a detailed review of our patients with acute descending aortic dissections. We found that most did well with exclusive medical management. We also found that those with discrete vascular complications of the dissection did poorly without surgical intervention. This led to our elaborating a so-called “complication-specific” approach to determine the treatment strategy for these patients.<sup>1</sup> Later on we conducted a more detailed investigation of 100 consecutive cases of Type B aortic dissections treated at Yale-New Haven Hospital, accumulating even more evidence of the effectiveness of this proposed management strategy.<sup>2</sup>

Our “complication-specific” approach for acute dissections of descending aortic aneurysms is as follows. The majority of uncomplicated cases of descending aortic dissection can be treated medically by so-called “anti-impulse therapy” (beta-blockade and afterload reduction), which remains the cornerstone of modern medical management. Thus, surgical management is only recommended for complicated cases of dissection. For each type of complication, we recommend a specific surgical technique:

- In cases of realized aortic rupture the only appropriate surgical treatment is direct surgical aortic replacement with a tube graft (or a stent graft) to prevent exsanguination.
- When the complication is organ ischemia from branch vessel occlusion we favour the fenestration procedure, which is a method for decompressing the false lumen of the dissected aorta by creating a window (or “fenestra”) in the intimal layer of the distal part of the aorta. This permits outflow of blood from the false lumen, reduces the intraluminal false lumen pressure, and reliably relieves branch vessel obstruction. Over the years aor-

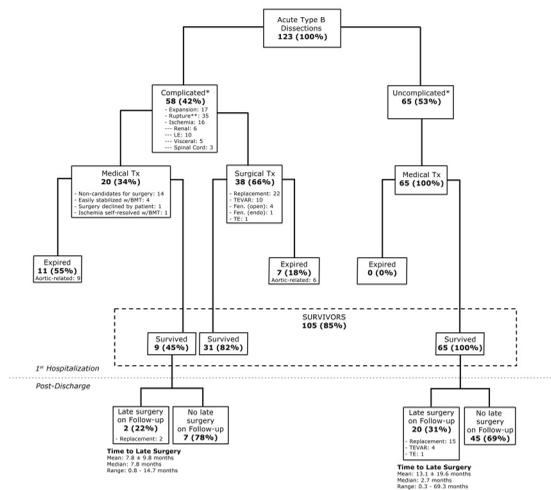
tic fenestration techniques have proven to provide a safe, effective, and durable treatment alternative to aortic replacement for the specific complication of branch vessel occlusion.<sup>3-4</sup> Fenestration can now be done by an endovascular as well as a surgical approach.

- Lastly, if the complication is threatened (impending) rupture (manifested by continued pain or rapid aortic expansion) – surgical aortic replacement of the aorta is indicated. This can also be performed by an endovascular approach.

Establishment of the “complication-specific” approach was much needed at the time since conventional graft replacement of the diseased aorta was seen as the only effective method of surgical treatment, and it bore (and still bears in the acute setting) a high incidence of postoperative complications (bleeding, paraplegia). The “complication-specific” approach for treating descending aortic dissection received widespread endorsement<sup>5</sup> and was introduced into practice by many of the major centres treating aortic diseases.

Most recently we revisited the complication specific approach to assess its efficacy in managing Type B aortic dissection in the current era of increasing endovascular therapy. We studied the outcomes of the complication-specific approach in treating patients with acute descending dissections in the years between 1999 and 2014. During this period of time, our group treated 123 acute type B dissection patients, whose treatment paths are outlined in **Fig. 1**.<sup>6</sup>

Of the 123 original patients, 58 had complications, of whom 38 were treated surgically. The remaining 20 complicated cases were diverted for a variety of reasons and were treated medically.<sup>6</sup> 7 of the 38 surgical patients expired in hospital, as compared to 11 of the 20 medically-treated complicated cases.<sup>6</sup> All 65 of the uncomplicated cases were treated medically, with no in-hospital mortalities.<sup>6</sup> These results demonstrate that the complication-specific approach is both safe and effective in assigning acute type B dissections for either surgical or medical treatment, and that medical therapy for uncomplicated cases is sufficient, at least for short-term management.

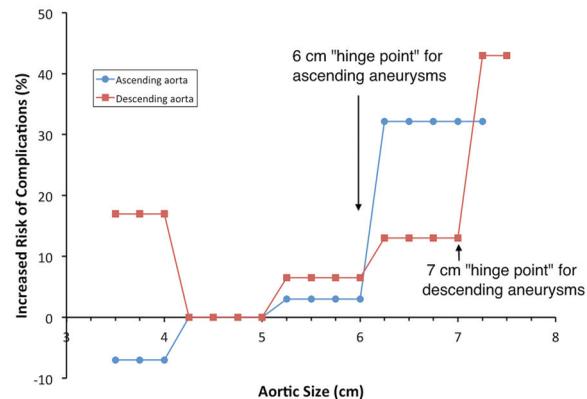


**Fig. 1.** Flowchart illustrating the classification and treatment of patients under the complication-specific model in treating type B dissections. (Reprinted with permission from Charilaou, P, Ziganshin, BA, Peters, S, et al: Current Experience With Acute Type B Aortic Dissection: Validity of the Complication-Specific Approach in the Present Era. *Ann Thorac Surg* **2016**, *101* (3), 936-43.)<sup>6</sup>

## 2: Size at which the aorta ruptures or dissects

In the 1990s, we began investigating the progression and long-term outcomes of thoracic aortic aneurysms (TAAs). Through a collaboration with John Rizzo, PhD, the team has been able to analyze clinical information collected from over three thousand patients and to model the average growth rate of a TAA. The patient data revealed that an average ascending aneurysm grows at 0.1 cm per year, while a descending aneurysm has a mean growth rate of 0.30 cm per year.<sup>7-9</sup> Further analysis demonstrated that aneurysms have certain critical diameters – termed “hinge points” – where the likelihood of a catastrophic tissue failure, either as a dissection or aortic rupture, is dramatically increased (Fig. 2). By the time an ascending aneurysm reached its hinge point of 6.0 cm, 34% of patients would have suffered one of the two devastating complications. In descending aneurysms, the hinge point is found at 7.0 cm, conferring a 43% risk of dissection or rupture by that point.<sup>8</sup>

These findings helped define the intervention criteria for aortic replacement surgery, and have influenced the current European<sup>10</sup> and American



**Fig. 2:** Graph displaying the increase in risk of complications (dissection or rupture) against aneurysm diameters. (Reproduced with permission from Coady MA, Rizzo JA, Hammond GL, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg* **1997**, *113* (3), 47691.)<sup>7</sup>

Guidelines<sup>11</sup> for management of thoracic aortic disease. Current practice at Yale is to recommend elective surgery when the diameter of the ascending aorta expands to 5.5 cm, or that of the descending aorta reaches 6.5 cm. For patients with a family history of Marfan disease or other syndromic aortic disorders, the maximum diameter for both ascending and descending aneurysms is reduced to 5.0 cm, as these individuals are especially susceptible to complications from their condition.<sup>8-9</sup> The intervention criteria defined from this study allow for diseased aortas to be removed before the risk of a complication becomes excessive. Further refinement of this method has allowed the team to develop an algorithm that sets intervention criteria depending on the patient’s body size.<sup>12</sup> In a clinical study performed at Yale, this tailored approach was shown to be effective at determining the appropriate time to perform aortic surgery.<sup>13</sup>

Further natural history studies have led to a greater understanding of the factors affecting the growth and size of aneurysms. An analysis of the Institute’s patient database found that the average diameter for an aortic aneurysm was 4.71 cm.<sup>14</sup> The same study also showed that an aneurysm’s rate of expansion depended on its location. On average, ascending aneurysms grew at 0.20 cm/year, arch aneurysms at 0.26 cm/year,

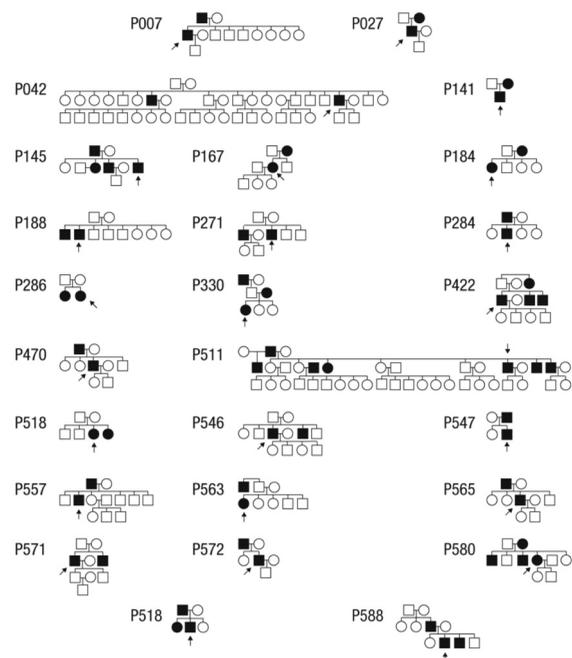
and descending aneurysms at 0.23 cm/year.<sup>14</sup> Another investigation revealed that patients who have one of the atypical aortic arch anomalies colloquially termed “bovine arch” are predisposed to faster aneurysm growth than those with a standard aortic arch.<sup>15</sup> These new findings will assist in the further refinement of intervention criteria, and consequently lead to better outcomes for patients.

### 3: Heritability of TAAs and dissections

Until recently, Marfan syndrome was the only genetic condition generally recognised to cause aortic aneurysms. However, these individuals comprise around 5% of the patient population at Yale. In an effort to gauge the heritability of aortic disease, our group investigated whether the remaining patients had a positive family history of similar conditions. In the course of the study, we reviewed the family histories of nearly 500 non-Marfan patients with TAAs. The family trees we constructed revealed that 21% of probands had a positive family history of arterial aneurysms.<sup>16-17</sup> These patients also had aneurysms that both presented earlier in life and grew at a faster rate.

We were also able to determine that aortic aneurysms are primarily an autosomal dominant condition, although both recessive and sex-linked inheritance patterns were observed in the patient population (**Fig. 3**). As many family members have never undergone imaging of the aorta, the actual rate of the condition’s inheritance may be much larger than 21%. Additional analysis of patients’ family histories revealed that the location of aneurysms was preserved between related individuals – patients with ascending aneurysms had relatives with ascending aneurysms while those with descending aneurysms had family histories primarily consisting of descending or abdominal aneurysms.<sup>17</sup>

Based upon the evidence presented in the pedigree studies that aortic aneurysms are primarily genetic, rather than idiopathic or arteriosclerotic, standard practice has evolved to include screening of immediate family members for the condi-



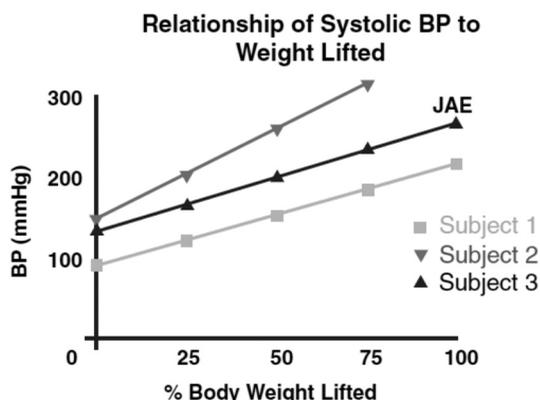
**Fig. 3:** Family pedigrees of nonsyndromic thoracic aortic aneurysm amongst the first 100 families studied. (Reproduced with permission from Elefteriades, J. A., Thoracic aortic aneurysm: reading the enemy’s playbook. *Yale J Biol Med* **2008**, *81* (4), 175-86.)<sup>35</sup>

tion. Our practice is to regularly screen the patients’ parents, siblings, children, and grandchildren. Other relatives, such as aunts, uncles, and cousins are often assessed as well.<sup>18</sup>

In 2017, we completed two studies that suggested an even greater influence of family history on the nature of a patient’s dissection. One study found that patients with a positive family history of aortic dissection demonstrated – amongst many other risks – a lower mean age of dissection ( $54.7 \pm 16.8$  versus  $62.4 \pm 13.0$ ), a greater occurrence of aortic dissection in their immediate family ( $2.3 \pm 0.6$  against  $1.0 \pm 0.0$ ), and an annual risk of dissection amongst immediate family members 2.77 times that of patients with no family history of the condition.<sup>19</sup> The other investigation revealed that the average age of dissection was lower in patients with two or more dissectors in their family, ( $54.1 \pm 15.2$  versus  $63.1 \pm 12.4$ ) and that more than 50% of familial dissections occurred within a decade of the median age of the first dissection in the family.<sup>20</sup> These findings emphasise the very powerful impact of family history on thoracic aortic disease.

#### 4: Aortic dissections in young weightlifters

In the early 2000s, our staff encountered five remarkably similar cases of aortic dissection. All five of the patients were superficially healthy young athletes, with no prior indications of aortic disorders. The common factor amongst the cases was that all five patients were performing high-intensity weightlifting at the time of aortic dissection. After publishing the case studies in *JAMA*,<sup>21</sup> we conducted a small investigation to assess the effect of strenuous weightlifting activity on an individual's blood pressure. The study found that lifting extremely heavy weights produced rapid and dramatic elevations in systolic blood pressure, in some instances approaching the range of 300 mm Hg (**Fig. 4**).<sup>22</sup> The extreme hypertension observed is unique to weightlifting, leading the investigators to conclude that episodic hypertension was the trigger for the dissections in all five cases.



**Fig. 4:** Systolic blood pressure versus percent of bodyweight lifted. (Reproduced with permission from Elefteriades, J. A., Thoracic aortic aneurysm: reading the enemy's playbook. *Yale J Biol Med* **2008**, 81 (4), 175-86.)<sup>35</sup>

Following the release of the case studies in *JAMA*, our team has analysed 31 similar patients from the entire United States.<sup>23</sup> Our efforts revealed that nearly every dissection occurred in young males with previously unknown, asymptomatic aortic dilation (within the range of 4.0 to 5.0 cm in diameter). Additionally, each case was initiated by the patient undertaking particularly strenuous physical activity. Based upon these findings, we recommend routine echocardiographic

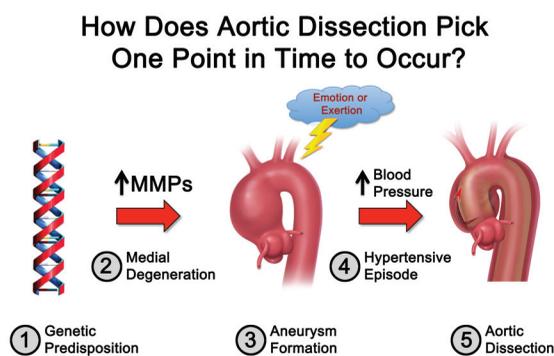
screenings for athletes performing heavy weightlifting or similarly intense physical activity.

#### 5: Inciting events of acute aortic dissections

One of the central priorities at the Institute is to determine the inciting events that lead to aortic dissections. As incidents follow both circadian and diurnal patterns – dissection rates peak during the winter and waking hours, when blood pressure reaches its highest levels – dissections are not random events, as they had been commonly thought to be. To determine if there were additional commonalities between cases, our group interviewed patients and family members about the events leading to the onset of dissection. Two-thirds of the responses revealed that the patient was either engaging in heavy physical exertion or experiencing severe emotional distress in the period immediately preceding dissection.<sup>24</sup>

Based on the responses received from patients and their families, we hypothesised that the episodes of strenuous exertion or emotional distress caused acute hypertension, causing the weakened aneurysm wall to fail. This progression to dissection is illustrated in a four-step model (**Fig. 5**).<sup>25</sup>

- An individual has a genetic predisposition to aortic aneurysms and dissection from birth.
- The aortic wall is degraded over the individual's life, in some capacity due to excess prote-



**Fig. 5:** Proposed model for the onset of acute aortic dissection. (Reproduced with permission from Elefteriades, J. A., Thoracic aortic aneurysm: reading the enemy's playbook. *Yale J Biol Med* **2008**, 81 (4), 175-86.)<sup>35</sup>

olysis by matrix metalloproteinases (MMPs).

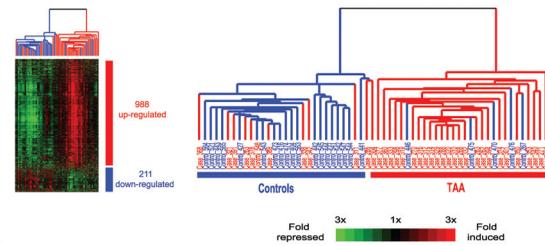
- The damaged section expands, losing its elasticity and experiencing greater wall stress as a result.
- The patient experiences acute hypertension – either through physical exertion or emotional distress – that exceeds the maximum tensile strength of the tissue, causing a dissection.

Using this model, new lifestyle adjustments have been implemented as part of the medical management of aneurysms. Heavy exertion should be avoided by patients with sizable thoracic aortic aneurysms. It is recommended that patients predisposed to aortic aneurysms receive medical advice regarding sedative medication to prevent acute hypertension in cases of severe emotional distress. Additionally, based on very recent data, patients should be made aware of the proposed link between the use of fluoroquinolone antibiotics and aneurysm formation or dissection.<sup>26-27</sup>

An alternative hypothesis posited by Yale colleagues Humphrey et al., suggested that the root cause of aortic dissections was the accumulation of glycosaminoglycans and proteoglycans in the aortic wall.<sup>28</sup> These pooled molecules are thought to lead to delamination of aortic tissue, eventuating in an initial medial tear instead of an intimal tear.<sup>28-29</sup>

## 6: General blood screening test for TAAs

Following the pedigree study into the heritability of aortic aneurysms, we were compelled to investigate the causative genes behind the condition and its inheritance. Our team analysed 33,000 RNA expression patterns in blood samples from patients with TAAs and contrasted them against healthy control samples. The 41 most common aberrations amongst the patient samples were compiled into a panel termed the “RNA signature” for TAAs (Fig. 6). These anomalies in RNA expression accurately distinguish between patients with a TAA and unaffected individuals 80 to 85% of the time.<sup>13, 30</sup>



**Fig. 6:** “RNA Signature” of Thoracic Aortic Aneurysm. The hierarchical cluster diagram (left, A) represents patients as vertical lines and RNAs as horizontal lines. Green represents repression, (underexpression) and red induction (overexpression). The figure on the right (B) represents the accuracy of the test – the few stray deviations from the clustering represent the error, yielding an overall accuracy of 82%. (Reprinted with permission from Elefteriades, J. A.; Farkas, E. A., Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol* **2010**, *55* (9), 841-57.)<sup>13</sup>

We believe that the RNA signature test’s accuracy may eventuate into a clinically useful indicator of TAAs, and perhaps a means of monitoring aneurysm progress. In addition to its potential use in forecasting rupture and dissection, this test may also be applied as a generalised screening test for TAAs. Due to its simplicity, the RNA signature test can be performed on relatives of patients, and even the general public, as an early, reliable marker for TAAs.

## 7: Structural alterations in the aortic wall that underlie dissections

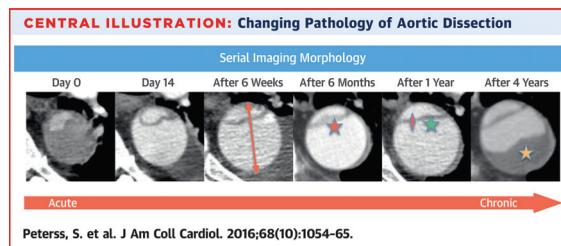
In the course of our inquiries into the mechanisms behind aortic aneurysms, we conducted a thorough bioengineering investigation into the physical characteristics of aortic tissue in patients with ascending aneurysms. Our team performed intra-operative epi-aortic echocardiography to measure six key “engineering” variables of the aneurysm – aortic pressure at systole and diastole, aortic diameter at systole and diastole, and aortic wall thickness at systole and diastole.

The measurements obtained show that as the aneurysm expands, its wall rapidly loses elasticity. By the time the ascending aorta reaches its critical diameter of 6.0 cm, the wall is completely

rigid, ensuring that the entirety of the force exerted by ventricular contraction is fully transferred to the diseased tissue in the form of wall stress.<sup>13, 31</sup> Consequently, a blood pressure of 200 mm Hg in an aorta over 6.0 cm in diameter will often be enough to surpass the tissue's maximum tensile strength of 800 kPa. The measured decline in the aorta's elasticity can be directly linked to the previously-observed "hinge point" at 6.0 cm. This has a significant implication for patients with severely distended aortas, as everyday activities have the potential to trigger a dissection or rupture.<sup>31</sup>

As echocardiography is able to measure the dimensions of the aorta during systole and diastole, it allows us to calculate quantities such as the wall stress and elasticity of the aorta. These factors could provide a useful scale in determining the risk of dissection or rupture for the patient's current condition. Therefore, we are currently pursuing a potential non-operative transoesophageal method of obtaining echocardiography accurate enough to measure wall thickness in systole and diastole, so that the mechanical properties of a patient's aneurysm can be monitored at regular intervals.

In addition to studying the factors leading to aortic dissection, we have also investigated the transition of an aortic aneurysm from its acute to chronic states. As type A dissections are most often acute and emergent, very little information can be ascertained about their chronic state. Using histopathological assessments, CT scans, and echocardiography, our team found that type B dissections go through a series of stages in the transition between acute and chronic. (**Fig. 7**) Following dissection, the aorta dilates, with the false lumen becoming increasingly pronounced.<sup>32</sup> The growth of the false lumen slows as the blood thromboses.<sup>32</sup> Eventually, the "flap" of tissue formed by the separation of the intima from the aortic wall stiffens, straightens, and thickens as it undergoes significant fibrosis.<sup>32</sup> These findings will help our group refine our management of chronic type B dissections.



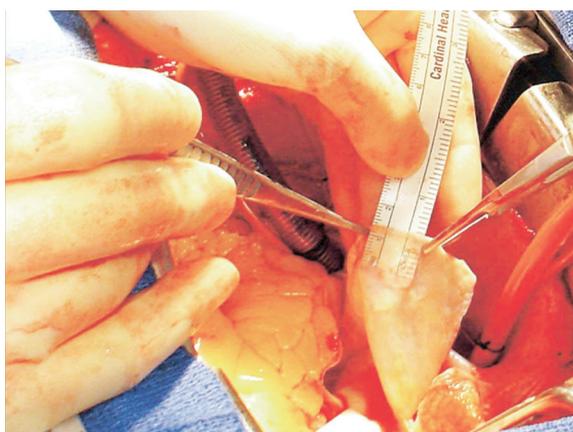
**Fig. 7:** Changing pathology of a chronic Type B dissection. The orange arrow indicates the large early increase in aortic diameter. The orange star indicates the thickening of the separated intima. The orange triangles and green star indicate the reduction in the intimal flap motion over time, and the straightening of the intimal flap, respectively. The yellow star indicates the increasing thrombosis within the false lumen following a long period of time. (Reproduced with permission from Peterss, S.; Mansour, A. M.; Ross, J. A.; Vaitkeviciute, I. et al; Changing Pathology of the Thoracic Aorta From Acute to Chronic Dissection: Literature Review and Insights. *J Am Coll Cardiol* 2016, 68 (10), 1054-65.)<sup>32</sup>

## 8: Identification of the role of matrix metalloproteinases in pathogenesis of thoracic aortic aneurysm

At Yale, we have made a significant effort to elucidate the pathophysiology of aneurysm formation. Indeed, this process is very complex and includes multiple aspects such as inflammation, proteolysis, and disturbed survival and function of smooth muscle cells in the aortic wall.<sup>25</sup> Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade elastin, fibrillin, and collagen – the main structural proteins of the aortic wall. Under normal conditions MMP tissue activity is regulated by the presence of tissue inhibitors of metalloproteinases (TIMPs). Previous studies had demonstrated excess MMP activity in patients with abdominal aortic aneurysms<sup>25, 33</sup>, however this was not proven for thoracic aneurysms.

In our investigations, we looked specifically at the profiles of proteolytic enzymes in the aortic wall of aneurysm patients and compared these profiles to those of normal individuals. We found a marked elevation of the proteolytic enzymes (MMPs) and a marked depression of the inhibitory enzymes (TIMPs) in ascending aortic aneu-

rysms and dissections<sup>34</sup>. Thus, we concluded that in aneurysm patients, the balance between MMPs and TIMPs is shifted strongly toward increased proteolysis, which explains the observed degradation of the aortic wall. Our current belief is that aneurysm patients are genetically programmed to manifest excessive MMP activity, leading ultimately to degradation and thinning of the aortic wall<sup>35</sup>. This is shown in **Fig. 8**, where the wall of



**Fig. 8:** A section of aortic tissue that became so thin that a ruler was visible through it. (Reproduced with permission from Elefteriades, J. A., Thoracic aortic aneurysm: reading the enemy's playbook. *Yale J Biol Med* **2008**, *81* (4), 175-86.)<sup>35</sup>

a patient's aorta became so thin in a six-centimetre aneurysm that a ruler placed behind the wall can be read clearly through the tissue. It is hard to imagine how such a thin structure was maintaining the main blood flow to all organs of the body and not rupturing under arterial pressure. The recognition of this pathophysiologic mechanism of aneurysm development raises the potential for innovative drug therapy, such as matrix protease inhibitors, in order to produce a slowing or halting of the evolution of thoracic aneurysm disease.

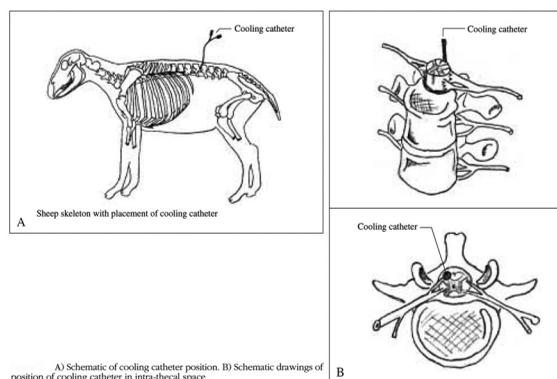
### 9: Development of a novel spinal “cooling catheter” for prevention of paraplegia in aortic surgery (supported by grants from the National Science Foundation).

Paraplegia continues to be one of the most serious complications of surgical procedures for descending and thoracoabdominal aortic aneurysms,

despite major advances in surgical technique. This devastating complication has its origin in multiple deleterious factors which are part and parcel of descending aortic surgery (temporary occlusion of aorta, permanent deletion of intercostal arteries, air and particulate embolism). Our extensive experience (described in the following section) shows the protective role of hypothermia for preventing cerebral damage due to ischemia; thus, we decided to try to develop a method of protecting the spinal cord during operations of the descending aorta by inducing local hypothermia in the spine, rather than having to cool down the whole body.

We developed a special “cooling catheter”, which was designed to cool the spinal cord topically after being threaded into the spinal canal (**Fig. 9**). This catheter was tested in a sheep laboratory model. During these experiments, the catheter effectively cooled the animal's spinal cord from a core temperature of 36.8°C to a spinal temperature of 30.5°C. Moreover, in post-mortem histological examinations of the spinal cords the neural tissue showed no evidence of hypothermic tissue damage.<sup>36</sup>

We believe that developing such a catheter is very promising for decreasing the incidence and severity of paraplegia in aortic surgery. It may also be of benefit in cases of spinal injury, either traumatic or iatrogenic. In the near future, we hope to embark on clinical trials of the spinal cooling catheter.



**Fig. 9:** Schematic of the placement of the cooling catheter in the animal test subject. (Reprinted with permission from Moomiaie, R. M.; Ransden, J.; Stein, J.; Strugar, J. et al., Cooling catheter for spinal cord preservation in thoracic aortic surgery. *J Cardiovasc Surg (Torino)* **2007**, *48* (1), 103-8.)<sup>36</sup>

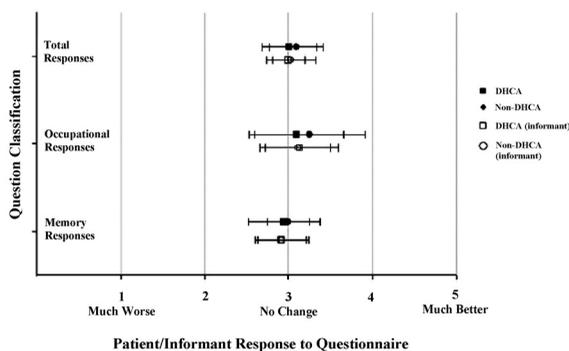
Moreover, recently we developed and successfully tested a similar concept for introducing a brain-cooling catheter into the lateral ventricles of the brain to induce local brain hypothermia. The results were very encouraging and hold promise for mitigation of traumatic and ischemic injuries of the brain, including post-resuscitation anoxic injury.<sup>37</sup>

### 10: Safety of deep hypothermic circulatory arrest in aortic arch surgery

Most thoracic aortic surgeries use the cardiopulmonary bypass machine to maintain perfusion during the procedure. This technique allows for the uninterrupted flow of blood, protecting oxygen-dependent organs such as the brain. More complex procedures, such as aortic arch repair, require the complete cessation of circulation, necessitating additional safeguards to protect the brain from injury. The Institute has amassed significant experience with one such technique, termed deep hypothermic circulatory arrest (DHCA). DHCA involves cooling the patient to a core temperature of 18-19°C, packing the head with ice, and then ceasing circulation for the duration of the arch replacement procedure. Cooling the patient minimises cellular metabolism – particularly in the brain – temporarily negating the need for perfusion, yet permitting a full neurological recovery after the procedure.

Our group conducted multiple clinical studies to assess the safety of DHCA. These investigations found that DHCA is a safe and simple technique that yields excellent clinical results. An initial short-term study of nearly 400 patients found that the safe period of circulatory arrest was 30 to 45 minutes, with only 3.1% of patients suffering post-operative strokes.<sup>38</sup> Furthermore, we found no detectable difference between pre-operative and post-operative cognitive function following DHCA.<sup>39-40</sup> DHCA's preservative effects on neurocognitive ability were further illustrated by a study of 50 patients, all of whom had occupations requiring high-level cognitive capabilities. Of this group, 29 underwent aortic surgery with DHCA, while the remainder had simpler opera-

tions that did not require DHCA. Our analysis revealed that there was no significant difference in postoperative neurocognitive recovery between DHCA and non-DHCA patients (**Fig. 10**).<sup>39-41</sup> A following study (2014) involving a new cohort of 490 patients demonstrated that the safe operating period extended to 50 minutes of DHCA, with a mortality rate of only 2.4% and a stroke rate of only 1.6%.<sup>42</sup>



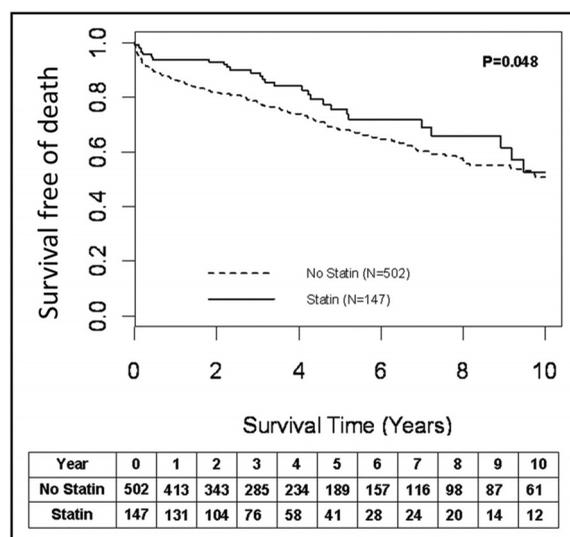
**Fig. 10:** Comparison of patients' preoperative and postoperative responses to a questionnaire found no significant difference in cognitive functions between pre- and post-DHCA, nor between DHCA and non-DHCA patients. (Reprinted with permission from Percy, A.; Widman, S.; Rizzo, J. A.; Tranquilli, M.; Elefteriades, J. A., Deep hypothermic circulatory arrest in patients with high cognitive needs: full preservation of cognitive abilities. *Ann Thorac Surg* 2009, 87 (1), 117-23.)<sup>39</sup>

In 2017, our team investigated the implications of DHCA on long-term postoperative survival. The Kaplan-Meier survival rates of 613 DHCA patients at 1, 5, and 8 years were 92.2%, 81.5%, and 68.6%, respectively.<sup>43</sup> These values are consistent with long-term survival rates of aortic surgery patients who did not undergo DHCA, demonstrating that DHCA does not seem to impart undesirable long-term consequences.<sup>43</sup>

### 11: Use of statins in preventing the progression and complications of TAAs

Medical management of aortic aneurysms has focussed on minimising shear stress on the diseased section of the aorta by controlling the patient's blood

pressure. Recent reports indicate that direct treatment of aneurysms is possible with the use of statins.<sup>25,44</sup> In addition to their use in managing lipid levels, statins have been shown to affect the activity of matrix metalloproteases (MMPs) and plasminogen activators –both of which are factors in aneurysm growth—to promote vascular repair.<sup>34,44</sup> A study conducted by the Institute investigated whether statins can slow the progression of aneurysm growth, and positively impact outcomes for patients with TAAs. The resulting data revealed that patients taking statins experienced significantly lower rates of death, dissection, and surgery, (**Fig. 11**)<sup>45</sup> suggesting that statin use may be beneficial in managing TAAs. This benefit was more prominent in the descending and thoracoabdominal aorta (where arteriosclerosis plays a role)<sup>13</sup> than in ascending TAAs.



**Fig. 11:** Kaplan-Meier survival curves for 649 patient separated by statin use, showing a statistically significant difference ( $p=0.048$ ) in survival between the groups. (Reprinted with permission from Jovin, I. S.; Duggal, M.; Ebisu, K.; Paek, H; et al., Comparison of the effect on long-term outcomes in patients with thoracic aortic aneurysms of taking versus not taking a statin drug. *Am J Cardiol* **2012**, *109* (7), 1050-4.)<sup>45</sup>

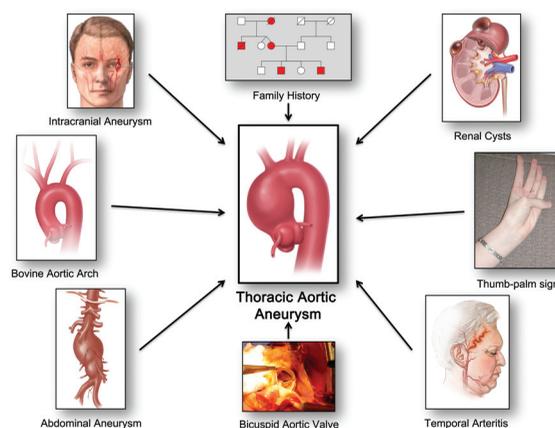
## 12: “Guilt by association” paradigm for detecting silent aortic aneurysms

Over the years of treating patients with aortic disorders, we began to notice certain that certain factors – such as the presence of a “bovine arch”<sup>15</sup> or a positive family history of aortic disease<sup>16</sup> – were

associated with a higher incidence of TAAs. Our group compiled eight such factors to devise a quick and simple list of characteristics which should raise suspicion of an asymptomatic (“silent”) aneurysm. These factors include the presence of (**Fig. 12**)<sup>46</sup>

- A family history of aortic disease (FHAD)
- A bicuspid aortic valve (BAV)
- Intracranial aneurysms (ICA)
- Aortic arch anomalies (e.g. “bovine arch”)
- Simple renal cysts (SRC)
- An abdominal aortic aneurysm (AAA)
- A positive thumb-palm sign
- Temporal arteritis

As TAAs are often completely silent (asymptomatic), they may go undetected until a lethal complication occurs (such as aortic rupture or dissection). We hope that these “guilty associates” will help both specialist and non-specialist physicians to detect patients at risk of harbouring a potential silent TAA, permitting accelerated imaging and diagnosis.



**Fig. 12:** The eight factors that compose the “guilt by association” paradigm for detecting a thoracic aortic aneurysm. (Reproduced with permission from Elefteriades, J. A.; Ziganshin, B. A., Paradigm for Detecting Silent Thoracic Aneurysm Disease. *Semin Thorac Cardiovasc Surg* **2016**, *28* (4), 776-782.)<sup>46</sup>

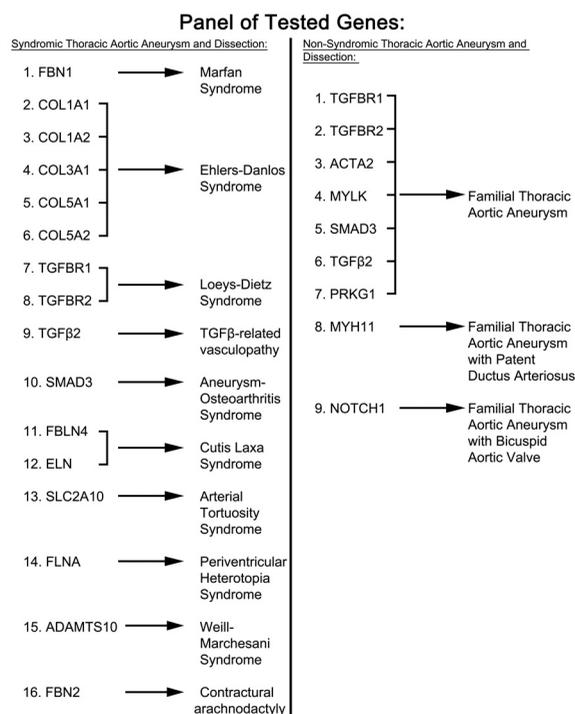
## 13: Routine genetic testing for thoracic aortic disease

Some of our most rewarding investigations strongly implicated thoracic aortic disease as a detectable, heritable disorder. Two recent studies integrated

these findings with new genetic testing methods via the introduction of Whole Exome Sequencing (WES) for thoracic aortic disease.

WES involves analysing the entire coding sequence responsible for variants producing the aneurysm phenotype instead of testing multiple narrow syndrome-specific sequences. The broad scope of WES and its ability to simultaneously test every identified mutation makes it significantly more efficient at identifying genetic aberrations than arrays of individual tests for distinct conditions. Our original study in 2015 tested 102 patients for a panel of 21 genes linked to the formation of TAAs. These genes were then separated by whether the TAAD was syndromic or non-syndromic (**Fig. 13**).<sup>47</sup> In our next paper<sup>48</sup>, we included more genes recently implicated in the formation of TAA, which now number 31.

It is our hope that as this method of testing is



**Fig. 13:** The panel of 21 genes initially identified as having a role in the formation of thoracic aortic aneurysms. (Reprinted with permission from Ziganshin, B. A.; Bailey, A. E.; Coons, C.; Dykas, D.; et al., Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting. *Ann Thorac Surg* **2015**, *100* (5), 1604-11.)<sup>47</sup>

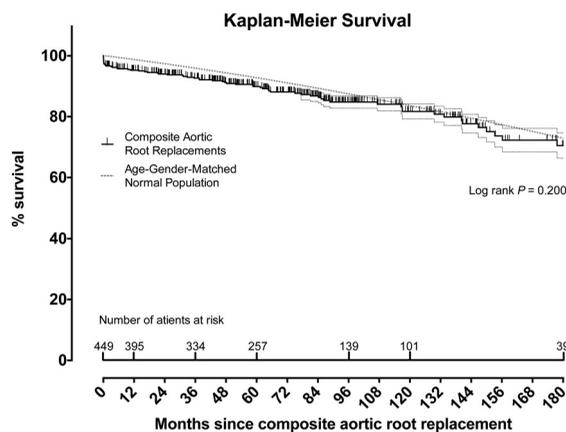
further refined and becomes more affordable, we will see widespread use of WES as a primary diagnostic tool. For patients with conditions such as Loeys-Dietz Syndrome – an aggressive condition with early onset of TAA disease and a mean death age of 26 years – WES has the potential to detect their condition even before symptoms arise, allowing for prompt and effective treatment.<sup>49</sup> WES also plays a role beyond a patient's treatment in the assessment of family members. Additionally, as new causative genes are identified, they can easily be added to the list of target genes, ensuring that the test maintains its relevance. Despite its relatively recent development, WES has already revealed many potential new avenues for the detection of thoracic aortic aneurysm disease.

#### 14: Safety and durability of current aortic surgery

Despite present surgical techniques and materials increasing the safety and durability of aortic surgery, surgical procedures still retain a risk of complications. The Institute is determined to both quantify and minimise the risk posed to patients by conducting reviews of patient outcomes, surgical techniques, and materials used. In one study, our researchers assessed the outcomes of over 500 consecutive patients who had surgery at Yale. The total perioperative mortality was approximately 3%, with 92% of descending and 96% of ascending and arch procedures free of any complications (stroke, paraplegia, or death). In younger patients, 98% of elective ascending/arch operations were complication-free. As expected, the rate of complications in emergency operations was higher.<sup>50</sup>

In a 2012 study focussing on the period from 2004 to 2012, our team found that the perioperative mortality of all patients with ascending aortic replacements with composite valved-conduit grafts was 1.4%.<sup>51</sup> Additionally, patients who underwent composite graft replacement had exceptional survival rates that did not differ significantly from that of the general population. In 2017, the Institute reassessed patient outcomes following composite graft root replacement in the

25 years between 1990 and 2015. Of the 449 original patients, 14 expired in an operative setting.<sup>52</sup> The long-term survival rates for patients younger than 60 at 5, 10, and 20 years after the procedure were 92.0%, 90.1%, and 79.8%, respectively, compared against 88.4%, 67.9%, and 42.6% for those patients aged 60 or older.<sup>52</sup> When assessed against an age- and sex-matched control population, there was no significant difference in rates of survival (**Fig. 14**).<sup>52</sup>



**Fig. 14:** Kaplan-Meier survival curve for patients who underwent aortic root and ascending aorta replacement with a composite graft (dark line). Shown with the 95% confidence intervals (light lines) and an age-gender-matched population (dotted curve). (Reproduced with permission from Mok, S. C.; Ma, W. G.; Mansour, A.; Charilaou, P.; Chou, A. S.; Peterss, S.; Tranquilli, M.; Ziganshin, B. A.; Elefteriades, J. A., Twenty-five year outcomes following composite graft aortic root replacement. *J Card Surg* 2017, 32 (2), 99-109.)<sup>52</sup>

A 2016 study showed that in elective patients, the practice of concomitant root-sparing ascending aortic resection with an aortic valve replacement (AVR) had a similar mortality rate to that of isolated aortic valve replacement procedures.<sup>53</sup> These findings justify concomitant aneurysm repair and AVR procedures in elective patients, negating the need for them to undergo later repeat surgeries.

These investigations by the Institute all show that aortic surgery has risen to a safety level equal to that of ordinary coronary artery bypass or valve replacement.

## Conclusion

The team at the Aortic Institute at Yale-New Haven Hospital and Yale University Medical School has been honoured to have the opportunity to contribute over many years to our understanding of thoracic aortic disease.

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# Applications of Nanoparticle Contrast Agents in Cardiovascular Imaging

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Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Ultrasound (US) are among the most used imaging modalities in clinical practice in terms of availability, efficiency and cost. Recent research has focused on the development of nanoparticle contrast agents, which seem to open new vistas in molecular MRI, CT and US imaging. Nanoparticle contrast agents have been used clinically in MRI and preclinically for CT and US applications.

The current unit gives an overview of the role of iron oxide nanoparticles (IONs) in cardiovascular clinical applications. IONs were first used in oncology for the imaging of liver and the detection of lymph node metastases. Nowadays, IONs have expanded their use in cardiovascular field. Several studies have demonstrated that USPIOs can be successfully used in the detection of atherosclerotic plaque, abdominal aortic aneurysm and myocardial infarction.

According to the literature, ultrasmall supermagnetic iron oxide nanoparticles (USPIOs) have been used to image atherosclerotic plaque, infarcted myocardium and inflammations involved in the development of abdominal aortic aneurysms.

USPIOs are more suitable for molecular imaging than SPIOs due to their longer circulation time. The prolonged blood pool circulation time of USPIOs increases the probability for macrophages in inflammation areas to capture and phagocytize the nanoparticles (Corot *et al* 2006).

## 1. CLINICAL APPLICATIONS IN MRI

In clinical practice, IONs were initially used in oncology for the diagnosis of lymph node metastases in prostate, pelvis, head and neck cancer as well for liver imaging. Several studies have shown that IONs offer higher diagnostic precision, sensitivity and specificity for the detection of primary tumors or metastases in relation to unenhanced MRI (Will *et al* 2005, Feldman *et al* 2008). In cardiovascular imaging the role of ION-enhanced MRI has not yet been fully established but is gaining increased acceptance because of the expanded utility of molecular imaging.

### 1.1 Atherosclerotic plaque imaging

Atherosclerosis is a chronic inflammatory disease affecting large and medium sized arteries (Ross *et al* 1995). Since inflammation is accompanied by macrophage activity, USPIOs are accumulated in the macrophages present in atherosclerotic plaques and cause a strong signal reduction in T2/T2\*-weighted sequences.

Several studies have investigated the USPIOs accumulation in atherosclerotic plaque and more specific the role of nanoparticles in the detection of carotid atheromatous plaque. All the results demonstrated that USPIO particles were captured by cells of mononuclear phagocyte system (MPS) within the carotid atheroma causing a significant signal intensity loss on T2\* GRE images. The areas of USPIO accumulation were also verified by histology analysis and electron microscopy.

The maximum post-contrast reduction in mean signal intensity was observed on T2\*-weighted sequence between 24 and 48 hr after USPIO injection. This observation is very useful as it defined an optimal-time window for post-USPIO infusion imaging.

Tang *et al.* evaluated the contralateral sides of symptomatic patients with carotid stenosis in an USPIO-based study (Tang *et al* 2006). The results revealed that all symptomatic carotid stenoses had inflammation while 95% of the patients showed bilateral USPIO uptake suggesting additionally inflammatory activity in the contralateral side. This study supports the assumption that inflammatory atheroma is a systematic disease and that one symptomatic inflammatory vessel is more likely to increase the probability of another vessel to be or become inflammatory (Tang *et al* 2007, Tang *et al* 2008). In this way, an inflammatory area may constitute a prognostic risk factor for inflammation in another territory.

### 1.2 Abdominal Aortic Aneurysm Imaging

Abdominal Aortic Aneurysm (AAA) is characterized by inflammation, neovascularization and extracellular matrix degradation. The inflammation is predominantly localized to the media and adventitia and contributes to the weakening of the vessel wall (Ailawadi *et al* 2003). As iron oxide

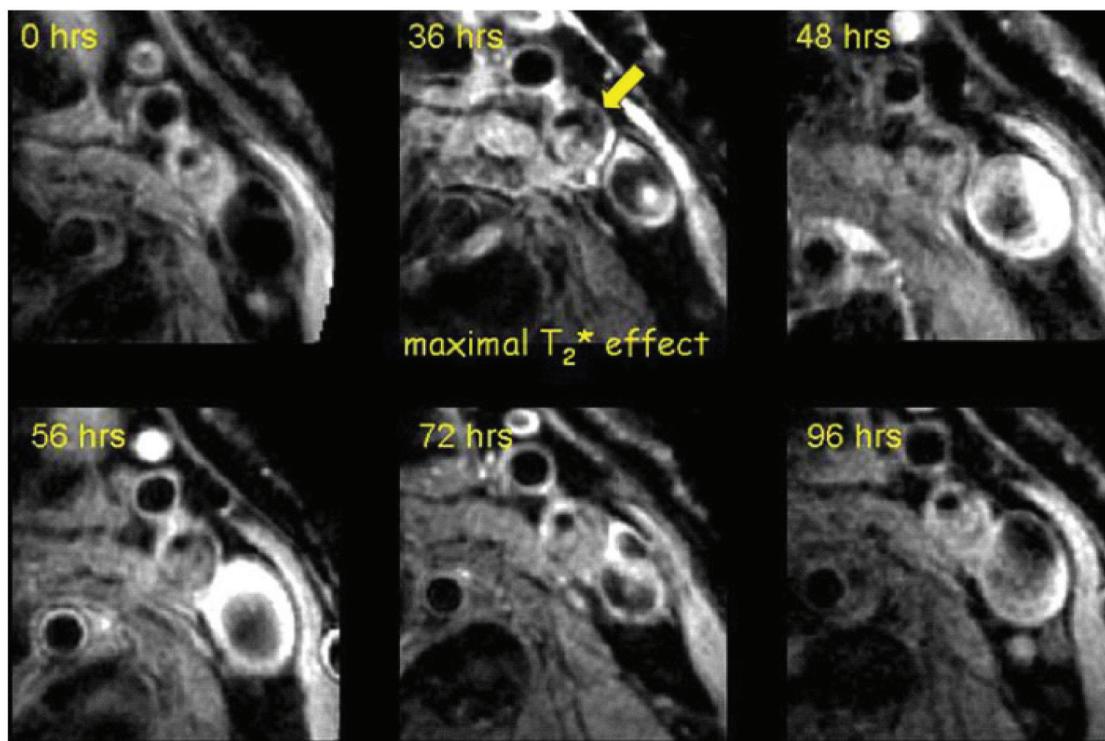


Figure 1. T2\*-weighted images through the same level of the internal carotid artery of a patient before infusion, at 36, 48, 56, 72 and 96 hr after infusion of USPIOs (Tang *et al* 2009)

nanoparticles are accumulated at sites of cellular inflammations (monocytes/macrophages), imaging inflammatory activity within aneurysms using USPIO-enhanced MRI is potentially feasible.

Recent studies (Richard *et al* 2011, Sadat *et al* 2011) evaluated the use of USPIOs in patients with AAAs. Patients with AAA underwent cardiac MRI before and after the administration of USPIO nanoparticles. USPIO accumulation resulted in a significant signal reduction on T2\*-weighted images within the wall of AAA.

The studies demonstrated that MRI combined with USPIO can successfully detect and quantify inflammation in AAA. Furthermore, USPIO uptake was associated with the AAA expansion. This last observation is an interesting clinical finding as the growth rate in AAA is a predictor of the potential risk of rupture and therefore sets the indications for surgical repair.

Color maps of patients with (a) no, (b) dif-

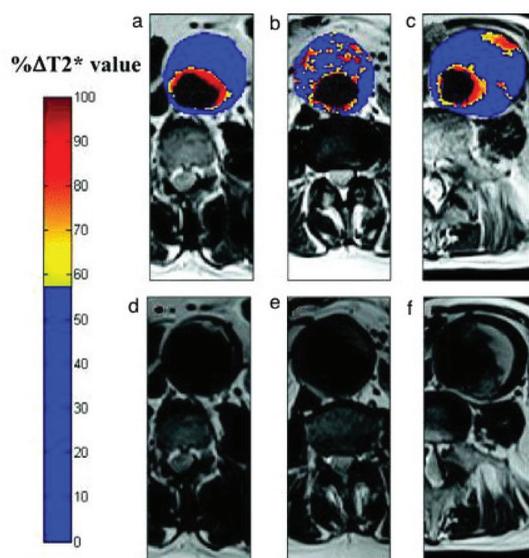


Figure 2. Anatomical images and color maps of three patients with AAA (Richard *et al* 2011)

fuse, and (c) distinct USPIO uptake within the aortic wall.

### 1.3 Myocardial Infarction Imaging

Myocardial infarction (MI) is characterized by a loss of cardiomyocytes (necrosis) caused by prolonged ischemia. Myocardial necrosis evokes an inflammation reaction, typically within 1 to 3 days

after MI. The inflammation process is followed by a wave of macrophages that remove necrotic cells and allow remodeling of the infarcted region representing an important mechanism for infarct wound healing and scar formation. However, excessive or chronic post-infarction inflammation response results in adverse myocardial remodeling and infarcted expansion (Nahrendorf *et al* 2010, Frangiannis *et al* 2012).

Recent studies test the T2\*-weighted imaging in combination with (U)SPIO contrast agents for the detection of post-inflammations in MI. The group of Yilmaz (Yilmaz *et al* 2013) sought to evaluate the diagnostic value of USPIOs for in vivo imaging of macrophages in the myocardial infarcted zone. Patients who had an acute ST-evaluation or non ST-evaluation MI underwent a standard pre- and post- USPIO CMR scan. The results showed a 64% and 44% reduction in T2\* values in the infarct and peri-infarct zone, respectively, confirming the accumulation of USPIO in inflammation areas. The study raised additional significant clinical findings:

i) The optimal time window for USPIO-enhanced MRI after MI was determined 48 hr after the administration of nanoparticles

ii) Except from the T2\* signal drop within the infarcted and peri-infarcted tissue, a considerable reduction (44%) was observed in the non-infarcted remote myocardium.

This last observation suggests that macrophages extend beyond the area at risk, which is in accordance with findings from a previous similar clinical study by Alam *et al* (Alam *et al* 2012). As expected, R2\* values are increased in organs of RES (liver, spleen).

## 2. CLINICAL APPLICATIONS IN CT

Several preclinical studies have shown that nanoparticle contrast agents can be safely used for the detection of cancer and for the imaging of cardiovascular diseases using CT. The breakthrough of nanoparticle contrast agents is that they can enable CT molecular imaging, which is not feasible with the conventional contrast agents (Popovtzer *et al* 2008).

Inflammation, associated with increased mac-

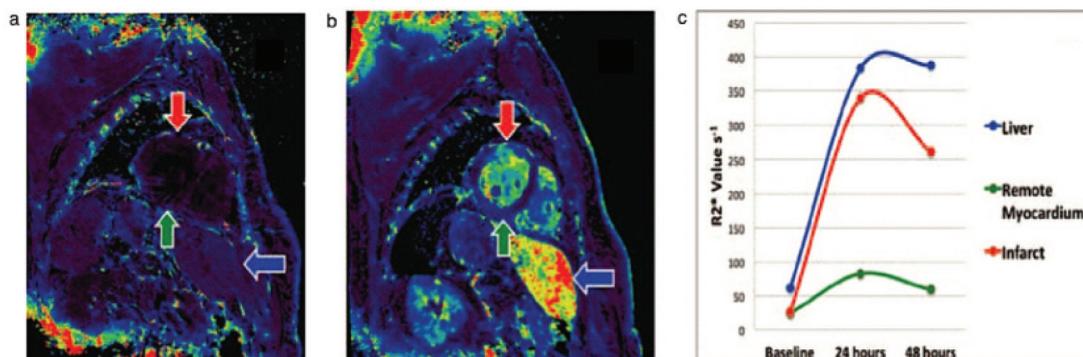


Figure 3.  $R2^*$  color maps and changes in  $R2^*$  value in patients who received USPIO (Yilmaz *et al* 2013)

rophage activity, is now considered an important contributing factor in pathogenesis of cardiovascular diseases. It is now well known that inflammation plays an important role in the formation and progression of atherosclerosis and is considered a risk factor for plaque rupture. GNPs are accumulated by macrophages. Cormode *et al* (Cormode *et al* 2010) demonstrated that GNPs in combination with spectral CT imaging can be used for the characterization of macrophage burden, calcification and stenosis of atherosclerotic plaque.

### Safety and Toxicity

Size, shape, chemical composition and surface coating are key factors in the toxicological profile of nanoparticle-based contrast agents. At present, there is a limited number of *in vivo* toxicity studies which mainly concern the gold nanoparticles.

Zhang *et al* (Zhang *et al* 2011) showed that GNPs between 10nm and 60nm are not sufficiently safe while GNPs with size between 5 and 30nm sized have relatively low toxicity. The influence of dose on toxicity has also been investigated. Lasagna *et al* (Lasagna-Reeves *et al* 2010) studied the biodistribution, accumulation and toxicity of GNPs after repeated administration in mice via animal behavior, tissue morphology, serum biochemistry, hematological analysis and histopathological examination. The results revealed that nanoparticles accumulation in tissues depend on the administered doses but did not produce mortality, renal damage or any other indication of toxicity.

### 3. CLINICAL APPLICATIONS IN US IMAGING

The nanoparticle contrast agents in ultrasound are mainly applied in tumor imaging and cardiovascular medicine. Targeted nanoparticles are suited to detect biomarkers that involved mainly in the process of angiogenesis which is a physiological process in wound healing, in the transition of a tumor to malignant one and its growth progress, in inflammation, and in atherosclerosis (Tran *et al* 2007). Another application of nanoscale US contrast agents is for liver imaging (Liu *et al* 2006).

A lot of research has been conducted concerning the development of nanoparticle ultrasound contrast agents in imaging key event in cardiovascular medicine such as atherosclerosis, post-ischemic inflammation, angiogenesis, transplant rejection and thrombus formation.

In particular, the development of contrast agents that enhance the detection of blood clots that are associated with stroke, myocardial infarction, and deep vein thrombosis was out of investigation until the time that Lanza and his colleagues utilized fibrin-targeted nanoparticles. They first reported a fibrin-targeted PFC emulsion nanoparticle to target arterial thrombi concluded that the developed system markedly enhanced the acoustic reflectivity of clots and dramatically increased the sensitivity of thrombosis diagnosis (Lanza *et al* 1996). In another study, the same research team produced a PFC acoustic agent that enhanced contrast from smaller thrombi at higher frequencies associated with intravascular ultrasound (Lanza *et al* 1997).

*Marsh et al* developed a fibrin-specific liquid perfluorocarbon nanoparticle in order to evaluate the effectiveness for targeted thrombolysis in vitro. They found that nanoparticles bound to the clot significantly increased the acoustic contrast of the targeted clot surface, permitting volumetric estimates (*Marsh et al 2007*).

### **Clearance - Toxicity**

Nanoscale ultrasound agents have favorable pharmacokinetics as their circulation half-time can be extended over several days. Their clearance depends on various factors such their size (clearance increases in direct proportion to the size), the presence of surface charge (in the case of liposomes), the administered dose (high doses decelerate the clearance mainly due to saturation of the mononuclear phagocyte system uptake) and their composition. Apart from these factors, particular lipids can be used for decreasing the clearance times (*Banerjee 2001*).

Despite the promising results of nanoparticles in ultrasound imaging, a major difficulty in their use as contrast agents is the high toxicity profiles. Their key difficulty is that many of them are not excreted quickly via the urine, as in the case of small-molecule contrast agents, but accumulate in the liver instead resulting in severe hepatotox-

icity as shown various animal studies (*Pan et al 2012*). Moreover, the in-vitro toxicity tests differ from one laboratory to another as there are no specific guidelines for nanomaterials and, additionally, in-vitro analysis may not be valid in vivo (*Hahn et al 2011*). Either way, a lot of research must be conducted in that field, as well.

### **Current status and future perspectives**

Currently the use of nanoparticles in ultrasound is not confined to the improvement of imaging instead up-to-date biomedical research is mainly focused on their use as both contrast agents and drug carriers for imaging and therapy at the same time. Many studies are currently working on the fabrication such theranostic ultrasound nanoagents with promising results (*Son et al 2014*).

Another popular approach is to combine two or more contrast agents into a single nanoparticle, which can be imaged by different modalities (multimodal imaging). For example, ultrasound is used in conjunction with photoacoustic or magnetic resonance imaging modalities to further characterize malignancies (*Tran et al 2007*). The fact that enables better visualization and treatment of the target with reduced contrast agent doses however, multimodal imaging may cause interferences between the two modalities (*Hahn et al 2011*).

### SYNOPSIS

- In clinical applications, (U)SPIOs recently, are used in cardiovascular imaging for the detection of atherosclerotic plaque, AAA and myocardial infarction.
- As atherosclerosis is a chronic inflammatory disease, USPIOs particles are captured by macrophages within the atheromatic plaque and therefore they can be used to image atherosclerosis.
- USPIO-enhanced MRI can be used to image inflammatory activity within AAA. The USPIO uptake is associated with the AAA growth rate.
- USPIOs allow the accurate visualization and detection of both the myocardial infarcted and peri-infarcted zone.
- CT nanoparticle contrast agents have been used in several preclinical studies for the detection of cancer (liver imaging, head and neck cancer, tumor microvasculature) and the imaging of atherosclerotic plaque.
- Targeted nanoparticles are suited to detect biomarkers that involved mainly in the process of angiogenesis, which is a physiological process in wound healing, in the transition of a tumor to malignant one and its growth progress, in inflammation, and in atherosclerosis.
- Active research is currently conducted in the field of theranostics and multimodal imaging.

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*Geroulanos Stefanos*

***PTOLEMY EVERGETES OR CACERGETES***  
*(Ptolemy benefactor or malefactor)*

The poet recited his poem that had to do  
with the feelings generated in Greece  
by Agesilaos' campaign.

Ptolemy the Bladder, obese, slothful  
and somnolent on account of gluttony,  
made the following remark: 'Wise poet  
your lines are somewhat exaggerated.  
And what has been said of the Greeks is historically inaccurate.'  
'Illustrious Ptolemy, these are trivialities'.

'Trivialities, how? You state explicitly  
*The pride of the Greeks ...the pure love  
for their country has been aroused...The impetuous  
heroic urge of the Greeks has been displayed.*

'Illustrious Ptolemy, those Greeks  
are the Greeks devoted to Art, given to allusion,  
and bound to feel the way I do.'

Ptolemy was shocked and pronounced  
'The Alexandrians are incurably flippant.'

The poet: 'Illustrious Ptolemy  
among the Alexandrians you are the First'.

'Up to a point', said Ptolemy softly, 'up to a point.  
I am also a full-blooded Macedonian by descend.—  
Ah, wise poet, that great Macedonian race,  
full of vigor and sagacity.'

And for obesity heavy as a stone,  
and for obesity somnolent,  
the full-blooded Macedonian  
could hardly keep his eyes open.

*Translated by E. Sachperoglou*

*Geroulanos Stefanos*

# “PICKWICK” OR “PTOLEMY” SYNDROME??

## Antedating by Historically Accurate Precursor Literary Descriptions

*Stefanos Geroulanos MD, PhD*

*...and from the heavy sluggishness and often lying down,  
considering a major problem the shortest walk,  
heavy from his obesity,  
and somnolent from gluttony and drinking,  
the full-blooded Macedonian  
could hardly keep his eyes open.<sup>1</sup>*

*(C. P. Cavafy: Ptolemy Evergetes or Cacergetes, first attempt)*

### Dedication

The paper is dedicated to Dino Anagnostopoulos, classmate, colleague, and lifelong friend. A human being the like of whom there can never be too many and of whom nature guarantees that there will always be too few; a jackpot of the genes, with only one exception!...

### Introduction

The reason for this exercise is the unfinished poem of C. P. Cavafy “Ptolemy Evergetes or Cacergetes” (see left page), written in 1922 and published by Renata Lavagnini in 1989, that drew our attention to the historical antedating of the medical literature descriptions of the Pickwickian Syndrome, long before its first medical description in 1956.

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*1....Κι απ' την πολλή νοθρότητα και τον πολύ τον ζαπλωμό, / θεωρώντας πρόβλημα δεινόν το πιο μικρό περπάτημα, / κι απ' την πολυσαρκίαν βαρύτατος, / κι απ' την πολυφαγίαν και πολυποσίαν υπναλέος, / ο Μακεδών ο ακραιφνέστατος / μόλις κρατούσεν ανοικτά τα μάτια του. (Κ. Π. Καβάφης, Πτολεμαίος Ενεργέτης ή Κακεργέτης πρώτη γραφή ποιήματος, Lavagnini R. 1994).*

## Obstructive Sleep Apnea Syndrome

*Pickwick Syndrome* is the well accepted “medical nick-name” for the *Obstructive Sleep Apnea Syndrome* that is characterized by morbid obesity, chronic severe snoring and multiple episodes of apnea during sleep, sleep disruption, excessive arousals, uncontrolled daytime somnolence and alveolar hypoventilation followed by recurrent nocturnal episodes of hypoxemia and hypercapnia. In the advanced stage it is often associated with pulmonary hypertension and right ventricular hypertrophy, polycythaemia and cyanosis. Patients are characterized by bulimia and voluptuousness (Kriaras et al, 2005).

The symptoms of the Syndrome were described for the first time by J. Elliot in 1781 and in 1819 by W. Wadd. The nick-name *Pickwick Syndrome* was given in 1956 by S. C. Burwell and co-workers after Charles Dickens book *The Posthumous Papers of the Pickwick Club* (1836). Dickens describes in this book a very fat boy, Joe, who suffered from abnormal somnolence (see Annex 1). The familiar incidence of the syndrome was described only in 1992 by S. Redline and co-workers. However laymen like Poseidonios (135-40 BC), Plutarch (40-120 AD), Athenaeos (2/3 c. AD), Ch. Dickens (1836), C. Paparrhegopoulos (1860/74), Bouché-Leclercq (1903/7) and C.P. Cavafy (1922) were their historical precursors.

### Literal Precursors

On February 1922 the Greek poet *Constantine P. Cavafy* (1863-1933), well known through his poem “*Ithaka*”, wrote a poem entitled: “*Ptolemy Evergetes or Cacergetes*” (Ptolemy benefactor or malefactor). The poem stayed unfinished; it was published after his death by Renata Lavagnini in 1994. For this poem Cavafy prepared two additional verses to be added, showing how exact he

wanted to describe the Syndrome of Ptolemy VIII (182/1-117 B.C.) King of Egypt (170-166 & 146-117 B.C.). Unfortunately they were not included:

*“Ptolemy felt sleepy, however the thunder strong voice of the poet succeeded to keep him awake”.*<sup>2</sup>

In the 8 verses of the first version of the poem Cavafy incorporates the knowledge of the Ancient Greek authors Plutarchos (40-120 AD) in his *Moralia* 60B and Athenaeos (2<sup>nd</sup>-3<sup>rd</sup> c. AD) in his *Deipnosophistae* XII 549-50. Both texts are included in Bouche-Leclercq’s book on the Ptolemies (Les Lagides) and in Paparrhegopoulos History of the Hellenic Nation that Cavafy possessed in his library.

The poem is set in the second reign of Ptolemy VIII, Evergetes II, King of Egypt between 170-166 and 146-117 B.C. but refers to the campaign by King Argesilaos of Sparta against the Persians in 296 B.C.

Although Cavafy could cite the whole Plutarch texts by heart the source of the poem is according to Lavagnini probably Bouché-Leclercq, *Lagides II*, who writes exhaustively of “Cacergetes” faults. He in his turn draws on Athenaeos XII 549, who says: “*Like him was also the seventh [now 8<sup>th</sup>] Ptolemy who ruled over Egypt, the king who proclaimed himself Benefactor, to be sure, but who received from the Alexandrians the name Malefactor. The Stoic Poseidonios, at least, who travelled with Scipio Africanus when he was invited to Alexandria and saw Ptolemy, writes in the seventh book of his Histories: ‘Through indulgence in luxury his body had become utterly corrupted with fat and with a belly of such size that it would have been hard to measure it with one’s arms; to cover it he wore a long tunic (a celebria) which reached to his feet and which had sleeves reaching to his wrists: but he never went abroad on*

2. *Κι απ’ την πολλή νωθρότητα και τον πολύ τον ξαπλωμό, / θεωρώντας πρόβλημα δεινόν το πιο μικρό περπάτημα, / κι απ’ την πολυσαρκίαν βαρύτατος, / κι απ’ την πολυφαγίαν και πολυποσίαν υπναλέος, / ο Μακεδών ο ακραιφνέστατος / μόλις κρατούσεν ανοικτά τα μάτια του. (Κ. Π. Καβάφης, Πτολεμαίος Ευεργέτης ή Κακεργέτης πρώτη γραφή ποιήματος, Lavagnini R. 1994).*

*foot except on Scipio's account' ”*. According to R. Lavagnini, other sources that influenced Cavafy are Plutarch, *Moralia 60 B*, and for Agesilaus, Plutarch, *Life of Argesilaus VI, 5-6*, as also Paparrhegopoulos, *History of the Hellenic Nation A, 74B*.

## Ptolemy VIII Evergetes II, Physkon

Ptolemy VIII Evergetes II or Physkon (=Pot belly) or Cacergetes, King of Egypt (170-166 and 146-117 B.C.) was the son of king Ptolemy V Epiphanes (210-181 B.C.) and Cleopatra I of Syria. He was the younger brother of Ptolemy VI Philometor (186-146 B.C.). Ptolemy VIII was born ca 182/1 B.C.; he came to power when his brother Ptolemy VI Philometor was arrested in 170 B.C. by the Syrian king Antiochus IV Epiphanes (175-164) and was held captive for four years. When Ptolemy VI returned from captivity, and on the order of the Roman envoy Popilius Laena, Libya, Cyrenaica and Cyprus were given to Ptolemy VIII. In 146 B.C. when his brother was mortally wounded outside Antioch, Ptolemy VIII came with an army from Cyprus and forced his sister Cleopatra II Tryphaena, who was also his brother's widow, to marry him. He was declared co-regnant to his nephew Ptolemy VII Eupator, whom he murdered one year later. In 142 B.C. he married his niece, Cleopatra III, without divorcing her mother, Cleopatra II. Hated because of his wickedness and brutality, he was forced to flee to Cyprus. However, thanks to the skill of his minister Hegelochos, he managed to return from there to Egypt in 131 B.C. and to reign until his death in 117 B.C. He was succeeded by his second wife Cleopatra III Cocce, at first with his son Ptolemy IX Soter II.

Next to the eponym he gave himself, Evergetes (Benefactor) the Alexandrians, well known for their malicious humor, called him Cacergetes (Malefactor) or Physkon, which means pot-bel-

lied or bladder, because of his obesity. This was accompanied by drowsiness and, as Cavafy says: *like his father he could hardly keep his eyes open*; Bouche-Leclercq writes of Ptolemy's VIII father Ptolemy V that he even dozed off in public audience; showing that the Ancient Greeks were aware of the heredity of the Syndrome. But was Ptolemy VIII the only one? Let us see what we can summarize from the antique sources:

## Pickwick Syndrome in the Royal Ptolemaic Dynasty

Ptolemy I Soter (367-285 B.C.) general of Alexander the Great and one of his best friends, ruled Egypt after the death of Alexander, initially as a satrap and later in 305 as a king. While ruling Egypt he entrusted his stepson Magas I to rule Cyrene (305-285 B.C.). He was a tall and very strong man with a protruding chin, long arms and big hands that some people think he could have suffered from an acromegaly. He was definitively not obese.

Magas I of Cyrene (325-250 B.C.) is up to now the first member of the Ptolemaic family known to have suffered from morbid obesity and excessive daytime somnolence. His mother Berenice was the second wife of Ptolemy I; his father a certain Philipp. Magas I was appointed by his step-father Ptolemy I, co-regnant of Cyrene. He declared himself later independent and died in 250 B.C. due to his obesity. Athenaeos characteristically reported: “He was so obese that he suffocated in his own fat”.<sup>3</sup>

Berenice I, mother of Magas I, and her third husband Ptolemy I had between them four children, two of whom were obese; Arsinoe II and Ptolemy II (285-246 B.C.). However no morbid obesity is reported. Ptolemy II and Arsinoe married each other, in a second / third marriage; they were well

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3. Αγαθαρχίδης δ' εν τη εκκαιδεκάτη Ευρωπιακών, Μάγαν φησί τον Κυρήνης βασιλεύσαντα έτη πενήκοντα απολέμητον γενόμενον και τρυφώντα κατάσαρκον γενέσθαι εκτόπως τοις όγκοις κατά τον έσχατον καιρόν και υπό του πάχους αποπνιγήναι δι' αργίαν σώματος και τω προσφέρεσθαι πλήθος τροφής. (Agatharchides as by Athenaeus, *Deipnosophistes XII, 74, Kaktos vol 12, p.190*).

known as *philadelphoi*. Following the tradition of the Pharaohs they initiated the intermarriages in the Ptolemaic dynasty, something, despite Zeus and Hera, not very common to the Greeks. Ptolemy II died at the age of 62 years; he had health problems all his life through and disliked physical exertion. About the other two children history stays unfortunately silent.

Ptolemy III Evergetes (246-221 B.C.) was the son of Ptolemy II and Arsinoe I, and was later adopted by the second wife of his father Arsinoe II; he was a strong man, active and energetic and lived until the age of 63. He was not obese nor suffered from somnolence. However he married his 4<sup>th</sup> degree cousin Berenice II daughter of Magas I. There are no reports on her suffering from obesity or daytime somnolence. The only information about her posture comes from a wine pot (*oinochoe*) exhibited in the museum of Antalya (Turkey). Here she is depicted offering to the altar of her deified parents-in-law; she looks slightly obese, with fatty cheeks and marked steatopygia. Her uncovered arms seem to be well nourished.

Ptolemy IV Philopator (221-204 B.C.), son of Ptolemy III and Berenice II succeeded his father and married his full-sister Arsinoe III. He was extremely licentious, obese with fleshy cheeks and double chin. He languished in habitual lethargy.

Ptolemy V Epiphanes (204-180 B.C.), son of Ptolemy IV and his sister Arsinoe III, was extremely obese. He used to fall asleep during social and political events. Athenaeos characteristically reports: “*One day, Aristomenes, his Prime Minister and chief advisor, had the effrontery to nudge the king awake when he had dozed off during a diplomatic reception*”. He married Cleopatra I Syra, daughter of Antiochus III the Great from Syria. This matrimony represents an important step, as it is the first time that foreign blood entered into the unalloyed Macedonian dynasty of Egypt. Ptolemy V died young at the age of twenty-eight. The cause of death is not known but, his morbid obesity obviously, at least in part, contributed to it.

Ptolemy V and Cleopatra I had three children who shared the kingship: Ptolemy VI Philometor (180-170 & 166-146 B.C.), Cleopatra II, “*the Sister*”, and Ptolemy VIII Evergetes II (*Cacergetes or Physcon*).

The historian Polybios reports that Ptolemy VI, although good and kind, was apt to be lethargic and inert, while Justinus adds that he was extremely obese and sluggish.

The younger brother Ptolemy VIII, Evergetes ruled Egypt in 170-166 and 146-116 B.C. As mentioned above the Alexandrians had named him Malefactor and because of his huge belly, Pot-belly or Bladder. He was abnormally obese and somnolent. His belly size was so large that its circumference was wider than two arms extended. In order to cover his belly, he wore a long tunic that extended to his ankles, with sleeves down to his wrists, today’s *kelembia*. Due to his obesity he was unable to walk apart from a single time when he forced himself in order to meet the Roman consul Scipio the African.

Ptolemy VIII, Evergetes, left the throne to his second wife-niece Cleopatra III who reigned jointly with her two sons: Ptolemy IX, nicknamed Lathyros (116-80 B.C.) and Ptolemy X, Alexander I, the “Intruder” (107-88 B.C.).

Ptolemy X Alexander I was so extremely obese, that he needed a man on either side to help him to walk.

So altogether over five generations at least six male members of the royal Ptolemaic family e.g. Magas I king of Cyrene, and Ptolemy IV, V, VI, VIII and X had a severe, probably morbid, obesity with somnolence; a “Pickwick Syndrome”. Ptolemy II and his sister and second wife Arsinoe II the Philadelpoi were only obese. It seems that they did not suffer from the same syndrome.

### The Flow of the Genes

The gene was probably introduced by Magas I king of Cyrene and transmitted into the Ptolemies through his daughter Berenice II.

In case that Ptolemy II suffered from the same syndrome, then the gene might have entered

through Magas' mother Berenice I, as two of her children with her third husband Ptolemy I Soter were obese. This part of the family tree should be better investigated. The investigation should include also the grandfather of Magas I, who carries the same name Magas and his grandmother Antigone, niece of Antigonos or Antipatros. We might be able to follow the gene further back.

The gene could have passed to the next generation either from the father Ptolemy IV, the mother Arsinoe III or both. Arsinoe was Ptolemy's youngest sister.

In the third generation, the mother Cleopatra I descended from the Seleucid family; she was not a gene carrier. In this generation the gene passed from Ptolemy V to the two Ptolemies VI and VIII by their father.

In the case of Ptolemy IX and X sons of Ptolemy VIII and his niece Cleopatra III the gene could have passed from both sides to the children.

### Additional Report by Athenaeos

In addition to the Royal Ptolemaic Family, Athenaeos reports also on the king Dionyssios of Herakleia Pontica in the Black Sea, who suffered from the same disease. He ruled his kingdom (347-305 B.C.) successfully despite his voluptuousness, bulimia and morbid obesity. Athenaeos writes char-

acteristically: *“His doctors ordered fine and long needles, so as to insert them into his chest and belly when he fell deeply asleep. However, the needles did not provoke any pain because of his fatness. He awoke only when the needles were touching parts of his body free of fat. Dionyssios was always standing behind a big trunk, (today's podium), in order to hide his body when he talked with an audience at any social or political event, leaving only his head to be seen over the trunk”* (Claudius Aurelianus, Kryger M.H., 1983).

### Conclusion

In conclusion at least six members of the Hellenistic Royal Ptolemaic Family of Egypt (305-30 B.C.) over five generations suffered from excessive obesity and severe somnolence; a typical “Pickwick Syndrome” or today's “Obstructive Sleep Apnea Syndrome”.

Athenaeos of Naucratis in his book *Deipnosophistae* (ca 200 AD) has to be credited for this report, which is the first description of the syndrome and its familiar incidence. An additional, however unrelated, case of king Dionyssios of Herakleia Pontica suffering from the same disease is also described by the same author. Following today's “western” rules the Syndrome should carry his name “Athenaeos Syndrome”!

Alternatively the Syndrome should be called “Ptolemy Syndrome”.

## Annex 1

### Dickens Charles: The fat boy Joe

*...They had no sooner arrived at this point, than most violent and startling knocking was heard at the door; it was not an ordinary double knock, but a constant and uninterrupted succession of the loudest single raps, as if the knocker were endowed with the perpetual motion, or the person outside had forgotten to leave off.*

*"Dear me, what's that" exclaimed Perker, starting.*

*"I think it is a knock at the door," said Mr Pickwick, as if there could be the smallest doubt of the fact! The knocker made a more energetic reply than words could have yielded, for it continued to hammer with surprising force and noise, without a moment's cessation.*

*"Dear me!" said Perker, ringing his bell, "we shall alarm the Inn. -Mr Lowten, don't you hear a knock?"*

*"I'll answer the door in one moment, Sir," replied the clerk.*

*The knocker appeared to hear the response, and to assert that it was quit impossible he could wait so long. It made stupendous uproar.*

*"It's quite dreadful," said Mr. Pickwick, stopping his ears.*

*"Make haste, Mr Lowten," Perker called out, "we shall have the panels beaten in".*

*Mr Lowten, who was washing his hands in a dark closet, tarried to the door, and turning the handle, beheld the appearance which is described in the next chapter.*



*Charles Dickens (1812-1870): The Pickwick Papers (1<sup>st</sup> edition 1836-7), Penguin English Library, London 2012, pp. 887-890*

**Chapter Fifty-Three**

*The object that presented itself to the eyes of the astonished clerk was a boy - a wonderfully fat boy - habited as a serving lad, standing upright on the mat, with his eyes closed as if in sleep. He had never seen such a fat boy in or out of a travelling caravan; and this, coupled with the utter calmness and repose or his appearance, so very different from what was reasonably to have been expected of the inflicter of such knocks, smote him with wonder.*

*“What’s the matter?” enquired the clerk.*

*The extraordinary boy replied not a word, but he nodded once, and seemed, to the clerk’s imagination, to snore feebly.*

*“Where do you come from?” enquired the clerk.*

*The boy made no sign. He breathed heavily, but in all other respects was motionless.*

*The clerk repeated the question thrice, and receiving no answer, prepared to shut the door, when the boy suddenly opened his eyes, winked several times, sneezed once, and raised his hand as if to repeat the knocking. Finding the door open he stared about him with great astonishment, and at length fixed his eyes on Mr Lowten’s face.*

*“What the devil do you knock in that way for?” enquired the clerk angrily.*

*“What way” said the boy in a slow, sleepy voice.*

*“Why, like forty hackney coachmen” replied the clerk.*

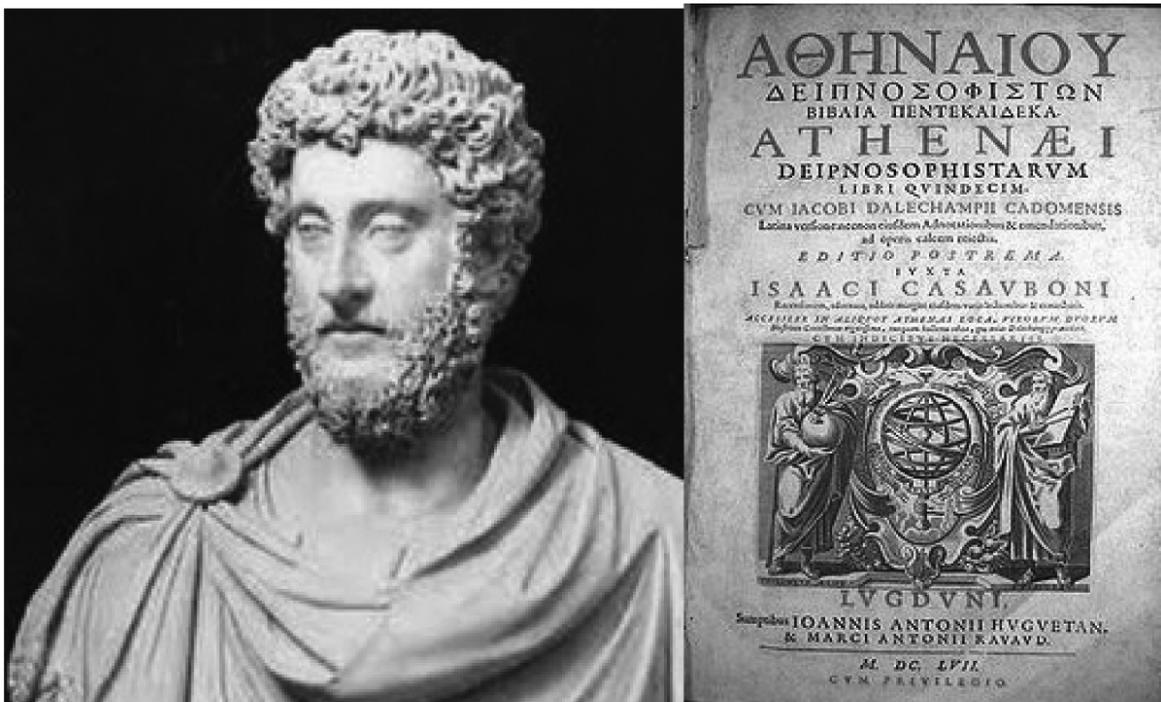
*“Because master said I wasn’t to leave off knocking till they opened the door, for fear I should go to sleep,” said the boy.*

*“Well,” said the clerk, “what message have you brought?”*

*“He’s down stairs,” rejoined the boy.*

*“Who?”*

*“Master. He wants to know whether you’re at home.”...*



Bust of Athenaeos (2<sup>nd</sup>/3<sup>rd</sup> c. AD), and early printing of his book Deipnosophistae.



Bust and gold coin of Ptolemy I Soter, the bust is in the Louvre Museum.



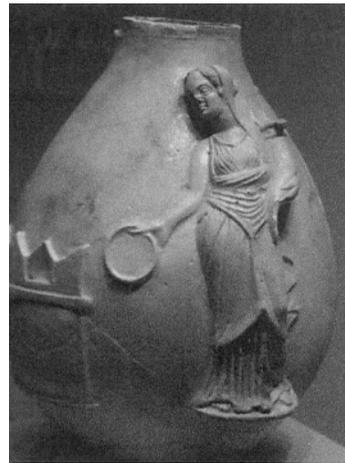
Ptolemy II & Arsinoe II Philadelphoi on a gold octadrachm.



Magas I of Cyrene on a silver tetradrachm.



Ptolemy III Evergetes on a gold octadrachm.



Berenice II, Queen of Egypt, daughter of Magas I of Cyrene, wife of Ptolemy III, Evergetis, on an oinochoe with Berenike II offering at the altar of her parents in law and on a gold octadrachm; note the steatopygia.



Ptolemy IV, Philopator son of Ptolemy III on a gold octadrachm.



Arsinoe III, Thea Philopator, daughter of Ptolemy III, and wife of Ptolemy IV, Philopator, Queen of Egypt on a gold octadrachm.



Ptolemy V, Epiphanes, son of Ptolemy IV on a silver tetradrachm.



Cleopatra I, Syra, daughter of Antiochos III, wife of Ptolemy V, Epiphanes, Queen of Egypt on a bronze coin.



Ptolemy VI, Philometor, son of Ptolemy V on a silver tetradrachm.



Ptolemy VIII, Evergetes II, Physcon on a gold octadrachm and statue of him.



Bronze coin of Cleopatra III, Kokke, daughter of Ptolemy VI, wife of Ptolemy VIII, Queen of Egypt, on a bronze coin.



Ptolemy IX, Soter II, Lathyros on a silver tetradrachm.



Ptolemy X, Alexander II, Pareisaktos on a silver tetradrachm.

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# Primary Anticholinergic-Responsive Pisa Syndrome

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Pisa syndrome is a form of dystonia characterized by truncal rotation and lateral flexion and was first described in 1972 by Ekbom and Lindholm.<sup>1</sup> It occurs almost exclusively in the context of chronic neuroleptic therapy rather than acute Neuroleptic-induced dystonic reaction after therapy initiation.<sup>2,3</sup> It has also been described, although less frequently, in the context of Alzheimer's disease<sup>4</sup> and multiple system atrophy.<sup>5</sup> Primary dystonia resembling Pisa syndrome is rare and may be underrecognized. In a recently reported series of 18 patients with axial predominant adult-onset primary dystonia, three patients had lordotic and scoliotic deviation similar to that seen in Pisa syndrome.<sup>6</sup> We report a case of sporadic adult-onset truncal dystonia with head, neck, and shoulder involvement, reminiscent of Pisa syndrome, with complete resolution on high doses of anticholinergic therapy.

## Case Report

A 38-year-old white woman was referred to our movement disorders unit. Four months earlier she had experienced sciatic pain down one leg while carrying a heavy load. On vacation that same month, she noted that she was tilting to the left,

which interfered with walking and swimming. During the next few weeks, her head began to pull toward the right, and her left shoulder pulled upward. The symptoms were alleviated when lying down and disappeared when asleep. Her medical history included sciatica and low back pain for a number of years. The patient was taking depot contraception only. There was no history of neuroleptic, vestibular, sedative, or antiemetic medication at any time. There was no family history of extrapyramidal disorder.

On examination there was dystonic spasm of the left sternocleidomastoid and left splenius capitis muscles, with marked torticollis and retrocollis. Overactivity of the left paraspinal muscles resulted in truncal twisting toward the left (video segment 1). The patient used stretching of the left arm as a trick maneuver to attenuate the truncal dystonia. The rest of the neurologic examination was unremarkable.

The following test results and levels were negative or normal: copper studies, detailed biochemical and hematologic profiles, autoimmune profile, white cell and lysosomal enzymes, acanthocytes, serum angiotensin-converting enzyme, and urinary amino acids. Findings from magnetic resonance imaging of the brain and spinal cord were normal. Genetic testing for dentatorubralpal-

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lido-luysian atrophy, Huntington's disease, spinocerebellar ataxia type III, DYT1 gene, and dopa-responsive dystonia were negative.

Treatment included targeting therapy with botulinum toxin A injections to the right sternocleidomastoid, left splenius capitis, and left trapezius muscles for torticollis. Anticholinergic therapy with benzhexol, using a dose-escalating regimen, was started at 1 mg a day. The dose of benzhexol was slowly increased to 20 mg a day for 6 months, and the patient noted virtually complete dissolution of the dystonia (video segment 2). After 1 year, she was discharged from the clinic and the use of anticholinergic drugs was tapered off. Recurrence of the truncal dystonia, retrocollis, and torticollis occurred 6 months later and required reinstatement of anticholinergic therapy. Currently, the patient remains free of symptoms and is treated with a maintenance dose of 20 mg benzhexol a day.

## Discussion

We report a case of adult-onset, sporadic, segmental dystonia resembling Pisa syndrome. Striking features of this case are the lack of previous exposure to neuroleptic medication, a nearly complete resolution of the dystonia with anticholinergic therapy, and recurrence of the syndrome on withdrawal of anticholinergic drugs.

*Pisa syndrome* is a descriptive term for a twisting truncal dystonia causing patients to veer to one side while walking.<sup>7</sup> The cases originally described did not have concomitant dystonic symptoms,<sup>1,3,7,8</sup> but the head and neck may be involved. Pisa syndrome is most frequently seen after chronic neuroleptic therapy,<sup>2,3,8</sup> with or without concurrent antidepressant medication. In the context of chronic neuroleptic exposure and antidepressant therapy, Pisa syndrome is thought to arise secondary to a complex interaction between several neurotransmitters, including serotonin, noradrenaline, dopamine, and acetylcholine.<sup>9</sup> Association with structural brain lesions (e.g., chronic subdural hygroma and cerebral cortical atrophy) has been described in some cases.<sup>1,7,9</sup>

Our patient had sporadic truncal and craniocervical dystonia. The only possible, but unlikely, causal association is the protracted history of sciatica and low back pain. Peripheral injury, often in association with reflex sympathetic dystrophy, has been documented as a cause of focal and segmental dystonia and posttraumatic hemidystonia.<sup>10</sup>

The response to high doses of anticholinergic therapy in our patient was virtually complete, with recurrence of the original presentation in its entirety after medication withdrawal and milder breakthrough symptoms on lower dosage. Open-labeled and double-masked trials have substantiated the benefits of anticholinergic therapy in focal, segmental, and generalized dystonia, quoted as 40% and 50% in adults and children, respectively.<sup>11</sup> It has been observed that the greatest benefit is obtained with treatment initiation within the first 5 years of dystonia onset. There is no evidence that anticholinergic drugs modify the course of the disease. Anticholinergic drugs are often given before neuroleptic therapy to prevent acute dystonic reactions and during neuroleptic treatment to treat tardive dystonia. They may increase the incidence of tardive dyskinesias. Therefore, recognition of each condition is important.<sup>12,13</sup> The exact mode of anticholinergic action in dystonia is uncertain, but restoration of the acetylcholine–dopamine balance probably plays a role, particularly in the context of neuroleptic-induced dopamine blockade.

In conclusion, we have described a rare phenotype of adult-onset, sporadic, segmental dystonia resembling Pisa syndrome, with virtually complete resolution of symptoms with high doses of anticholinergic medication.

## Legends to the Videotape

**Segment 1:** Before treatment, dominant left laterocollis with lateral bending of the trunk, scoliosis to the right, and retrocollis spasms are seen.

**Segment 2:** After treatment, mild laterocollis to the right and some anticholinergic-induced chorea of the fingers in both hands are seen.

A videotape accompanies this article.

**Grapsa Julia - Nihoyannopoulos Petros**

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# Strain balance of papillary muscles as a prerequisite for successful mitral valve repair in patients with mitral valve prolapse due to fibroelastic deficiency

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## Introduction

Mitral valve repair for mitral regurgitation (MR) is the preferred surgical option for patients with fibroelastic deficiency (FED). To date, emphasis has been put on leaflet tissue preservation by resecting as little as possible and implanting neochords.<sup>1-7</sup> Although many studies have shown successful left ventricle (LV) remodelling following mitral valve repair,<sup>7-12</sup> the role of the papillary muscles into the risk for residual MR remains undetermined. We therefore hypothesized that asymmetric tension on the papillary muscles as assessed by the longitudinal strain may jeopardize an otherwise successful mitral valve repair and may predict residual valve regurgitation in patients with FED.

## Methods

### Study design and methods

#### *Study population and sample size calculation*

Sixty-four consecutive patients with isolated posterior mitral valve prolapse and severe MR referred for surgery were prospectively recruited and consented for participation in the study between 2008 and 2012.

According to the current guidelines, patients were selected for surgical repair for MR.<sup>13</sup> Patients with cardiomyopathy and/or concomitant coronary artery disease were excluded from the study. In addition, we excluded patients with heart block (second or third degree) and with fast atrial fibrillation (AF; defined as heart rate >100 bpm). Patients who underwent mitral valve replacement because of failure to repair were also excluded from the study.

Patients with either paroxysmal or persistent AF were included in the study. In those with

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controlled AF, care was taken to obtain three consecutive sequences for three-dimensional echocardiography (3DE) and speckle-tracking data sets. All patients had intraoperative transoesophageal echocardiography confirming successful mitral valve repair without residual MR. All patients underwent preoperative right and left catheterization, as a part of their surgical workup. New York Heart Association (NYHA) functional class was assessed according to clinical presentation. Standard echocardiographic assessment took place prior and 6 months after the mitral valve repair.

### **Echocardiography**

The echocardiographic protocol consisted of conventional 2DE, 3DE, and LV segmental and global longitudinal strain. The study was performed using a Toshiba Aplio Artida ultrasound system and a phased-array transducer with a centre frequency of 3 MHz (PST: -230 BT), native frequency selection 4.8 MHz, field-of-view angle  $\approx 90^\circ$ , biopsy adapter 680-106 (TG-2), and in tissue harmonic mode (Toshiba Medical Systems Europe BV, Zoetermeer, The Netherlands). Following the completion of the 2D examination, ECG-gated 3D images of the LV were acquired using the 3 MHz PST-25SX 3D matrix-array transducer from the apical view. Four beats stitched 3D volumes, 908 by 22.58, were used in each subject. Care was taken to include the LV apex, the entire LV free wall, and the septum.

The 3D images of the LV were analysed online using Toshiba's proprietary software. The apical four-chamber and apical two-chamber projections derived from the 3D data sets are displayed along with short-axis views of the basal, middle, and apical section of the LV. After ensuring inclusion of the LV apex, the endocardium at the margins of the mitral annulus and at the apex was marked for each apical view. The automated endocardium tracking software was used in all instances. The identified endocardial and epicardial borders were then adjusted manually in each of the two apical and three short-axis views to correct for assumptions made by the software regarding LV shape. The ability of the software to adequately track the myocardium was evaluated, with further minor adjustments of the myocardial borders applied as necessary. The 3D strain patterns for each of the

16 segments of the LV were reviewed as an objective assessment of wall tracking.

### **Two-dimensional strain**

For standard longitudinal strain analysis, grey-scale 2D images were acquired in the two- and four-chamber apical views as well as the parasternal short-axis views at the level of papillary muscles.<sup>14,15</sup> Frame rate was used at 50-80 frames per second (fps). The following parameters were measured:

- *2DE*: LV dimensions, wall thickness, fractional shortening, left atrial size, and Doppler measurements with pulsed and continuous wave were made.
- *3DE*: LV end-diastolic, end-systolic, stroke volume, and ejection fraction. Right ventricle volumes and ejection fraction were also calculated.
- *Two-dimensional speckle-tracking*: longitudinal and radial strain of the LV.

### **Speckle tracking of LV papillary muscles**

Based on the principle of preservation of mechanical energy in a closed circuit, we assumed that the forces exerted by the two papillary muscles during systole will be equal in the absence of any MR. The mitral apparatus was equated to a closed circuit composed of the two mitral leaflets, the two papillary muscles, as well as the respective chordae, the left atrium, and the mitral annulus. The best view for the assessment of the mitral circuit was the transthoracic apical two-chamber view in zoomed views to increase the frame rate. Subsequently, the papillary muscles were traced at a frame rate of 60-80 fps (specifically for the papillary muscles). Care was taken to define the body of the papillary muscle and to exclude the chordae (*Figure 1*). Chordae were excluded from the analysis due to the postoperative employment of Gortex neochordae.

The longitudinal strain of the anterolateral (AL) and posteromedial (PM) papillary muscles was first individually calculated before and after the repair. The global longitudinal strain of both papillary muscles was also calculated as:

$$\Sigma_{\text{strain}} = \text{AL} - \text{PM}$$

LV and papillary muscle strains were norma-

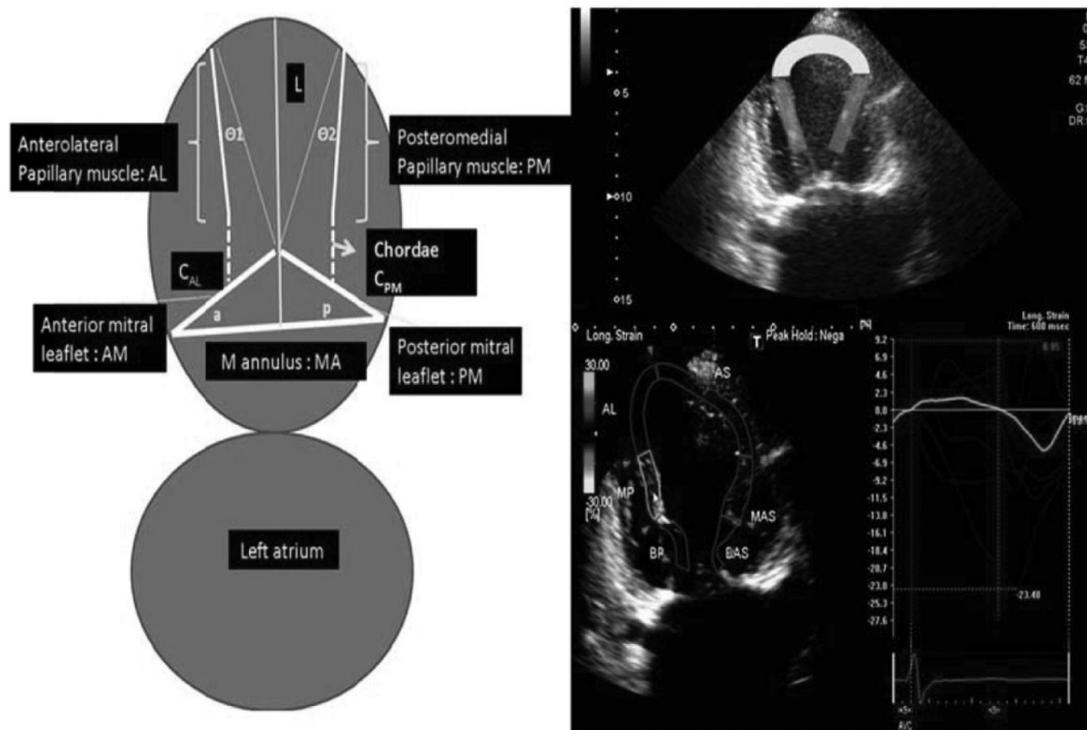
lized to LV end-diastolic volume, to correct for the volume overload due to MR. The single end point for this study was the presence of before mild MR 6 months post mitral valve repair defined as a regurgitant volume of  $>30$  mL.<sup>13</sup>

The same echocardiographic protocol was repeated 6 months following surgery.

### ***Preoperative assessment of the mitral valve and surgical technique***

MR preoperatively was quantified with 2D and 3D echocardiography, according to the most recent EAE/ASE guidelines.<sup>16,17</sup> Following preoperative analysis of the valvular pathology, patients were consented for mitral valve repair and/or replacement. All patients had posterior leaflet prolapse with or without chordal rupture. There were no patients with Barlow's disease. All patients underwent posterior mitral valve repair with mitral annuloplasty. All procedures were carried out by the same surgeon (P.P.P.) who has 25 years' experience in mitral valve repair, to eliminate surgical bias, using a median sternotomy with subse-

quent institution of cardiopulmonary bypass via aortobicaval cannulation according to standard practice. Combined repair techniques were used techniques designed to address the main pathology. In the majority of cases, triangular/quadrangular resection followed by plication and Gortex neochordae were used. All repairs were reinforced by the flexible annuloplasty band (St Jude tailor band) to ensure bileaflet movement and stabilize the annulus. Surgical technique was the same to all patients. After completing the repair, the valve was inspected to ensure that there were no areas of leaflet prolapse or residual MR. The LV was filled with saline to assess leaflet mobility and area of coaptation. The left atriotomy was closed in a standard fashion and the heart de-aired before removing the aortic cross clamp. After a period of recovery, the heart was allowed to fill and eject, and mitral valve function was assessed using transoesophageal echocardiography after raising the systolic blood pressure to  $>90$  mmHg. If the repair was successful (MR 1+ or less), the patient was weaned off cardiopulmonary bypass and the valve



**Figure 1:** Methodology of the calculation of the longitudinal strain of papillary muscle. We employed apical two-chamber view in zoomed views, and subsequently, the papillary muscles were traced at a frame rate of 60–80 fps. Care was taken to define the body of the papillary muscle and to exclude the chordae. The longitudinal strain of the AL and PM papillary muscles were first individually calculated before and after the repair.

was once again assessed by transoesophageal echocardiography with the systolic blood pressure >100 mmHg.

### **Statistical analysis**

The sample size was determined regarding the evaluation of global longitudinal strain parameters between two groups: absence of MR and presence of MR. We had a pilot study of 10 patients with MR and 10 healthy volunteers. Sample size was calculated as  $n = 50$  to achieve 90% power with significance of type I error:  $\alpha < 0.01$  to detect a significant difference between the two groups with regard to global longitudinal strain parameters as referenced in previous work from our group.<sup>18</sup>

Data were expressed as mean  $\pm$  standard deviation (SD) for normally distributed values and median  $\pm$  interquartile range when variables were not normally distributed. Normal distribution of each variable was assessed using the Kolmogorov-Smirnov test. For the non-normally distributed variables, comparison of groups was performed with non-parametric tests, and the cut-off value for significance was set to the value of 0.05. Comparison of groups was performed with the paired *t*-test, and the *P*-value for comparison was reported. Bland-Altman analysis was employed for the assessment of the interobserver reproducibility of the method. Intracorrelation coefficient (ICC) was employed for the agreement of the methods. Receiver operating curves (ROCs) were used for the prediction of outcome.

Statistical analyses were performed using the SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) and Medcalc 11.1 (Medcalc Software bvba, Belgium) software.

The study was approved by the local ethics committee (08/H0707/144), and the subjects gave written informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

## **Results**

### **Demographic data**

Patients' demographics and operative data are summarized in *Table 1*. Mean age was  $63.6 \pm 13.03$

years. Thirty-two patients had P2 and P3 prolapse; 14 patients had isolated P2 prolapse while 18 patients had P1 prolapse. Eight patients (12.5%) were in controlled AF with a mean heart rate of  $81.1 \pm 14.2$  bpm, whereas 34 (56%) were in paroxysmal AF. Those with paroxysmal AF were in sinus rhythm while they had the echocardiogram. Immediately post repair, only 12 patients (18.4%) were in controlled AF while the rest of the population was in sinus rhythm.

An age-matched group of 14 healthy volunteers served as a control group.

### **Two- and three-dimensional echocardiographic data**

Two- and three-dimensional echocardiographic data were compared pre- and 6 months post repair (*Table 2*). As expected, there was a reduction in LV volumes, wall thickness, and LA size postoperatively. It was important that LV ejection fraction did not demonstrate any change.

### **LV speckle tracking – FED patients**

All the LV strain values were reduced after mitral valve repair (*Table 3*). Longitudinal strains of all segments were reduced with the exception of longitudinal strain of the mid and distal lateral segments.

### **Longitudinal strain of papillary muscles in FED patients**

Preoperatively, the longitudinal strain of the PM papillary muscle was greater than the AL papillary muscle, but that was similar postoperatively when there was no residual MR (*Table 4*). Longitudinal strain of the AL and the PM papillary muscles as well as the global strain of both papillary muscles were all reduced after mitral valve repair, but the greatest reduction was observed in the longitudinal strain of the PM papillary muscle (*Table 4*).

Eight (12.5%) patients, who had P2-P3 prolapse, presented MR recurrence (regurgitant volume  $46.5 \pm 17.6$  mL) at 6-month follow-up. The value of longitudinal strain of the posterior papillary muscle was significantly higher (magnitude) in patients with MR recurrence when compared with their counterparts (*Table 5*).

**Table 1** Demographics of patients

Values	Pre-repair (n = 64 patients)	Post repair no MR (n = 56 patients)	Post repair recurrent MR (n = 8 patients)	P-value
Sex (male/female)	33/64 male	24/56 male	5/8 male	
Age (years)	63.6 (58.6–76.9) <sup>a</sup>	62.8 (57.2–78.3) <sup>a</sup>	65.9 (61.2–75.4) <sup>a</sup>	0.15
AF/PAF (% of population)	8 AF/34 PAF	8 AF	4 AF	
BMI (kg/m <sup>2</sup> )	26.67 (22–29.5) <sup>a</sup>	27.24 (22.5–30.9) <sup>a</sup>	26.8 (21.8–29.5) <sup>a</sup>	0.28
Creatinine (mg/dL)	90 (84.2–102.4) <sup>a</sup>	82.14 (69.7–96.4) <sup>a</sup>	90 (75.9–114) <sup>a</sup>	0.2
Bypass time (min)	92.5 (86–101.5) <sup>a</sup>	89.45 (80.5–98) <sup>a</sup>	92.9 (79–102) <sup>a</sup>	0.57
Cross-clamp time (min)	60 (53–68.9) <sup>a</sup>	67.2 (62.3–74.5) <sup>a</sup>	78.6 (71.9–85.3) <sup>a</sup>	0.07
EuroSCORE	5.37 (2.6) <sup>b</sup>	6.4 (2.4) <sup>b</sup>	5.8 (2.3) <sup>b</sup>	0.89

MR, mitral regurgitation; SD, standard deviation; IQR, interquartile range; AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; BMI, body mass index.

<sup>a</sup>Median (Q1–Q3).

<sup>b</sup>Mean (SD).

**Table 2** Comparison of echocardiographic values before and after surgery

Echocardiographic value	Pre-surgery (n = 64 patients)	Post-surgery (n = 64 patients)	P-value
LVED (mm)	54.6 (6.7) <sup>a</sup>	49.2 (5.8) <sup>a</sup>	<0.001
LVES (mm)	36.4 (6.4) <sup>a</sup>	34.6 (6.6) <sup>a</sup>	0.14
FS (%)	33 (7) <sup>a</sup>	38.4 (20.9) <sup>a</sup>	0.1375
IVS (mm)	9.1 (0.96) <sup>a</sup>	8.7 (0.85) <sup>a</sup>	0.0147
LVPW (mm)	9.2 (1.04) <sup>a</sup>	8.97 (0.91) <sup>a</sup>	0.14
LA diameter (mm)	54.2 (9) <sup>a</sup>	45.8 (7.1) <sup>a</sup>	<0.001
LA volume (mL)	119.2 (18) <sup>a</sup>	78.5 (9.2) <sup>a</sup>	<0.001
LVEDV (mL)	172.2 (145.7–189.4) <sup>b</sup>	126.2 (120.8–156.8) <sup>b</sup>	<0.001
LVESV (mL)	72.9 (67.9–87.6) <sup>b</sup>	60.1 (53.3–67.2) <sup>b</sup>	0.0009
LVSV (mL)	100.64 (83.2–102.7) <sup>b</sup>	82.47 (65–88.5) <sup>b</sup>	<0.001
LVEF (%)	58.07 (10.6) <sup>a</sup>	57.2 (10.2) <sup>a</sup>	0.66

All measurements were indexed for body surface area. LVED, left ventricular end-diastolic diameter; LVES, left ventricular end-systolic diameter; FS, fractional shortening; IVS, interventricular septal thickness; LVPW, left ventricular posterior wall thickness; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction.

<sup>a</sup>Mean (SD).

<sup>b</sup>Median (Q1–Q3).

**Table 3** Strain of LV segments—comparison before and after surgery

Echocardiographic value	Pre-surgery (n = 64 patients)	Post-surgery (n = 64 patients)	P-value
Global longitudinal strain (%)	−10.66 (9.5–12.3) <sup>a</sup>	−7.36 (5.9–8.5) <sup>a</sup>	0.002
Longitudinal basal septal (%)	−10.13 (9–12) <sup>a</sup>	−7.81 (5–9.2) <sup>a</sup>	0.0005
Longitudinal mid septal (%)	−11.09 (9.4–12.3) <sup>a</sup>	−7.65 (5.1–9.7) <sup>a</sup>	0.0001
Longitudinal apical septal (%)	−12.35 (9.7–13.2) <sup>a</sup>	−6.1 (4–10.7) <sup>a</sup>	0.0045
Longitudinal apical lateral (%)	−10.99 (9.3–12.4) <sup>a</sup>	−5.96 (4.1–10) <sup>a</sup>	0.1427
Longitudinal mid lateral (%)	−9.68 (6.9–10.5) <sup>a</sup>	−8.75 (5–11.5) <sup>a</sup>	0.1936
Longitudinal basal lateral (%)	−9.77 (7.8–10.7) <sup>a</sup>	−7.88 (4.2–8.8) <sup>a</sup>	0.003

All strain values were corrected for left ventricular end-diastolic volume.

<sup>a</sup>Median (Q1–Q3).

Note that for SD we have employed absolute values for the convenience of the reader.

**Table 4** Comparison of papillary muscle longitudinal strain in the global population ( $n = 64$  patients) before and after surgery

Echocardiographic value	Pre-surgery ( $n = 64$ patients)	Post-surgery ( $n = 64$ patients)	P-value
AL longitudinal strain <sup>a</sup> (%)	-4.94 (2.2) <sup>b</sup>	-3.28 (1.3) <sup>b</sup>	<0.001
PM longitudinal strain <sup>a</sup> (%)	-12.64 (5.3) <sup>b</sup>	-4.12 (6.77) <sup>b</sup>	<0.001
Global strain <sup>a</sup> (%)	-7.59 (3.48) <sup>b</sup>	-1.07 (6) <sup>b</sup>	<0.001

All strain values were corrected for left ventricular end-diastolic volume.

<sup>a</sup>AL, anterolateral; PM, posteromedial.

<sup>b</sup>Mean (SD).

**Table 5** Comparison of papillary muscle longitudinal strain in successful repair and in patients with recurrent MR

Echocardiographic indices	No MR ( $n = 58$ patients)	Recurrent MR ( $n = 8$ patients)	P-value
Pre-surgery			
LVEDV	194.5 (147.4–209) <sup>a</sup>	147.4 (105.2–196.3) <sup>a</sup>	0.18
LVESV	75.5 (29.4) <sup>b</sup>	61.4 (22) <sup>b</sup>	0.29
LVSV	119 (84.6–124) <sup>a</sup>	125.8 (52.4–132) <sup>a</sup>	0.29
LVEF	59.5 (12.6) <sup>b</sup>	58.6 (11.9) <sup>b</sup>	0.9
AL longitudinal strain <sup>a</sup> (%)	-4.8 (1.73) <sup>b</sup>	-6.74 (1.66) <sup>b</sup>	0.1305
PM longitudinal strain <sup>a</sup> (%)	-11.46 (3.5) <sup>b</sup>	-20.36 (4.9) <sup>b</sup>	0.0047
Global longitudinal strain <sup>a</sup> (%)	-6.65 (2.7) <sup>b</sup>	-13.62 (4.59) <sup>b</sup>	0.0046
Post-surgery			
LVEDV	173.2 (95–189.2) <sup>a</sup>	130 (67–142.5) <sup>a</sup>	0.28
LVESV	77.1 (52.3) <sup>b</sup>	54.7 (19.2) <sup>b</sup>	0.29
LVSV	96.1 (45.2–106) <sup>a</sup>	75.3 (48–97.8) <sup>a</sup>	0.3
LVEF	57.2 (5.8) <sup>b</sup>	57.5 (10.1) <sup>b</sup>	0.91
AL longitudinal strain <sup>a</sup> (%)	-2.99 (1.58) <sup>b</sup>	-4.97 (1.05) <sup>b</sup>	0.0038
PM longitudinal strain <sup>a</sup> (%)	-3.94 (2.26) <sup>b</sup>	-22.56 (6.89) <sup>b</sup>	0.0002
Global longitudinal strain <sup>a</sup> (%)	-0.96 (1.17) <sup>b</sup>	-17.58 (6.63) <sup>b</sup>	0.002

All strain values were corrected for left ventricular end-diastolic volume.

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; AL, anterolateral; PM, posteromedial.

<sup>a</sup>Median (Q1–Q3).

<sup>b</sup>Mean (SD).

### Longitudinal strain of papillary muscles in healthy volunteers

Fourteen healthy volunteers were employed as the control group. LV volumes, ejection fraction, as well as the longitudinal strain of papillary muscles are demonstrated in *Table 6*. Compared with patients with the FED prior to mitral repair, healthy volunteers had a global papillary longitudinal strain equal to zero and significantly lower values ( $P < 0.001$ ).

### Reproducibility of papillary muscle longitudinal strain

This was assessed between an observer certified in echocardiography and 7 years experience (J.G.) against one without certification and only 1 year of echo experience (G.J.) in a blinded fashion. There was good agreement between the two observers for the longitudinal strain: AL papillary muscle (mean bias: 0.48%, SD of bias: 1.1%, ICC = 0.86,  $P < 0.001$ ), PM papillary muscle (mean bias: 0.1%, SD of bias: 2.78%, ICC = 0.85,  $P < 0.001$ ), and global papillary muscle longitudinal strain (mean bias: -0.39%, SD of bias: 2.6%, ICC = 0.75,  $P < 0.001$ ; *Figure 2*).

**Table 6** Mean values of echocardiographic indices in healthy volunteers and comparison with the FED patients

Echocardiographic indices	Healthy volunteers (n = 14 patients)	P-value
LVEDV (mL)	76.3 (11.6) <sup>a</sup>	<0.001
LVESV (mL)	29.7 (4.4) <sup>a</sup>	<0.001
LVSV (mL)	46.6 (8.7) <sup>a</sup>	0.002
LVEF (%)	60.8 (3.7) <sup>a</sup>	<0.001
AL longitudinal strain <sup>b</sup> (%)	-0.035 (0.012) <sup>a</sup>	<0.001
PM longitudinal strain <sup>b</sup> (%)	-0.037 (0.011) <sup>a</sup>	<0.001
Global strain <sup>b</sup> (%)	-0.001 (0.003) <sup>a</sup>	<0.001

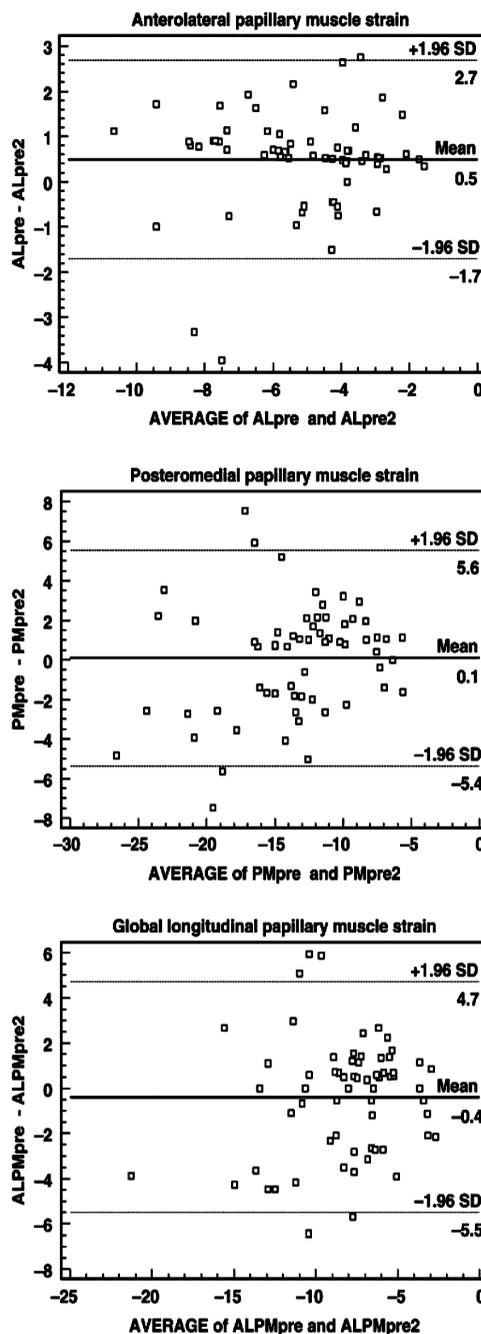
All strain values were corrected for left ventricular end-diastolic volume. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction. <sup>a</sup>Mean (SD). <sup>b</sup>AL, anterolateral; PM, posteromedial.

**ROCs for the prediction of recurrent MR**

Eight patients (12.5%) had equalled to or more than moderate MR, 6 months post mitral valve repair. Longitudinal strain of the PM papillary muscle before surgery was the strongest predictor of recurrent MR (ROC for Pmpre/ left ventricular end-diastolic volume (LVEDV): area under the ROC = 0.902, 95% CI: 0.801-0.962, sensitivity: 100%, specificity: 78.6%, for a cut-off value: less than or equal to -14.78). Furthermore, the preoperative global papillary muscle strain was also a determinant of recurrent MR when the global strain was greater than 29.05% (area under the curve: 0.895, 95% CI: 0.793-0.958, sensitivity: 100%, specificity: 76.8%; Figure 3).

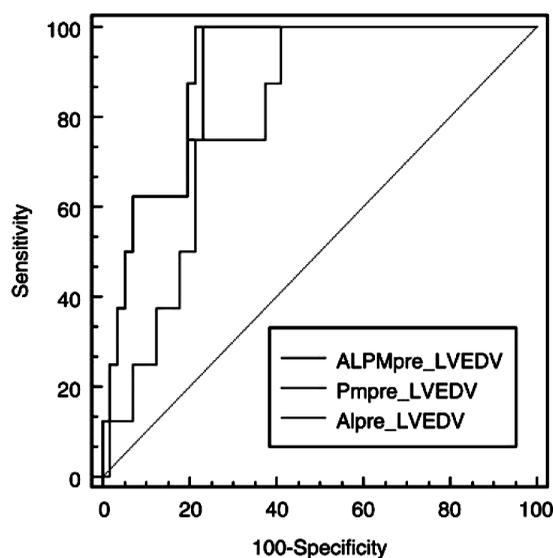
**Discussion**

In this study group of patients with an isolated posterior mitral leaflet prolapse due to FED, we found that very high strain values exerted on the PM papillary muscle (greater than 214.78) as well as on the global strain of both papillary muscles preoperatively (greater than 29.05) predict recurrent MR following an otherwise successful mitral valve repair. It may not be surprising that the persistence of asymmetric strain values postoperatively with increased strains in the PM papillary muscle may lead to recurrent MR. To prove our hypothesis that excessive strain on the papillary muscles may jeopardize an otherwise suc-



**Figure 2:** Bland-Altman graphs for reproducibility of the longitudinal strain of AL (mean bias: 0.48%, SD of bias: 1.1%, ICC = 0.86, P < 0.001), PM (mean bias: 0.1%, SD of bias: 2.78%, ICC = 0.85, P < 0.001), and global papillary muscles (mean bias: 20.39%, SD of bias: 2.6%, ICC = 0.75, P < 0.001). All strain values were corrected to left ventricular end-diastolic volume.

cessful mitral valve repair, we chose the clinical model of isolated posterior mitral leaflet prolapse secondary to FED while in all patients the choice of ring utilized was the same. With persisting



**Figure 3:** Comparison of ROCs—AL, PM, and global papillary muscle longitudinal strain. ROC for ALpre/LVEDV: area under the ROC = 0.799, 95% CI: 0.680–0.889, sensitivity: 100%, specificity: 58.9%, cut-off value: less than or equal to  $-5.0251$ ; ROC for Pmpre/LVEDV: area under the ROC = 0.902, 95% CI: 0.801–0.962, sensitivity: 100%, specificity: 78.6%, cut-off value: less than or equal to  $-14.78$ . ROC for global preoperative papillary muscle strain/LVEDV: area under the curve: 0.895, 95% CI: 0.793–0.958, sensitivity: 100%, specificity: 76.8%, cut-off value: less than or equal to 29.05.

asymmetry of papillary muscle strains, with higher strains on the PM papillary muscle, there is an increased incidence of persisting MR. Although a lot of emphasis has been put into the size and shape of the mitral annulus leading to the development of multiple rings over the years,<sup>19,20</sup> the importance of the papillary muscle tension has been largely underestimated. Mitral papillary-annular continuity is important for optimal LV systolic performance and mitral competence,<sup>21</sup> while the anterior and posterior leaflet chordae have similar but additive contributions to LV systolic elastance.<sup>22</sup>

The assumption that global longitudinal strain is equal to zero was based on the Principle of Law of the Conservation of Energy which was formulated by Maxwell<sup>23</sup> in 1871 and was defined as «The total energy of any body or system of bodies is a quantity that can neither be increased nor diminished by any mutual action of these bodies». Early studies<sup>21–23</sup> showed that the total mechanical

energy in a system remains constant as long as the only forces acting are conservative forces. We therefore assumed that, within the mitral apparatus, longitudinal strain of the papillary muscles should remain constant, and that the global strain of both papillary muscles should remain equal to zero following a successful mitral valve repair.

Furthermore, in our study, there was no difference in LV remodelling in the patients with postoperative MR, compared with a successful repair (Table 5). Therefore, it might be possible that further fibrosis and degeneration of papillary muscle, which may be represented by the reduction of global longitudinal strain, may explain the significant difference between longitudinal strains, despite similar LV remodelling.<sup>24,25</sup> It is more likely that asymmetric tension on the papillary muscles may be exerted from the respective prolapsing leaflet that, when successfully repaired, the tension is then reduced and mitral competence restored.<sup>24</sup>

#### Longitudinal strain of papillary muscles

Despite the extensive reference on mitral shape<sup>26,27</sup> and the beneficial role of repair vs. replacement,<sup>28–31</sup> the role of the mitral papillary strain has been overlooked. The first experiments on the papillary muscle strain were performed *in vitro*<sup>32,33</sup> and most recently *in vivo*,<sup>34</sup> and Krishnamurthy *et al.*<sup>18</sup> created an *in vivo* model for the measurement of strain on mitral valve leaflets. They showed that both circumferential and radial stress – strain curves are linear over a physiological range of pressures, in the closed mitral valve. In our study, we examined the longitudinal strain of both papillary muscles (AL and PM) together with the assessment of LV volumes and strain in the same cardiac cycle. Furthermore, considering the influence of volume overload on the strain, we normalized all strain values to the LV end-diastolic volume.<sup>35</sup> As previously shown,<sup>36,37</sup> the LV remodels favourably following mitral valve repair, and both longitudinal and radial strains were reduced. This was also shown in the current study despite the removal of the volume-loading component, with LV radial strain being significantly reduced post mitral valve repair reflecting LV recovery which may take more than the time period of 6 months.

A similar model has been described by Tigen<sup>38</sup> for

the prediction of the severity of functional MR in patients with non-ischaemic-dilated cardiomyopathy. When compared with our study, they used two different planes for the assessment of the papillary muscle strains one at a time, and therefore, strain measurements were performed at different cardiac cycles and times. In our model of isolated posterior mitral leaflet prolapse due to FED, we found that when the presurgical global papillary muscle strain is markedly asymmetrical and significantly high (greater than  $-9.05$ ), the likelihood of recurrent MR post-surgery increases. Furthermore, to achieve the greater balance within the mitral apparatus and minimal regurgitation post-surgery, it is important for the global papillary muscle strain post-surgery to be close or equal to zero. In this study, we specifically chose not to include patients with functional or ischaemic MR because of the possible contribution of segmental LV dysfunction with reduced strain values of the LV wall as a confounding variable on papillary muscle strains. In addition, we would not be able to rule out possible papillary muscle fibrosis due to ischaemia as a contributor to reduced papillary muscle strains.

### **Limitations**

In this study, no other aetiologies of MR were included so that our results cannot be extrapolated to other causes such as functional MR. However, the highly selected clinical model of isolated posterior leaflet prolapse due to FED allowed us to prove our hypothesis of the importance of individual papillary muscle strain on the recurrence of MR. Further studies on functional, non-ischaemic MR, or prolapse of the anterior mitral leaflet may be useful to evaluate the papillary muscle mechanics in patients with MR. Finally, 67.7% of patients pre-operatively were in slow AF which may limit strain analysis –for that purpose the mean value of three consecutive beats was obtained.

### **Clinical implications**

In the context of «respecting the mitral valve and not resecting», the main aim of the cardiothoracic surgeon is usually to repair the valve, especially in degenerative disease. This might, however, lead into recurrent MR in the long term, which leads the patient into heart failure. The measurement of the longitudinal strain of papillary muscles and the

calculation of the global strain will allow a more rational approach, and if the global strain is disproportional, mitral valve replacement may be a better option. This will allow better surgical planning for the patient, by taking into account the mitral apparatus balance prior and after surgery.

Furthermore, further studies specifically on MitralClip patients may help eliminating recurrent MR post MitralClip insertion.

### **Conclusion**

Patients with FED and isolated posterior mitral valve prolapse who undergo mitral valve repair are less likely to have recurrent MR when the postoperative global papillary muscle strain is close or equal to zero. The longitudinal strain of the papillary muscles may therefore play an important role in preoperative planning of patients who undergo mitral valve repair for degenerative mitral valve disease.

### **Ethical policy**

The manuscript and the material within the manuscript have not been published and are not being considered for publication elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers, except as an abstract.

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**Hatzitolios Apostolos**

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# N-Terminal Pro-Brain Natriuretic Peptide Levels Are Elevated in Patients with Acute Ischemic Stroke

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Brain natriuretic peptide (BNP) is a counterregulatory hormone released by the ventricles of the heart. Its main actions are natriuresis and vasodilation. The authors studied N-terminal pro-brain natriuretic peptide (NT-proBNP) levels soon after an acute ischemic stroke. They compared plasma NT-proBNP concentrations in 30 patients with an acute ischemic stroke with those of 30 controls. The 2 groups were adjusted for age and gender, and there were no significant differences in vascular risk factors and left ventricular systolic and diastolic function. Venous samples were collected within the first  $11.8 \pm 1.2$  hours after the onset of symptoms and again on day 6. Brain computed tomography/magnetic resonance imaging (CT/MRI) was performed on the same days (day 0 and day 6) in order to assess the site (carotid or vertebrobasilar), cause (atherothrombotic, cardioembolic, or lacunar), and size (large, medium, or small) of the brain infarct. NT-proBNP levels were elevated in patients with acute stroke ( $129.9 \pm 9.9$  fmol/mL) compared with the controls ( $90.8 \pm 6.3$  fmol/mL,  $p < 0.05$ ). These levels remained elevated at day 6 ( $113.5 \pm 13.0$  fmol/mL). NT-proBNP at admission was significantly higher in cardioembolic compared with atherothrombotic infarctions. There was no correlation between circulating NT-proBNP and stroke topography, infarct size, or severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) at any of the 2 time points (admission and day 6). NT-proBNP levels were raised in patients with acute ischemic stroke; this effect persisted until day 6. The authors suggest that neurohumoral activation occurs in patients with acute ischemic stroke, either reflecting a counterbalancing vasodilating response to the cerebral ischemia or direct myocardial dysfunction.

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## Introduction

Brain natriuretic peptide (BNP), which was isolated from porcine brain in 1988, promotes natriuresis and diuresis, acts as a vasodilator, and antagonizes the vasoconstrictor effects of the renin-angiotensin-aldosterone system.<sup>1</sup> BNP levels correlate directly with left ventricular (LV) mass.<sup>2</sup> Any condition that increases the volume or activates the stretch receptors of the ventricle can elevate BNP levels. BNP, which is increased in patients with heart disease such as congestive heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy, hypertensive heart disease, and lone atrial fibrillation (AF), has been used as a biochemical marker of heart disease.<sup>3</sup> BNP is a novel clinical tool for diagnosis and management of heart failure. In a community-based study, plasma natriuretic peptide levels predicted the risk of death and cardiovascular events after adjustment for traditional risk factors.<sup>4</sup>

N-terminal pro BNP (NT-proBNP) is the more recently identified circulating aminoterminal precursor of BNP. NT-proBNP correlates equally with BNP with clinical variables in patients with heart failure and it has become a promising new alternative marker for the detection of LV dysfunction.<sup>5,6</sup> Furthermore, NT-proBNP is a more discerning marker of early systolic LV dysfunction than BNP.<sup>7</sup> Unlike BNP, NT-proBNP is stable in EDTA plasma for 3 days at room temperature or longer at 4 °C.<sup>8</sup> Since NT-proBNP is elevated in acute ischemic conditions, such as acute myocardial infarction<sup>9</sup> and pulmonary embolism,<sup>10</sup> we hypothesized that it is also elevated in patients presenting with acute ischemic stroke. In the present study, we examined the question of whether NT-proBNP levels are higher in patients with acute ischemic stroke than in control subjects and, if so, whether these levels correlate with the site of the infarction, its primary cause, the infarct size, and the neurologic status of the patient.

## Methods

### Study Population

We prospectively studied 30 patients with acute ischemic stroke admitted to the Department of Internal Medicine of this Institution, within 24 hours after onset of symptoms ( $11.8 \pm 1.2$  hours). A detailed history of vascular risk factors was obtained from each patient. Patients with (1) cerebral ischemia due to causes other than atherothrombosis and cardioembolism, such as subarachnoid hemorrhage, intracerebral hemorrhage, hematoma, and complicated migraine; (2) previous transient ischemic attack or stroke; (3) major cardiac, renal, hepatic disease, cancer, or obvious signs of infection after admission; and (4) current or recent myocardial infarction or cardiogenic shock were excluded from the study. The diagnosis of acute ischemic stroke was confirmed by a complete neurologic workup that included a brain computed tomography (CT) scan or magnetic resonance imaging (MRI) on admission and at day 6, which also defined the final infarct size, subtype, and topography and evaluated the presence of hemorrhagic transformation. Patients were classified as having a large infarct (largest diameter of infarct  $>4$  cm), a moderate infarct ( $>1.5$  cm and  $<4$  cm), or a small infarct ( $<1.5$  cm).

Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.<sup>11</sup> To identify the potential mechanism of the cerebral infarction, a set of diagnostic tests was performed that included electrocardiography, chest radiography, carotid ultrasonography, and transthoracic echocardiography. The differentiation of atherothrombosis from cardioembolism was based on the findings of either an arterial stenosis/occlusion or a potential source of cardiogenic embolism. A possible cardiogenic mechanism was assumed if a major risk source was present. The diagnosis of lacunar infarcts was established on the basis of the clinical features and CT/MRI results. The diagnosis of the site of the infarction was based on the clinical assessment in conjunction with the imaging results; this was classified as anterior (carotid) and posterior (vertebrobasilar) circulation. Stroke se-

verity was quantified by an experienced neurologist using the NIHSS on admission and at day 6. Stroke etiology and topography, infarct size, and stroke severity are shown in Table I.

Thirty age- and sex-matched subjects undergoing routine medical examinations who had no recent infection or history of serious illness or recent head trauma were used as controls. The demographics and clinical characteristics of patients and controls are presented in Table II. All control subjects underwent a complete physical examination, blood pressure measurement, a complete 2-dimensional and Doppler echocardiographic examination, and also measurement of NT-proBNP levels from blood samples taken the same day. The control group had the same clinical and echocardiographic profile as the patient group.

Complete 2-dimensional and Doppler echocardiographic examinations were performed in all patients at the same day of the initial NT-proBNP evaluation. We used a commercially available system (Vivid 7, Vingmed, GE, Norway). All sub-

jects were examined in the left semilateral recumbent position. All 2-dimensional and Doppler echocardiographic studies included standard parasternal and apical views and were stored on SVHS video tape for subsequent analysis. Left ventricular (LV) end-diastolic and end-systolic volumes were determined from apical 2- and 4-chamber views by using the Simpson biplane formula according to the recommendations of the American Society of Echocardiography.<sup>12</sup> Optimal tracings of endocardial borders in end-diastole and end-systole were performed in the technically best cardiac cycle. LV ejection fraction (LVEF) was calculated as (end-diastolic—end-systolic volume)/end-diastolic volume. LV systolic and diastolic dimensions (fractional shortening), left atrial dimensions, and LV wall thickness were measured from the M-mode echocardiogram, according to the recommendations of the American Society of Echocardiography.<sup>13</sup> LVEF was calculated by means of the biplane Simpson formula. The LV mass index (LVMI) was calculated according to the Devereaux–Reichek formula.<sup>14</sup> The LV-diastolic indices were assessed from the transmitral flow velocity waveform from the apical 4-chamber view by positioning a sized 2–4 mm sample volume at the tips of the mitral leaflets during diastole. The Doppler beam was aligned so as to be parallel to the blood flow vector. The following parameters of LV diastole were calculated: (1) the maximal flow at the beginning of diastole (early filling velocity, “E wave”), (2) the corresponding flow during atrial contraction (late filling velocity, “A wave”), (3) the resulting E/A ratio, and (4) the deceleration time of the early filling velocity (“DT”). LV-isovolumic relaxation time (IVRT) was defined as the time between aortic valve closure and mitral valve opening and was calculated by pulsed Doppler from the apical 5-chamber view—allowing for simultaneous recording of transaortic and transmitral flow—by positioning a sized 5–7 mm sample volume between the LV-outflow tract and the anterior mitral leaflet. Table II shows the echocardiographic characteristics of patients and controls.

All patients received subcutaneous low-molecular-weight heparin as prophylaxis for deep

Table I. Stroke etiology and topography, infarct size, and stroke severity.

Stroke etiology, n (%)	
Atherothrombosis	17 (56.7%)
Cardioembolism	8 (26.7%)
Lacunar	5 (16.7%)
Infarct topography, n (%)	
Carotid	22 (73.3%)
Vertebrobasilar	8 (26.7%)
Infarct size, n (%)	
Large infarct	11 (36.7%)
Medium infarct	8 (26.7%)
Small infarct	11 (36.7%)
Mean NIHSS	
At day 0	10.5
At day 6	9.6

Table II. Demographic clinical and echocardiographic data of stroke patients and controls.

	Patients	Controls	p
Number	30	30	NS
Age, mean $\pm$ SEM	73.8 $\pm$ 1.1	71.5 $\pm$ 1.4	NS
Men/women	16/14	16/14	NS
BMI, kg/m <sup>2</sup> , mean $\pm$ SEM	28.3 $\pm$ 1.1	27.8 $\pm$ 0.9	NS
SBP, mm Hg, mean $\pm$ SEM)	150.1 $\pm$ 3.9	144.3 $\pm$ 2.1	NS
DBP, mm Hg, mean $\pm$ SEM	87.4 $\pm$ 1.5	86.2 $\pm$ 1.2	NS
Heart rate, bpm, mean $\pm$ SEM	79.3 $\pm$ 3.3	80.3 $\pm$ 2.4	NS
Calculated GFR, mL/minutes, mean $\pm$ SEM	80.4 $\pm$ 2.13	81.6 $\pm$ 1.99	NS
Hypertension, n (%)	26 (86.7%)	25 (83.3%)	NS
Diabetes mellitus, n (%)	12 (40%)	13 (43.3%)	NS
Coronary heart disease, n (%)	13 (43.3%)	11 (36.7%)	NS
Current smoking, n (%)	8 (26.7%)	8 (26.7%)	NS
Atrial fibrillation, n (%)	10 (33.3%)	11 (36.7%)	NS
Dyslipidemia, n (%)	14 (46.7%)	15 (50%)	NS
Echocardiographic parameters			
LVEF, %	59.2 $\pm$ 3.04	60.3 $\pm$ 3.21	NS
FS, %	31.4 $\pm$ 2.26	31.9 $\pm$ 2.01	NS
LVIDd, cm	5.32 $\pm$ 0.19	5.28 $\pm$ 0.11	NS
LVIDs, cm	3.42 $\pm$ 0.21	3.36 $\pm$ 0.27	NS
IVSd, cm	1.05 $\pm$ 0.04	1.02 $\pm$ 0.05	NS
PWd, cm	1.04 $\pm$ 0.03	1.02 $\pm$ 0.03	NS
Left atrial diameter, cm	3.90 $\pm$ 0.17	3.84 $\pm$ 0.18	NS
LVM, g/m <sup>2</sup>	92.1 $\pm$ 4.8	90.8 $\pm$ 4.2	NS
E wave, m/s	0.85 $\pm$ 0.06	0.83 $\pm$ 0.05	NS
A wave, m/s	0.72 $\pm$ 0.05	0.69 $\pm$ 0.05	NS
E/A ratio	1.17 $\pm$ 0.16	1.21 $\pm$ 0.17	NS
IVRT	0.09 $\pm$ 0.01	0.09 $\pm$ 0.01	NS
DT, s	0.19 $\pm$ 0.01	0.18 $\pm$ 0.02	NS

SEM = standard error mean, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, GFR = glomerular filtration rate, LVEF = left ventricular ejection fraction, FS = fractional shortening, LVIDd = left ventricular internal diameter at end diastole, LVIDs = left ventricular internal diameter at end systole, IVSd = interventricular septal thickness at end diastole, PWd = posterior wall thickness at end diastole, LVM = left ventricular mass, E = early diastolic filling velocity, A = diastolic filling velocity during atrial contraction, IVRT = left ventricular isovolumic relaxation time, DT = deceleration time of the early filling velocity.

venous thrombosis and subsequent pulmonary embolism. Antiplatelet drugs (aspirin or clopidogrel) were prescribed during hospitalization in atherothrombotic and lacunar infarctions, while the majority of patients with a cardioembolic infarction received warfarin. No patient received intravenous thrombolysis. The experimental protocols and the process for obtaining informed consent were approved by the appropriate institutional review committee.

### NT-ProBNP Determinations

Blood samples were taken in all patients at study entry and at day 6. Venous blood samples were taken with the subject, having taken his or her usual medication, lying quietly in a semi-recumbent position. Samples were put into chilled EDTA tubes, placed immediately on ice, and centrifuged within 20 minutes at +4 °C. The plasma was stored at -70 °C before being assayed for NT-proBNP. Plasma NT-proBNP concentration was measured using a commercial enzyme immunoassay kit (Biomedica GmbH Wien). This is a competitive Enzyme Immunoassay (EIA) designed to measure the N-terminal portion (1–76) of proBNP. The kit uses an immunoaffinity purified polyclonal antibody specific for proBNP (8–29) that is attached to the plastic surface of a microtiter 96 well plate and a horse radish peroxidase labeled peptide (8–29) as a tracer. The detection limit of the assay is 5 fmol/mL. The intra assay variation for a concentration of 100 fmol/mL was estimated to be 7.5%.

Statistical Analysis NT-proBNP values were normally distributed (Kolmogorov-Smirnov and P-P plot). The Student's t test for unpaired data was applied to assess the statistical significance of differences between patients and controls. Student's t test for paired data was applied in order to compare NT-proBNP levels at different time points. All the analyses were 2-tailed. Correlation coefficients were calculated by linear regression analysis to evaluate the degree of linear association between NT-proBNP and NIHSS.

Statistical analysis was performed with Graph Pad Prism version 4.01 for Windows, Graph Pad Software, San Diego California USA. A value of

$p < 0.05$  was considered significant. Data are expressed as mean  $\pm$  SEM.

## Results

### Serum Concentrations of NT-ProBNP

The mean serum NT-proBNP concentration in the patients presenting with acute ischemic stroke was significantly higher than that of the controls. At the time of admission, mean NT-proBNP levels were  $129.9 \pm 9.9$  fmol/mL, compared with the control level of  $90.8 \pm 6.3$  fmol/mL ( $p < 0.05$ ). NT-proBNP levels remained elevated in the patients at day 6 ( $113.5 \pm 13.0$  fmol/mL) (Figure 1). The difference in NT-proBNP levels between days 0 and 6 was not significant. The difference in NT-proBNP levels between patients at day 6 and controls was not significant.

### Correlation of NT-ProBNP Levels with Infarct Location, Subtype, Size, and NIHSS

Subjects with cardioembolic stroke expressed NT-proBNP levels that were significantly higher on admission than those from the atherothrombotic group ( $p < 0.05$ , Table III; Figure 2). There were no significant differences in the NT-proBNP levels between strokes of carotid or vertebrobasilar location at any time point. No significant correlation was found between the NT-proBNP levels and the neurologic deficit at any time point as assessed by the NIHSS, or between large, medium, or small infarctions.

## Discussion

Acute ischemic stroke causes profound neuroendocrine changes and neurohormonal activation.<sup>15,16</sup> It induces a number of responses, which are local in their extent of action, but their induction stimulates the activation of systemic physiological reactions, although the mechanisms by which the initial ischemic insult induces these peripheral effects are not fully understood.<sup>17</sup> Some of the systemic responses are probably mediated by increased activity of the hypothalamic-pituitary-adrenal axis and the adrenal medulla, which results in high levels of adrenocorticotropic hor-

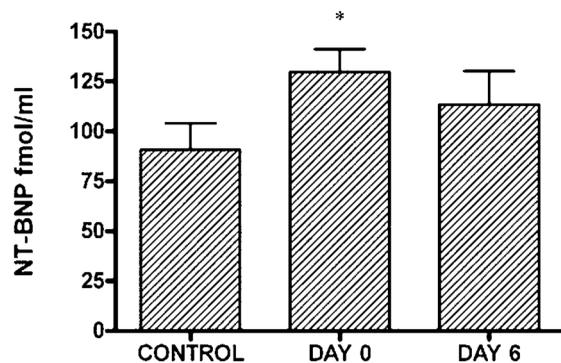


Figure 1. Plasma NT-proBNP concentrations in controls and stroke patients on admission and on day 6 (\* $p < 0.05$  vs control).

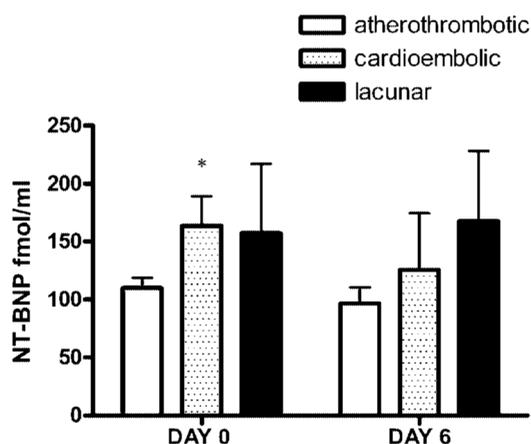


Figure 2. Serum concentrations of NT-proBNP in patients with atherothrombotic ( $n = 17$ ), cardioembolic ( $n = 8$ ), and lacunar ( $n = 5$ ) stroke subtypes at different time points (\* $p < 0.05$  vs atherothrombotic at day 0).

none, cortisol, and catecholamines.<sup>18</sup>

BNP levels correlate with the degree of cardiac dysfunction. Several reports showed that BNP is a useful indicator of prognosis in chronic heart failure. BNP levels are elevated in both systolic and diastolic dysfunction, with the highest values being reported in patients with systolic dysfunction plus a decreased mitral valve deceleration time. A low BNP level makes echocardiographic indices of LV dysfunction (both systolic and diastolic) highly unlikely.<sup>19</sup> A number of other clinical and laboratory variables can influence the

Table III. NT-proBNP (fmol/mL) plasma concentrations in patients after acute ischemic stroke.

Stroke Type	Day 0	Day 6
Small infarct	135.2 $\pm$ 23.2	131.1 $\pm$ 33.3
Moderate infarct	111.1 $\pm$ 16.1	100.2 $\pm$ 21.6
Large infarct	135.6 $\pm$ 16.2	99.7 $\pm$ 18.2
Anterior	136.4 $\pm$ 12.7	126.2 $\pm$ 19.6
Posterior	99.4 $\pm$ 17.4	71.2 $\pm$ 13.4
Atherothrombotic	108.4 $\pm$ 8.3	99.3 $\pm$ 12.3
Cardioembolic	166.3 $\pm$ 25.3*	129.3 $\pm$ 37.2
Lacunar	153.8 $\pm$ 42.2	161.3 $\pm$ 51.2

\*Values significantly different ( $p < 0.05$ ) at day 0 from atherothrombotic.

NT-proBNP value. In 1 study sample, female sex, greater age, increasing dyspnea, diabetes mellitus, valvular heart disease, low heartrate, LVEF  $\leq 45\%$ , abnormal ECG, high plasma creatinine, low plasma glycosylated hemoglobin A<sub>1c</sub>, and high urine albumin were independently associated with a high plasma NT-proBNP by multiple linear regression analysis.<sup>20</sup> In our study there were no differences in the incidence of hypertension, diabetes mellitus, AF, and coronary heart disease between the 2 groups. Furthermore, both patients and controls had no differences in indices of systolic or diastolic LV function and there were no differences in blood pressure or heart rate measurements. Also, there were no significant differences between the 2 groups concerning previous medical treatment.

The major finding in our study is that NTproBNP levels are significantly elevated in acute ischemic stroke. The NT-proBNP levels were more profoundly increased during the first 24 hours after the onset of symptoms, and they did not correlate with the severity of neurologic deficit or with the site and the size of the infarct. Furthermore, NT-proBNP remained elevated over the 6-day study period, although nonsignificantly compared with the baseline levels.

The mechanism for this increase may be a counterbalancing vasodilating response to the cerebral ischemia. Recent evidence showed that there is some immunore activity of BNP through the brain, including the cerebral cortex, thalamus, cerebellum, pons, and hypothalamus, thus indi-

cating that BNP secretion may be induced by pathological processes involving these regions.<sup>21</sup> A potent paracrine action of BNP may explain the counterbalancing vasodilation occurring after the acute ischemic insult. Saper et al<sup>22</sup> demonstrated that the internal carotid artery and the proximal portions of the middle and anterior cerebral and posterior communicating arteries are the most intensely innervated by BNP-immunoreactive fibers in the rat. These findings suggest that an ischemic insult to the brain may induce BNP secretion, which serves as a vasodilatory neuro-modulator in the cerebral circulation. It is also known that BNP is cosecreted with atrial natriuretic peptide (ANP) and both are released in response to the same stimuli.<sup>23</sup> An acute increase in ANP levels in patients with acute ischemic stroke was reported; this was attributed to a vasodilator response to the potent constrictor effect of endothelin-1.<sup>24</sup> Ischemic stroke is associated with marked and sustained increases in endothelin-1, which can cause gene induction of BNP.<sup>25</sup> Another study showed that BNP and endothelin-1 interact in the central nervous system to regulate cardiovascular and hormonal functions.<sup>26</sup> The increase of ANP in patients with acute ischemic stroke is documented by previous studies and it has been implicated as a cause of the accompanying hyponatremia in stroke.<sup>27</sup> An experimental study reported a statistically significant increase in the number of ANP-immunoreactive glial cells (mainly astrocytes) in the white matter surrounding the brain infarction compared with the intact area, suggesting that glial ANP may increase in brain infarction and that it may be involved in the regulation of the cerebral blood flow in the infarcted area.<sup>28</sup>

It is also known that subarachnoid hemorrhage (SAH) causes an elevation in plasma concentrations of BNP, peaking 7 to 9 days after the onset of symptoms. This increase may be related to the rise in noradrenaline levels at exactly the same period.<sup>29</sup> The mechanism and source of BNP are not yet clarified in patients with SAH. Patients with SAH sometimes demonstrate cardiac damage, including serial ECG changes and wall motion abnormalities.<sup>30</sup> Perhaps the same pattern of BNP elevation occurs after an acute ischemic insult.

Another explanation may be direct myocardial dysfunction and high ventricular wall stretch caused by the acute ischemic stroke. There is a high incidence of cardiac damage (17%), being reflected by raised troponin T serum concentrations and a strong association with inpatient mortality (a threefold increase in the risk of death) in patients presenting with an ischemic stroke and troponin elevation, not attributed to a prior cardiac event.<sup>31</sup> A previous study has suggested that cardiac damage after a stroke is neurally mediated through abnormal autonomic discharges.<sup>32</sup> Noradrenaline concentrations are raised after a stroke, and higher concentrations have been associated with myocardial changes.<sup>33</sup> Mean NT-proBNP levels were higher in the serum of patients with a definite cardioembolic source, which suggests that NT-proBNP could be a marker indicating the type of event. Cardioembolism usually occurs in the setting of underlying cardiac dysfunction, while atherothrombotic and lacunar strokes suggest end-organ damage with or without cardiac dysfunction. It is known from a previous study that acute cardioembolic stroke and AF produce significantly higher ANP values than acute lacunar stroke and healthy controls.<sup>34</sup>

Our study has limitations. The sample size is small, especially the size of the subgroups.

In conclusion, we report an increase in NT-proBNP levels in subjects with acute ischemic stroke independently of the preexisting cardiovascular risk factors and cardiac echocardiographic parameters. Further studies may clarify the pattern of this NT-proBNP elevation and the influence of thrombolytic therapy.

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# Acquired von Willebrand disease in a patient with Wilms tumor

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VON WILLEBRAND DISEASE is usually inherited as an autosomal dominant trait, and is generally characterized by a prolonged bleeding time, abnormally low levels of Factor VIII coagulant activity and Factor VIII-related antigen, as well as decreased platelet adhesiveness and abnormal ristocetin aggregation.<sup>1</sup> However, not all of these features are necessarily present consistently in every individual with this disorder.<sup>2-4</sup>

Several patients with acquired bleeding disorders resembling von Willebrand's disease have previously been reported; most of these patients had an associated immunologic or lymphoproliferative disease.<sup>2-4</sup> In this report we describe the clinical and laboratory findings of an infant with unilateral Wilms tumor and a bleeding diathesis consistent with von Willebrand disease, which resolved following surgical resection of the tumor.

## CASE REPORT

A 7½-month-old-boy was admitted to Children's Memorial Hospital with symptoms of increasing abdominal girth, bruises, and gingival bleeding of several weeks duration. His past history, including circumcision, revealed no hemorrhagic problems. The family history was entirely nega-

tive for bleeding symptoms.

On physical examination there was marked abdominal distension with a prominent venous pattern and a large firm mass measuring 10 X 11 cm palpable in the right upper quadrant and flank. Multiple ecchymotic areas were noted over the upper and lower extremities. An intravenous pyelogram revealed a large right-sided intrarenal mass. Results of roentgenogram of the chest, bone scan, and hematologic studies were normal. Coagulation studies were performed preoperatively and serially in the postoperative period (Table).

Pooled cryoprecipitate, which was assayed and administered in a Factor VIII dose of 40 units/kg, resulted in a transient rise to 25% in the level of Factor VIII activity. Subsequently, commercial Factor VIII concentrate infusions were administered preoperatively and resulted in a Factor VIII level of 60% at the time of surgery. Further infusions were given daily in the postoperative period. In spite of diminishing doses of Factor VIII concentrate in the first postoperative week, there was a sustained level of Factor VIII activity within the normal range, and a shortening of the bleeding time. No further concentrate was given after day 7. The histopathologic diagnosis was consistent with typical Wilms tumor (Group I) and he was treated with vincristine and actinomycin

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† Deceased

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Dover a six-month period according to the National Wilms Tumor Study II Protocol. Two years following surgery, he remains free of tumor and has had no recurrence of hemorrhagic symptoms.

#### Abbreviations used

VIII:C: Factor VIII coagulant activity

VIII:Ag: Factor VIII-related antigen

## METHODS

The prothrombin time, partial thromboplastin time, thrombin time, and assays of fibrinogen, Factors VIII and IX were measured by standard techniques using a fibrometer clot-timer.<sup>5</sup> Screening tests for the presence of a circulating inhibitor to Factor VIII were performed by assaying the residual Factor VIII:C activity after incubating mixtures of test and control plasma at 37° C for 60 minutes.<sup>6</sup> The bleeding time was measured using the modified Ivy template technique. Factor VIII:Ag determinations were performed in the laboratory of Dr. Leon Hoyer, Farmington, Conn., using a radioimmunoassay technique which employs an anti-human Factor VIII antibody.<sup>7</sup> Platelet adhesion was measured by passing whole blood through a glass bead column. Platelet aggregation studies were performed on a

Chronolog aggregometer using adenosine diphosphate, epinephrine, collagen, and ristocetin as aggregating agents. The ristocetin co-factor assay was performed in the laboratory of Dr. Charles Abildgaard, using a modified technique of Macfarlane et al.<sup>8</sup>

## DISCUSSION

The laboratory features of a prolonged bleeding time and reduced levels of Factor VIII:C and Factor VIII:Ag support the diagnosis of von Willebrand disease in this child. The development of bleeding symptoms co-incidental with the occurrence of Wilms tumor, the resolution of all clinical signs of bleeding postoperatively, and the presence of normal coagulation studies obtained on repeated determinations over a two-year period of time following surgery lend support to the possibility that the von Willebrand disease in this patient was related to the presence of the tumor. It is unlikely that these findings were the result of a hereditary coagulopathy inasmuch as there was no family history of hemorrhagic problems and no coagulation abnormalities were demonstrated in all members of the immediate family who could be adequately studied. The patient's father has demonstrated slightly prolonged bleed-

**Table.** Results of coagulation studies in the patient

	Normal values	Initial studies	Post-infusion*	Postoperative			
				24 hours	14 days	6 mo	15 mo
Prothrombin	10.5-14.5 sec	14.7/11.0	—	—	11.7/11.0	11.8/10.8	11.1/10.5
Partial thromboplastin time	30-45 sec	94.7	60.0	—	40.7	43.3	37.2
Fibrinogen	150-350 mg/dl	115	300	—	330	—	195
Thrombin time	15-19 sec	17.3/15.7	—	—	—	—	—
Fibrinogen split products	10 mg/dl	<10	—	—	—	—	—
Factor V	50-120%	60	—	—	—	—	—
Factor VIII:C	50-150%	5	25	124	180	61	78
Factor VIII:Ag	60-185%	<2	8	—	118	59	72
Ristocetin co-factor	50-150%	—	—	—	—	92	134
Bleeding time	<12 min	>20	—	—	7	—	8½
Platelet count	250-400,000/mm <sup>3</sup>	340,000	315,000	—	265,000	—	315,000
Platelet adhesion	>25%	55	—	—	36	—	53
Platelet aggregation	Normal	Normal	—	—	Normal	—	Normal
Inhibitor screen	Negative	Negative	—	—	—	—	—

\*Levels measured 10 minutes following first infusion of cryoprecipitate; 48 hours later he received 80 units/kg of Factor VIII concentrate which raised the Factor VIII level to 60% immediately preoperatively.

ing times and variability of aggregation responses which we feel are most likely related to the large quantities of aspirin which he ingests daily.<sup>9</sup>

Although the presence of a circulating inhibitor to Factor VIII was considered because of the less than expected response to Factor VIII containing materials infused, no evidence of such an inhibitor could be detected by our screening technique and this problem remained unexplained. Although the reduced fibrinogen level in association with a deficiency of Factor VIII could suggest the presence of a consumptive coagulopathy, the normal platelet count, normal red cell morphology, negative fibrinogen degradation products, and normal Factor V level make this an unlikely explanation for the bleeding disorder in this patient. Platelet functional abnormalities were excluded by the findings of normal platelet adhesion and aggregation.

The occurrence of von Willebrand disease as an acquired condition is rarely observed. Most of the previously reported cases have been in patients with connective tissue disease, immunologic disorders, and lymphoreticular malignancies.<sup>2-4</sup> The presence of an antibody with inhibitory activity against the Factor VIII molecule in some of these cases suggests the possibility of an immunologic basis for the acquired forms of von Willebrand disease. Handin et al<sup>2</sup> described an adult male with lymphosarcoma and von Willebrand disease in whose plasma they were able to demonstrate an IgG-type antibody that prevented aggregation of normal platelets by ristocetin. In contrast, Joist et al<sup>3</sup> studied an adult male with lymphoma and von Willebrand disease in whom they could find no evidence of a circulating inhibitor. However, by immunoelectrophoretic techniques they were able to demonstrate a quali-

tative Factor VIII abnormality; they suggested that the bleeding diathesis in their patient may have been due to abnormal binding or destruction of the abnormal protein by neoplastic cells.

Whether these or other mechanisms were responsible for the bleeding disorder observed in our patient is unknown. However, Wilms tumor, one of the most common malignant tumors in children, is not usually associated with any immunologic abnormality. One other child with Wilms tumor and an apparently acquired von Willebrand-like syndrome has been briefly described.<sup>10</sup> In that patient, levels of Factor VIII:C, VIIIIR:Ag, and VIIIIR:AgII were abnormally low without any evidence of a circulating inhibitor to Factor VIII. Three months following surgical removal of the tumor all coagulation values were normal.

As in some of the other patients with acquired von Willebrand disease reported, treatment of the associated malignant disorder resulted in the resolution of bleeding manifestations in our patient. It would thus seem reasonable to speculate that the tumor itself may have produced or released a substance that selectively inhibited a plasma factor resulting in a defect similar to that observed in genetic von Willebrand disease.

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# Effect of profound hypothermia during circulatory arrest on neurologic injury and apoptotic repressor protein Bcl-2 expression in an acute porcine model

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## ABSTRACT

**Objectives:** We reported that the neocortex and hippocampus are selectively vulnerable to injury in an acute porcine model of hypothermic circulatory arrest at 18°C. We hypothesize that further cooling to 10°C could reduce neurologic injury in these regions. To further elucidate the mechanisms of neurologic injury and protection, we assessed the expression of the anti-apoptotic protein Bcl-2.

**Methods:** Twelve piglets underwent 75 minutes of hypothermic circulatory arrest at 18°C (n = 6) and 10°C (n = 6). After gradual rewarming and reperfusion, animals were put to death and brains were perfusion-fixed and cryopreserved. Regional patterns of neuronal apoptosis after hypothermic circulatory arrest were characterized by in situ DNA fragmentation with terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) histochemistry. Bcl-2 protein expression was characterized with immunohistochemistry. Statistical comparisons were made by *t* test, analysis of variance, and Mann-Whitney *U* test, as appropriate.

**Results:** Concentrations of TUNEL(+) cells were significantly lower after profound hypothermia at 10°C compared with 18°C hypothermia in the sensory and motor neocortex and hippocampus (*t* test,  $P < .0001$ ;  $P < .006$ ;  $P < .006$ , respectively). Positive Bcl-2 immunostaining was observed only in the motor and sensory neocortex and hippocampus after 18°C hypothermic circulatory arrest. Profound cooling to 10°C resulted in a significant increase in Bcl-2 immunostaining in the motor and sensory cortex as compared with 18°C (Mann-Whitney *U* test,  $P < .05$ ).

**Conclusions:** Deep hypothermia at 10°C protects the neocortex and hippocampus from insult during hypothermic circulatory arrest as suggested by significantly reduced TUNEL(+) staining in these areas. Although a concomitant increase in Bcl-2 expression was observed in the neocortex at 10°C, it remains unclear whether profound hypothermia deters from neuronal injury by activation of the anti-apoptotic protein Bcl-2.

Experimental studies have demonstrated that prolonged hypothermic circulatory arrest (HCA) can lead to neuronal cell death, probably as a consequence of a number of different pathways triggered by ischemia.<sup>1-3</sup> Cerebral ischemia can lead to neuronal injury by the process of apoptosis, as well as by necrosis, with a series of steps existing between the initial ischemic insult and neuronal death. Within this cascade, several proteins that facilitate neuronal survival compete with molecules that contribute to cell death. Ultimately, the final balance between cell survival-promoting proteins versus cell death-promoting proteins determines the fate of the cell.<sup>4</sup> The Bcl-2 family of proteins plays an important role in cell survival-cell death decision.<sup>5-6</sup>

HCA has been used for some 40 years as a means of interrupting normal perfusion of the brain and preventing subsequent cerebral ischemic injury during various cardiovascular surgical procedures. Neuroprotection appears to be effectively achieved by hypothermia during HCA, although the mechanisms underlying this effect remain to be elucidated. Hypothermia acts by reducing cerebral metabolic activity and oxygen demand, preventing the release of neurotransmitters, and delaying the onset of fatal biochemical cascade.<sup>7-9</sup> Although reduced, brain metabolism is not adequately suppressed and remains relatively high in conventional HCA protocols at 18°C.<sup>7</sup> In a previous report, we<sup>10</sup> characterized acute brain injury after HCA in a juvenile pig model. We found that after 75 minutes of HCA at 18°C, there were increased terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL)-positive staining cells indicating DNA fragmentation, especially in the neocortex and hippocampus, with the absence of morphologic evidence of apoptosis. We hypothesized that these findings were compatible with the early activation of the apoptotic pathway.

In light of evidence suggesting that the cascade of events leading to apoptosis may be inhibited in the earlier stages,<sup>11</sup> the present study was undertaken to assess whether profound cooling to 10°C can reduce neurologic injury during 75 minutes of HCA in an acute porcine model compared with less profound cooling (18°C). To further elucidate the mechanisms of neurologic injury and protection, we assessed the expression of the anti-apoptotic protein Bcl-2.

#### Abbreviations and Acronyms

ANOVA	= analysis of variance
CPB	= cardiopulmonary bypass
HCA	= hypothermic circulatory arrest
PLSD	= protected least significant difference
TUNEL	= terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling

#### Materials and Methods

Sixteen male juvenile pigs from a commercial farm, 2.5 to 35 months of age and weighing 30 to 35 kg, were used for this study. The animals were divided into three groups: group A (n = 6) underwent HCA at 18°C for 75 minutes, group B (n = 6) underwent HCA at 10°C for 75 minutes, and group C (n = 4) served as normal controls. All animals were treated in accordance with the "Principles of Laboratory Animal Care," as described by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Resources, National Research Council. The protocol used in this study was also approved by the Animal Care and Use Committee of the University of Ioannina.

#### Animal Preparation

Preparation and surgery were performed as pre-

viously described.<sup>10</sup> In brief, catheters were inserted in an ear vein and the left femoral artery for monitoring purposes and withdrawal of blood samples. Anesthesia was induced with intramuscular ketamine hydrochloride (15 mg/kg), atropine (0.05 mg/kg), and midazolam (Dormicum; 0.1 mg/kg) and was maintained with intravenous fentanyl (50-200 µg/kg), midazolam, and 1% to 2% isoflurane. Paralysis was achieved with an intravenous bolus of rocuronium (0.6 mg/kg) and was maintained with 20% of the total dose every 30 minutes.

Animals were ventilated mechanically with 100% oxygen, after endotracheal intubation. Ventilator rate and tidal volume were adjusted to maintain the  $P_{aCO_2}$  tension at 40 mm Hg. Hematocrit values during cardiopulmonary bypass (CPB) were maintained between 13% and 23%. A temperature probe was placed in the rectum, and brain temperature was determined with bilateral tympanic membrane probes. Urine output was collected through a bladder catheter (Foley 8F-10F). Arterial pressure, end-expired carbon dioxide, electrocardiogram, and blood gases (ABL Radiometer Medical A/S DK-2700, Copenhagen, Denmark) were monitored.

### CPB and HCA

As previously described, the chest was opened via a right thoracotomy in the fourth intercostal space.<sup>10</sup> After administration of intravenous heparin (300 IU/kg), cannulas were advanced to the ascending aorta (16F arterial cannula) and to the right atrium (single 26F cannula). Nonpulsatile CPB was initiated at a flow rate of  $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and then adjusted to maintain a minimum arterial pressure of 50 mm Hg. To avoid chslection of the left ventricle during CPB, we inserted a 1 OF vent catheter via the superior pulmonary vein. The lungs were allowed to collapse after CPB was initiated. The CPB circuit was primed with a bloodless solution consisting of 1000 mL lactated Ringer's solution, 50 mL mannitol, and 5000 IU heparin. Sodium bicarbonate was added to adjust the pH to 7.4, as necessary.

CPB was continued for an average 58 or 106 minutes, to reach a deep brain temperature of 18°C

or 10°C, respectively. Myocardial protection was afforded by applying iced saline (4°C) topically during the 75-4minute interval of HCA. When the tympanic membrane temperature reached 18°C or 10°C, bypass was discontinued, the blood was drained into the oxygenator reservoir, and circulatory arrest was maintained for 75 minutes. Ice bags were positioned around the head to maintain the brain temperature during HCA. At the end of the arrest, bypass was initiated again with gradual rewarming to a rectal temperature of approximately 35°C to 36°C. A temperature gradient exceeding 10°C between the perfusate and the core temperature was avoided. A temperature of 36°C was reached after an average of 83 or 104 minutes of reperfusion for animals treated with 18°C or 10°C HCA, respectively. Systemic pressure was maintained above 60 mm Hg during reperfusion. Measurements of hemodynamics (heart rate, mean arterial pressure), arterial blood gases, hematocrit, glucose, as well as temperatures were recorded at 5 time points during the experiment: (1) baseline at 37°C and before CPB; (2) at the initiation of CPB; (3) during CPB, while cooling to a brain temperature of 18°C or 10°C just before HCA; (4) during rewarming; and (5) at the end of CPB.

### Histologic Preparation and Evaluation

At the end of the experiment (approximately 170 minutes after the onset of circulatory arrest), brains were perfused in situ with chilled saline solution 0.9% (1L) followed by 4% paraformaldehyde in 0.1 mol/L phosphate-buffered saline solution (1 L, pH 7.4). The descending aorta was crossclamped to avoid significant loss of perfusion solution to the lower body. The brains were removed en toto, immersed in 4% paraformaldehyde, and stored at 4°C in phosphate-buffered saline solution. Control animals (n = 4) received no intervention and were put to death for histologic analysis.

All brains were bisected in the sagittal plane. Tissue blocks from the left hemisphere were cut to encompass brain regions known for their vulnerability to hypoxia and ischemia. Brain regions evaluated included the precentral gyms (motor

neocortex), the postcentral gyrus (sensory neocortex), hippocampus, cerebellum, thalamus, and anterior ventral medulla. Tissue blocks were dehydrated in ethanol and xylene and embedded in paraffin. Serial 8- $\mu$ m sections were cut from each tissue block and were mounted onto slides. Hematoxylin and eosin was used to characterize cell damage morphologically.

Neuronal apoptosis was characterized by in situ DNA fragmentation with TUNEL histochemistry. The TUNEL assay was performed as described elsewhere<sup>4</sup> with the Apop Tag in situ Apoptosis Detection Kit-Peroxidase (Oncor, Gaithersburg, Md). Each assay included positive and negative controls. All slides were evaluated by a neuro-anatomist in a blind fashion. Cell damage was categorized as either necrotic or apoptotic according to classic morphologic criteria in sections prepared with hematoxylin and eosin, as previously described.<sup>10</sup>

TUNEL(+) cells were identified by a red-stained, condensed nucleus with apoptotic bodies, along with a diminutive or absent cytoplasm. To describe the extent of apoptosis in the various brain regions, we used a semiquantitative scoring system.<sup>11</sup> Each slide was scored on a scale of 0 to 5, as follows: grade 0, no TUNEL(+) cells; grade 1, less than 10% TUNEL(+) cells; grade 2, 10% to 25% TUNEL(+) cells; grade 3, 25% to 50% TUNEL(+) cells; grade 4, 50% to 75% TUNEL(+) cells; and grade 5, greater than 75% TUNEL(+) cells. Scores from histologic evaluation and TUNEL assays were averaged from 4 to 8 slides from every region in each animal.

### **Bcl-2 Immunohistochemistry**

Cryosections were fixed in 75% acetone and 25% ethanol for 10 minutes, then treated with 10  $\mu$ g/mL proteinase K (Dako Corporation, Carpinteria, Calif) for 15 minutes and 0.5% Triton X-0.03% H<sub>2</sub>O<sub>2</sub>-0.1% body surface area for 20 minutes. Sections were incubated in 1.5% normal goat serum for 1 hour, then incubated overnight at 4°C in specific first Bcl-2 antibody (Dako). Slides were then incubated for 1 hour at room temperature in appropriate biotinylated secondary immunoglobulin G preabsorbed to normal serum. After being

washed in phosphate-buffered saline solution, the sections were incubated for 1 hour at room temperature in 2% avidin-biotin complex, followed by 3,3'-diaminobenzidine as the chromogen. Negative controls consisted of sections incubated without the antibodies. Iliymus was used as a positive control.

The number of immunopositive cells in 4 to 5 fields was counted by an investigator blinded to the treatment groups. Staining intensities were graded according to the number of positive cells counted with a 4-grade scale: (1) negative: 0 cells stained; (2) weakly positive: 1 to 5 cells stained; (3) positive: 6 to 15 cells stained; and (4) moderately positive: more than 15 cells stained.

### **Statistical Analysis**

Values are expressed as mean  $\pm$  standard deviation (SD) unless indicated otherwise. When appropriate, differences between two groups were assessed by the unpaired 2-tailed *t* test. Differences among groups in TUNEL histochemistry studies were compared by analysis of variance (ANOVA) followed by the Fisher protected least significant difference (PLSD) post hoc analysis. Differences between groups in Bcl-2 immunohistochemistry studies were assessed with the Mann-Whitney *U* rank sum test for noncontinuous data.

## **Results**

### **Physiologic and Metabolic Parameters**

All experimental animals survived the surgical protocol and HCA, as described above. All animals used in this study were male and were housed for at least 3 days in the Animal Housing Facilities of the University of Ioannina. Mean ( $\pm$ SD) preoperative body weights for animals treated with 18°C and 10°C HCA and normal controls were 30.7  $\pm$  3.7, 34.2  $\pm$  3.1, and 31.3  $\pm$  3.0 kg, respectively. Respective mean ( $\pm$ SD) ages were 70.5  $\pm$  7.7, 86.2  $\pm$  5.6, and 74.8  $\pm$  3.8 days.

The mean duration ( $\pm$ SD) of CPB cooling for animals with 18°C versus 10°C HCA was 57.5  $\pm$  17.3 and 105.8  $\pm$  21.8 minutes, respectively (*t* test; *P*  $\leq$  .002). The mean duration ( $\pm$ SD) of CPB warming for animals with 18°C versus 10°C HCA was 82.5  $\pm$  10.4 and 104.2  $\pm$  19.8 minutes, respec-

**TABLE 1. Physiologic variables**

Variable	Baseline	Initial CPB	Cooling	Warming	End CPB
<b>Brain temperature (°C)</b>					
18°C	36.5 ± 0.4	34.1 ± 1.8	18.0 ± 0.0	25.8 ± 3.2	36.5 ± 0.8
10°C	36.5 ± 0.4	33.2 ± 1.6	10.0 ± 0.0	28.2 ± 3.1	36.9 ± 0.2
<b>MAP (mm Hg)</b>					
18°C	114.0 ± 14.9	57.2 ± 16.3	55.2 ± 8.1	67.8 ± 15.7	68.3 ± 25.7
10°C	118.7 ± 13.0	59.7 ± 10.1	54.0 ± 3.4	69.4 ± 16.5	85.0 ± 8.9
<b>Arterial pH</b>					
18°C	7.40 ± 0.12	7.26 ± 0.19	7.26 ± 0.12	7.20 ± 0.07	7.35 ± 0.14
10°C	7.34 ± 0.13	7.32 ± 0.11	7.28 ± 0.11	7.32 ± 0.08	7.38 ± 0.13
<b>Po<sub>2</sub> (mm Hg)</b>					
18°C	409.9 ± 67.8	751.4 ± 202.8	787.1 ± 319.06*	429.0 ± 126.9	424.6 ± 112.1
10°C	378.4 ± 118.3	689.5 ± 45.5	1066.0 ± 122.8	562.8 ± 123.4	459.4 ± 45.4
<b>Pco<sub>2</sub> (mm Hg)</b>					
18°C	51.32 ± 19.0	73.7 ± 37.8	67.2 ± 31.3	69.3 ± 14.4	38.7 ± 18.7
10°C	58.1 ± 23.3	60.0 ± 17.7	58.2 ± 12.4	44.0 ± 12.9	31.7 ± 9.0
<b>Hematocrit (%)</b>					
18°C	26.4 ± 3.8†	16.4 ± 3.4	15.51 ± 3.3	16.6 ± 3.9	15.5 ± 3.1
10°C	26.0 ± 3.8†	18.5 ± 3.0	18.6 ± 3.7	19.2 ± 3.5	19.2 ± 3.0
<b>Lactate (mmol/L)</b>					
18°C	2.7 ± 1.8	4.5 ± 2.1	5.6 ± 2.5	6.3 ± 1.7*	11.0 ± 4.3
10°C	3.1 ± 1.03	4.4 ± 1.6	8.3 ± 3.0	11.6 ± 2.8	11.9 ± 3.5

All values are expressed as mean ± SD. \* $P \leq .05$  between animals treated with HCA at 18°C versus 10°C (unpaired 2-tailed  $t$  test). † $P \leq .05$  between sample times (ANOVA followed by Fisher PSLD).

tively ( $t$  test;  $P \leq .05$ ). Perioperative physiologic variables are shown in Table 1. Although there were some minor variations, no apparent clinically relevant hemodynamic differences were observed between treatment groups. Lactate levels were significantly higher after HCA at 10°C compared with 18°C during rewarming. Pa levels were significantly lower in 18°C HCA animals than in 10°C during cooling, and hematocrit levels dropped to a similar degree in all experimental animals during the procedure.

### Histologic Evaluation

None of the treatment animals undergoing HCA or the controls in this short-term protocol demonstrated histologic evidence of neuronal injury in any of the brain regions assessed by hematoxylin and eosin staining.

### Acute Neuronal Injury—TUNEL Assay for DNA Fragmentation

**18°C HCA.** HCA for 75 minutes at 18°C resulted in significantly higher TUNEL(+) scores compared with normal controls in all brain regions examined. Compatible with our previous findings, a significantly higher concentration of TUNEL(+) cells were observed in the sensory cortex, motor cortex, and hippocampus than in the cerebellum,

thalamus, and medulla ( $P \leq .05$ ; ANOVA followed by Fisher PSLD) (Figure 1, Table 2)

**10°C HCA.** HCA for 75 minutes at 10°C also resulted in significantly higher TUNEL(+) scores compared with normal controls in all brain regions assessed, although scores were generally lower than those observed at 18°C HCA. TUNEL(+) staining was elevated in the motor and sensory neocortex of animals treated with 10°C HCA compared with controls ( $P \leq .04$  and  $P \leq .002$ , respectively), hi these regions, positive staining

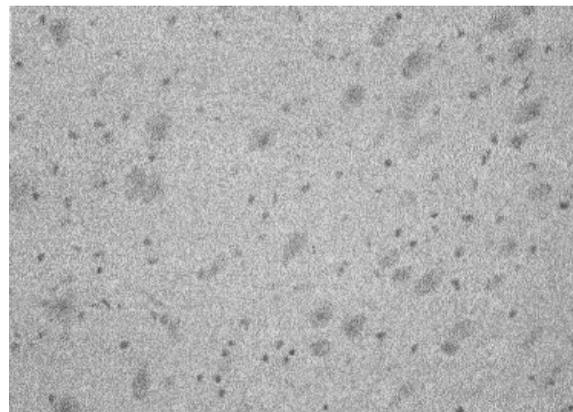


Figure 1. Photomicrograph showing apoptosis in the brain after HCA in a short-term model. Cluster of TUNEL(+) apoptotic neurons (nucleus red stained) are interspersed among normal neurons in die antero-ventral medulla. (Original magnification x400.)

**TABLE 2. TUNEL scores in brain regions of animals treated with HCA at 18°C or 10°C compared with controls**

Brain region	18°C	10°C	Control
Motor cortex	3.28 ± 0.32*	1.79 ± 0.38‡	0.50 ± 0.22
Sensory cortex	3.88 ± 0.13†	1.60 ± 0.31¶	0.14 ± 0.14
Hippocampus	2.67 ± 0.36*	1.39 ± 0.24§	0.17 ± 0.17
Cerebellum	2.13 ± 0.48	1.82 ± 0.23§	0.71 ± 0.18
Medulla	2.00 ± 0.41	2.08 ± 0.23¶	0.57 ± 0.20
Thalamus	2.33 ± 0.67	1.54 ± 0.31¶	0.00 ± 0.00

All values are expressed as mean ± SE. \* $P \leq .006$  and † $P \leq .0001$  compared with values from animals treated with 10°C HCA. ‡ $P \leq .05$ ; § $P \leq .005$ ; ¶ $P \leq .002$  compared with normal control levels.

cells were primarily located in the superficial gray matter. Normal neurons were found interspersed. TUNEL(+) staining was higher in 10°C-treated animals than in controls in the hippocampus ( $P < .005$ ) and was dispersed throughout the CA1-3, CA4, and the dentate gyrus. TUNEL(+) staining was also significantly higher in the anteroventral medulla, thalamus, and cerebellum in animals treated at 10°C compared with controls ( $P \leq .001$ ,  $P \leq .002$ , and  $P < .004$ , respectively). In the cerebellum, TUNEL(+) cells were located in the deep layer of the cerebellar gray matter.

In contrast with our findings at 18°C HCA,<sup>10</sup> animals treated with 75 minutes of HCA at 10°C HCA showed no differences in tissue-specific

vulnerabilities among the neural regions assessed. ( $P > .05$ ; ANOVA followed by Fisher PLSD) (Figure 2).

### Neural Protection

**Region-specific differences.** The mean number of TUNEL(+) cells in serial sections from the sensory cortex, motor cortex, and hippocampus showed a significant reduction when cooled to 10°C as compared with 18°C ( $t$  test  $P < .0001$ ,  $P < .006$ , and  $P < .006$ , respectively). Although levels were lower at 10°C, sections from the thalamus, anteroventral medulla, and cerebellum failed to show any significant reduction in TUNEL(+) staining when animals were treated with deep hypothermia at 10°C as compared with 18°C (Figure 3).

**Bcl-2 immunostaining.** Positive Bcl-2 immunostaining was observed in the motor and sensory neocortex and hippocampus after HCA at 18°C and at 10°C. Bcl-2 immunostaining was absent in the cerebellum, thalamus, and medulla. Profound cooling to 10°C resulted in a significant increase in Bcl-2 expression in the neocortex compared with that observed at 18°C ( $P \leq .05$

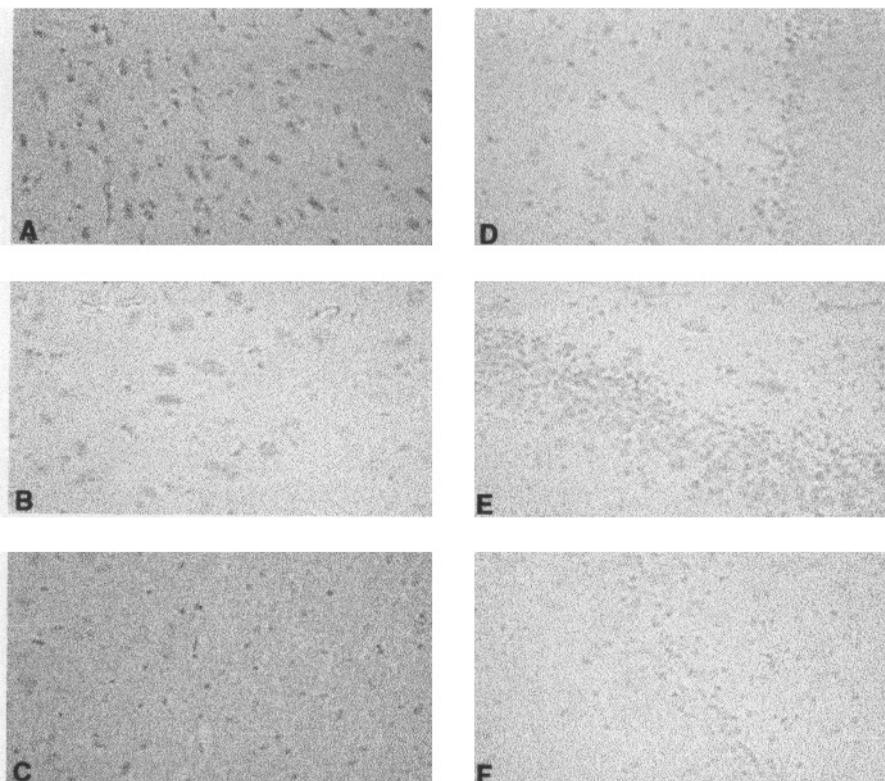


Figure 2. Photomicrographs of brain tissue sections after TUNEL histochemistry. A, B, and C, the precentral gyms (motor neocortex); D, E, and F, the hippocampus. Photomicrographs A and B are from HCA at 18°C HCA; C and E are from WC HCA; and D and F are from normal controls. Note elevated TUNEL(+) staining at 18°C compared with 10°C and the lack of any staining in normal controls. (Original magnification  $\times 400$ .)

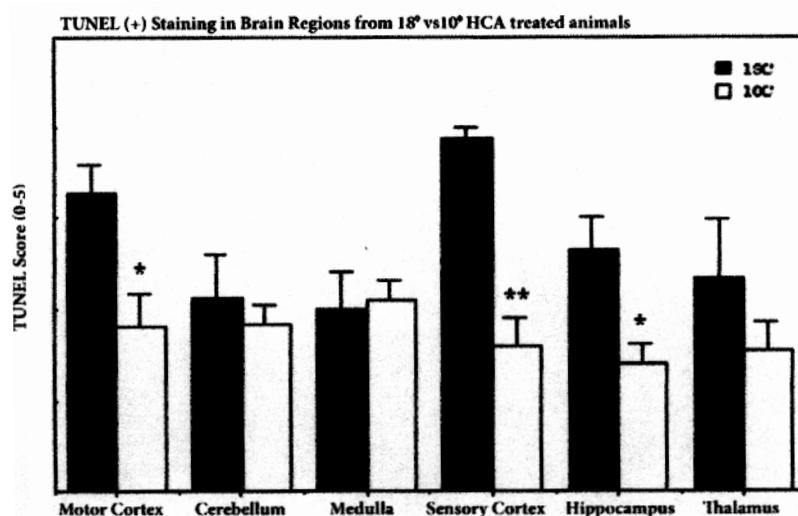


Figure 3. Differences in mean TUNEL (+) scores between HCA at 18°C (solid bars) and profound cooling at 10°C (open bars). Whiskers indicate ± SE. (\*P < .006 and \*\*P ≤ .0001.)

Mann-Whitney U). No significant change was observed in Bcl-2 expression in the hippocampus after profound cooling to 10°C compared with 18°C HCA (Figure 4, Table 3).

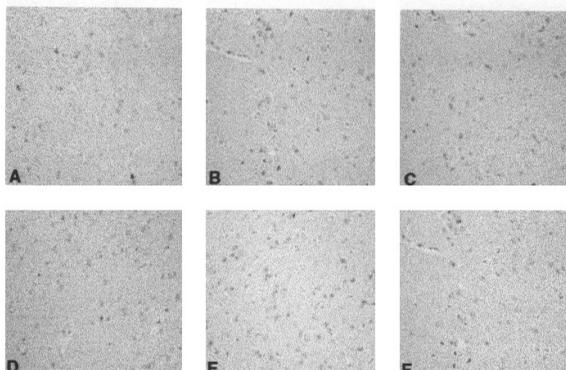


Figure 4. Photomicrographs of brain tissue sections after Bcl-2 immunohistochemistry: A, B, and C, the precentral gyms (motor neocortex); D, E, and F, the post-central gyms (sensory cortex). Photomicrographs A and D are from HCA at 18°C HCA; B and E are from ITC HCA; and C and F are from normal controls. (Original magnification x 400.)

TABLE 3. Regional Bcl-2 immunoreactivity in neocortex and hippocampus

Brain region	18°C	10°C	Control
Motor cortex	1.67 ± 0.33	2.5 ± 0.22*	1.8 ± 0.25
Sensory cortex	0.83 ± 0.31	1.8 ± 0.31*	1.8 ± 0.63
Hippocampus	1 ± 0.52	1 ± 0.45	1 ± 0.41

All values are expressed as mean ± SE. \*P ≤ .05 compared with values from animals treated with 18°C.

### Discussion

Hypothermic metabolic suppression remains a major protection strategy for the brain during intervals of circulatory arrest required for complex aortic reconstruction, among other surgical procedures.<sup>7</sup> Concern about brain intolerance to anoxia has limited ischemic intervals despite cooling to 18°C. This has prompted a search for improved ways of implementing HCA in the hope that the duration of arrest can be tolerated without apparent ill effects.

Previously, we assessed acute neuronal injury in various regions of the brain after HCA at 18°C in a short-term porcine animal model. We reported that neurons in the sensory and motor neocortex, as well as in the hippocampus, were selectively vulnerable to cell injury acutely after 75 minutes of HCA, as determined by a positive TUNEL reaction for DNA fragmentation.<sup>10</sup> Although nerve cell populations in the cerebellum, thalamus, and ventral medulla also showed cell injury, the percentage of TUNEL(+) cells in these areas was significantly less than that observed in the primary motor and sensory cortex and in the hippocampus.<sup>10</sup> These findings were compatible with those reported in models of long-term HCA.<sup>1,2,12</sup> Taken together, it appears that hypoxia-ischemia results in variable injury to selected regions of the brain, rather than global injury.<sup>10-13</sup> Selective vulnerability occurs in both the adult and neonatal brain and reflects heightened sensitivity of spe-

cific neuron groups to injury.<sup>12</sup> It should be noted that although TUNEL testing is a hallmark for apoptosis, it shows poor sensitivity and specificity, inasmuch as the TUNEL assay is unable to distinguish DNA fragmentation associated with apoptotic versus necrotic cell death.

In the present study, we found that profound hypothermia at 10°C during HCA resulted in a significant reduction in neurologic injury as indicated by TUNEL(+) staining in these selectively vulnerable brain regions. TUNEL(+) staining was significantly reduced at 10°C in the motor and sensory cortex and the hippocampus compared with 18°C HCA, indicating increased cerebral protection in these areas. These findings are compatible with previous reports that profound hypothermia results in a better neurologic outcome than conventional HCA methods.<sup>13</sup> Although this study does not elucidate the mechanisms, it does affirm that profound hypothermia exerts a neuroprotective effect. It is noteworthy that the magnitude of the tissue-specific vulnerabilities to insult among the neural regions is less if not altogether absent at 10°C. This is compatible with the findings of Laptok and colleagues,<sup>14</sup> which showed less protection of the hippocampus, thalamus, and striatum with hypothermia compared with other nerve cell populations.

Delayed cell death via apoptotic pathways is of special interest because of the potential for intervention. Although questions remain regarding its specificity and sensitivity, a hallmark of apoptosis is the fragmentation of DNA into smaller ordered oligonucleosomes with 3'-OH end groups, detectable with *in situ* labeling (TUNEL).<sup>15-17</sup> Recent studies using a variety of methods have noted multiple different patterns of apoptotic cell damage in brains after HCA.<sup>1,12,18</sup> Most previous studies use long-term animal models and investigate the extent of brain injury at a later time, resulting in a potential underestimation of the contribution of apoptotic mechanisms to the cerebral sequelae after HCA.<sup>13</sup> Several authors have expressed concern regarding the temporal pattern of brain damage and apoptosis after HCA.<sup>1,12,13</sup> In an effort to evaluate the time course of cerebral injury, Hagl and colleagues<sup>1</sup> put animals to death

at 6,24,48, and 72 hours and at 7,10, and 12 days after HCA. The authors reported that the brain already exhibited serious brain injury at 6 hours after HCA. For the most part, previous reports using a long-term model, although able to assess behavioral outcome, express concern about missing the optimal time for detection of apoptosis.<sup>13</sup> To our knowledge, the only other short-term model is that of Ye and colleagues,<sup>19</sup> who used a much longer insult (120 minutes) and a temperature intermediate (15°C) to that used in the present study. As a result of these previous reports, we selected a very early time point (80-100 minutes after HCA). At this time point we found not morphologic evidence of apoptosis, but significantly greater levels of TUNEL(+) cells in the brain regions assessed, suggesting that damaged cells are being shunted into apoptosis.

Although there is a consensus about the benefits of profound hypothermia, the optimal temperature for maximizing cerebral protection has yet to be identified. Moreover, the exact mechanism of cerebral protection during hypothermia is not clear. It is assumed that, at least in part, protection is achieved secondary to metabolic suppression.<sup>7</sup> In this regard, cerebral oxygen metabolism has been found to be significantly reduced with profound hypothermia at 8°C, whereas at 18°C it remains as high as 24% of baseline, suggesting a less complete cerebral protection at the latter temperature.<sup>8</sup> As further lowering of metabolic rate is achieved with profound cooling, we hypothesize that better cerebral protection is also achieved. Despite this apparent benefit, deep hypothermia has not only been associated with side effects, such as coagulation disorders, but also results in an increase in the time necessary for prolonged CPB owing to the time needed for rewarming. As the temperature decreases, the rate of venous return to the oxygenator pump decreases, as a result of the trapping of blood in areas of capillary stasis. Although low-molecular-weight dextran is able to lessen this effect, limited clinical experience indicates that hypothermia can be associated with hemodynamic instability, cardiac arrhythmias, increased serum lipase and amylase levels, thrombocytopenia, and de-

creased total white blood cell counts.<sup>20-21</sup>

The majority of reports use the classic 90-minute HCA, 20°C model, which results in more severe cerebral injury than that usually observed clinically, where HCA is carried out for shorter intervals.<sup>1,11-13</sup> In the present short-term model, animals were treated with HCA for 75 minutes and were evaluated after approximately 80 to 100 minutes of reperfusion. We found no morphologic evidence of apoptosis, but significantly greater levels of TUNEL(+) cells in the brain regions assessed. It has been suggested that subtle injury results in a greater proportion of damaged cells being shunted into apoptosis, as compared with necrosis. Thus, long-term models may have underestimated the contribution of apoptosis to the cerebral sequelae after HCA.<sup>1</sup> The observation that TUNEL-labeled cells may eventually, but not necessarily, progress into morphologically distinct apoptotic cells also confirms the idea that different morphologic characteristics may reflect different stages of the same death process.<sup>22</sup> A wide variety of stimuli can initiate the apoptotic cascade. After an appropriate stimulus, the first stage or the decision phase is initiated. This is referred to as the genetic control point of cell death, which appears to be regulated by the Bcl-2 family of genes. This is followed by the “execution phase,”

which is responsible for the morphologic changes of apoptosis.<sup>18</sup> Cellular disruption results from activation of the caspases family. Inasmuch as we lack clear morphologic evidence of apoptosis, we hypothesize that our findings indicate an early point of activation of the apoptotic pathway (decision phase).

This hypothesis is supported by our findings in Bcl-2 expression. The Bcl-2 family of proteins are important for the regulation of apoptosis during the “decision phase.”<sup>18</sup> An increase of Bcl-2 has been suggested as an internal protective mechanism against apoptotic cell death, where Bcl-2 is persistently expressed in neurons that survive in ischemia.<sup>4,14</sup> In the present study, brain regions that were selectively vulnerable to neurologic injury, particularly the neocortex and hippocampus, showed higher levels of Bcl-2 expression after HCA at 18°C compared with other brain regions (thalamus, cerebellum, and medulla). Moreover, profound hypothermia at 10°C resulted in a significant decrease in TUNEL(+) staining in these brain regions. Although a concomitant increase in Bcl-2 expression was observed in the neocortex, it remains unclear whether profound hypothermia deters from neuronal injury by activation of anti-apoptotic protein Bcl-2 expression.

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## Discussion

**Dr Frank L. Hanky** (*Stanford, Calif*). Dr Ananiadou, you and your colleagues have designed and executed an excellent study that convincingly shows in this particular porcine model that increased levels of hypothermia from 18°C down to 10°C during 75 minutes of HCA results in less DNA fragmentation and greater expression of the anti-apoptotic protein Bcl-2 in the vulnerable neocortex and hippocampus.

The results of this nicely designed study stand on their own. They are very clear and I would have no argument with what you have shown. However, when it comes to the suggested mechanism and causality that you have implied, there is a little less clarity. That is where I would like to focus just one comment and question and see what you think about it

You have stated very specifically that reduced temperature activates Bcl-2, implying a proposed specific protective effect of lower temperature itself. This would obviously have extremely important implications for how we manage patients clinically and in patients in whom deep HCA is used. However, is it really the lower temperature that activates (his anti-apoptotic mechanism or is it simply that the lower temperature reduces the overall ischemic insult and it is this lesser ischemic insult itself that allows for the increased Bcl-2 activity? Clearly, the ischemic insult is related to two things, the length of circulatory arrest and the temperature at which that length of circulatory arrest exists. The combination of the length and the temperature define the ischemic insult in rough terms.

What I am really asking is, have you looked at this in another way? Would an insult of less length of circulatory arrest, say 50 minutes rather than 75, with a temperature of only 18°C result in increased Bcl-2 activity? Or alternatively, if you increased the ischemic time, the circulatory arrest time to, say, 90 minutes at 10°C, would that not increase Bcl-2 activity, getting

more to the mechanism of what actually is increasing your protective anti-apoptotic protein expression?

**Dr Ananiadou.** What has changed in this protocol, in the two groups, is not the duration of ischemia; it is only the temperature. That is why we hypothesize that the lower temperature is the mechanism that causes increased Bcl-2 immunoreactivity. It is the only parameter to change in this model. The arrest time is the same, 75 minutes. Thus the ischemic interval is the same. The ischemic insult is the same. The protective mechanism that induces the increase of Bcl-2 immunoreactivity is the lowering temperature. That is what I think.

**Dr Hanky.** I understand. But I think there is a fine point here that is very, very important. The ischemic insult is the same, 75 minutes, there is no question, but the injury induced by an ischemic insult may be very different at different temperatures. It is the injury to the neuron that is critical here.

If you are arguing that temperature in and of itself directly, mechanistically increases Bcl-2, then if we are going to do a circulatory arrest operation and have only 20 minutes of circulatory arrest, it would mean we should go down to 10°C. However, if we might need to do circulatory arrest for 40 or 50 or 60 minutes, knowing whether going down to 10°C is more important in that setting than in the shorter setting is critical to how we would manage our patients.

You are implying that the temperature of 10°C in and of itself is always going to be helpful, whereas I am saying it does not seem that clear to me from your model that that is actually the case. Rather, it is the level of neuroinjury that is a combination of arrest time and the lower temperature that may well be what is important.

**Dr Ananiadou.** It is believed that hypothermia alters the pattern of sensitivity of cells. That is why we have different damage. But, on the whole, I agree with you; profound hypothermia is not the only parameter.



# Classification, Electrophysiological Features and Therapy of Atrioventricular Nodal Reentrant Tachycardia

*Demosthenes G Katritsis and Mark E Josephson*

## Abstract

Atrioventricular nodal reentrant tachycardia (AVNRT) should be classified as typical or atypical. The term ‘fast-slow AVNRT’ is rather misleading. Retrograde atrial activation during tachycardia should not be relied upon as a diagnostic criterion. Both typical and atypical atrioventricular nodal reentrant tachycardia are compatible with varying retrograde atrial activation patterns. Attempts at establishing the presence of a ‘lower common pathway’ are probably of no practical significance. When the diagnosis of AVNRT is established, ablation should be only directed towards the anatomic position of the slow pathway. If right septal attempts are unsuccessful, the left septal side should be tried. Ablation targeting earliest atrial activation sites during typical atrioventricular nodal reentrant tachycardia or the fast pathway in general for any kind of typical or atypical atrioventricular nodal reentrant tachycardia, are not justified. In this review we discuss current concepts about the tachycardia circuit, electrophysiologic diagnosis, and ablation of this arrhythmia.

**Keywords** Atrioventricular, nodal, reentrant, tachycardia

**Disclosure** The authors have no conflicts of interest to declare.

Atrioventricular nodal reentrant tachycardia (AVNRT) denotes re-entry in the area of the AV node, and represents the most common regular arrhythmia in the human.<sup>1</sup> Although several models have been proposed to explain the mechanism of the arrhythmia in the context of the complex anatomy and the anisotropic properties of the

atrioventricular (AV) node and its atrial extensions (see *Figure 1*),<sup>2</sup> the actual circuit of AVNRT still remains elusive. Recent studies suggest a three-dimensional AV node with greater variability in the space constant of tissue and poor gap junction connectivity due to differential expression of connexin isoforms, that provide an explanation

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† Deceased

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of dual conduction and nodal reentrant arrhythmogenesis.<sup>3,4</sup>

AV junctional arrhythmias are presented in *Table 1*. Classification schemes for AVNRT have been mainly based on the conventional concept of longitudinally dissociated dual AV nodal pathways that conduct around a central obstacle (see *Table 2*).

In typical slow-fast AVNRT the onset of atrial activation appears prior to, at the onset, or just after the QRS complex, thus maintaining an atrial–His/His–atrial ratio, AH/HA >1. The HA interval is usually <70 ms, measured from earliest deflection of the His bundle activation to the earliest rapid deflection of the atrial activation in the His bundle electrogram, and the VA interval, measured from the onset of ventricular activation on surface ECG to the earliest rapid deflection of the atrial activation on the His bundle electrogram, is <60 ms.<sup>5,6</sup> The atypical, slow-slow form, represents, by definition, an arrhythmia utilising two slow pathways. The AH/HA ratio is  $\geq 1$  but the HA interval is  $\geq 70$  msec, and the AH interval exceeds 200 ms.<sup>7–9</sup>

There are several inherent limitations of this classification. The distinction between fast-slow and slow-slow atypical AVNRT is often arbitrary in view of the lack of a unanimously accepted definition. In order to establish the diagnosis of a truly fast-slow form, it has been proposed that the AH interval should be less than 185 ms<sup>10</sup> or 200 ms.<sup>6</sup> This criterion, however, has not been adopted by other investigators.<sup>11–13</sup> Thus, tachycardias with a relatively prolonged AH interval but an AH/HA ratio <1 cannot be reliably classified as either fast-slow or slow-slow (see *Figure 2*). Furthermore, the term ‘fast-slow’ implies that the fast component of slow-fast AVNRT is the same as the fast in the fast-slow type. There is now evidence that this is not the case in patients who present with both types of tachycardia.<sup>14,15</sup> Typical slow-fast and atypical fast-slow AVNRT appear to utilise different anatomical pathways for fast conduction. In addition, electrophysiological behaviour compatible with multiple pathways may also be seen, and in some patients, several forms of AVNRT may be inducible at electrophysiology study.

We have previously published a simplified classification scheme (see *Table 2*) that takes into ac-

count the shortcomings of conventional classification, and reflects evolving concepts regarding the nature of the AVNRT circuit in various forms of the arrhythmia (see *Figure 1*).<sup>5</sup> AVNRT should be classified either as typical or atypical. In addition, not only the AH/HA and absolute HA intervals should be necessarily used as criteria for diagnosis of typical AVNRT. The ventriculoatrial (VA) interval is also a practical and easily obtainable criterion, when the His bundle potential cannot be reproducibly and reliably recorded during tachycardia (see *Table 3*). As discussed later, retrograde atrial activation sequence or demonstration of a lower common pathway, should not be necessarily considered as reliable criteria for classification of AVNRT types.

## Electrophysiological Features

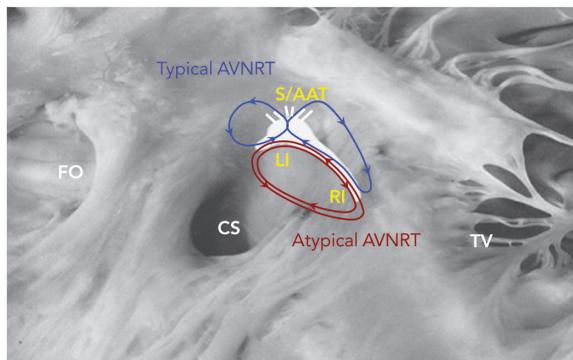
### *Earliest Atrial Retrograde Activation*

Heterogeneity of both fast and slow conduction patterns has been well described, and all forms of AVNRT may display anterior, posterior and middle retrograde activation patterns. In typical, slow-fast AVNRT, posterior or even left atrial Fast pathways may occur in  $\leq 8\%$  of patients.<sup>12,13,16,17</sup> There has also been evidence that were left septal His recordings routinely performed in patients with AVNRT, the proportion of left-sided retrograde Fast pathways might be considerably higher than previously reported.<sup>18</sup> *Figure 3* and *Figure 4* present typical AVNRT (slow-fast) with variable earliest retrograde atrial activation.

In atypical AVNRT, the earliest retrograde atrial activation is traditionally reported at the base of the triangle of Koch, near the coronary sinus ostium. Detailed mapping of retrograde atrial activation in large series of patients, however, has produced variable results. Earliest atrial activation can be well recorded at the coronary sinus ostium, the low right atrial septum, or the His bundle area.<sup>11–13,17</sup> In certain cases of atypical AVNRT, retrograde atrial activation is even suggestive of a left lateral accessory pathway.<sup>8,9</sup>

It is obvious, therefore, that classification based on earliest atrial retrograde activation is inappropriate. *Figure 5* and *Figure 6* depicts fast-

**Figure 1: Proposed Circuit of Atrioventricular Nodal Reentrant Tachycardia**



During typical AVNRT (slow-fast), right- or left-sided circuits may occur with antegrade conduction through the inferior inputs and retrograde conduction through the superior inputs (S) or the anisotropic atrionodal transitional area (AAT). In atypical AVNRT conduction occurs anterogradely through one of the inferior inputs, left (LI) or right (RI) and retrogradely through the inferior inputs and retrogradely through the other one. Depending on the orientation of the circuit we may record the so-called ‘fast-slow’ or slow-slow’ types. AVNRT = atrioventricular nodal re-entrant tachycardia; CS = coronary sinus; FO = foramen ovale; TV = tricuspid valve.<sup>5</sup>

**Table 1: Atrioventricular Junctional Arrhythmias**

Atrioventricular nodal reentrant tachycardia
Non-reentrant junctional tachycardia
Non-paroxysmal junctional tachycardia
Focal junctional tachycardia
Other non-reentrant variants

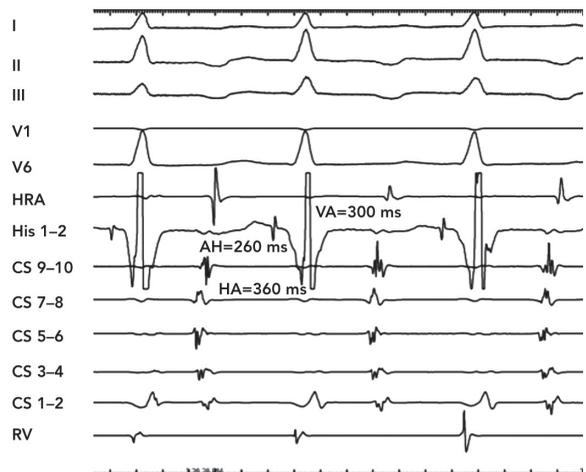
**Table 2: Conventional Classification of Atrioventricular Nodal Reentrant Tachycardia Types**

	AH/HA	VA (His)	Usual ERAA
Typical AVNRT			
Slow-Fast	>1	<60 msec	RHis, CS os, LHis
Atypical AVNRT			
Fast-Slow	<1	>60 msec	CS os, LRAS, dCS
Slow-Slow	>1	>60 msec	CS os, dCS

Variable earliest retrograde atrial activation has been described for all types. AH = atrial–His interval; CS os = ostium of the coronary sinus; dCS = distal coronary sinus; ERAA = earliest retrograde atrial activation; HA = His–atrium interval; LHis = His bundle electrogram recorded from the left septum; LRAS = low right atrial septum; RHis = His bundle electrogram recorded from the right septum. Interval measured from the onset of ventricular activation (VA) on surface ECG to the earliest deflection of the atrial activation in the His bundle electrogram.<sup>1</sup>

slow and slow-slow AVNRT, respectively, with earliest retrograde atrial activation at the His bundle electrode.

**Figure 2: Atypical Atrioventricular Nodal Reentrant Tachycardia**



The form is fast-slow according to the AH<HA definition, but slow-slow according to the AH >200 ms criterion. AH = atrial–His; CS = coronary sinus; HA = His–atrium; HRA = high right atrium; RV = right ventricle; VA = ventriculoatrial interval.<sup>5</sup>

**Table 3: Novel Proposed Classification of Atrioventricular Nodal Reentrant Tachycardia Types**

	HA	VA (His)	AH/HA
Typical AVNRT	≤70 ms	≤60 msec	>1
Atypical AVNRT	>70 ms	>60 msec	Variable

The distinction is for categorisation only, and not relevant for mechanism or therapy. Atypical AVNRT has been traditionally classified as fast-slow (HA >70 ms, VA >60, AH/HA <1, and AH <200 ms) or slow-slow (HA >70 ms, VA >60 ms, AH/HA >1, and AH >200 ms). Not all of these criteria are always met and atypical AVNRT may not be subclassified accordingly. AH = atrial–His interval; HA = His–atrium interval. Interval measured from the onset of ventricular activation (VA) on surface ECG to the earliest deflection of the atrial activation on the His bundle electrogram.<sup>5</sup>

**Relative AH/HA Intervals**

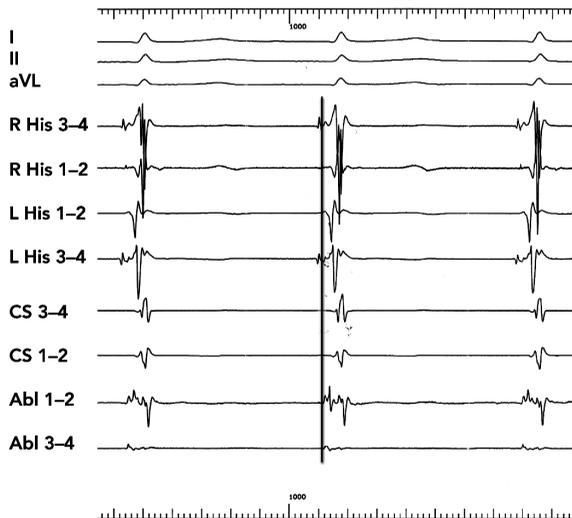
The AH time and the relative AH/HA intervals have been proposed as a criterion for distinction between fast-slow and slow-slow AVNRT. However, both absolute and relative values may be meaningless in certain occasions. They depend on autonomic status, age, use of isoprenaline and sedatives and conduction properties of pathways involved, and may change during a single electrophysiology study. We have often noticed different AH/HA times in the same patient at simi-

**Figure 3:** Typical Slow-Fast Atrioventricular Nodal Reentrant Tachycardia



Earliest retrograde atrial activation is simultaneously recorded at distal CS (CS 1-2) and proximal His (His 3-4). I to V6: 12-lead ECG leads. CS = coronary sinus; His = His bundle electrogram; HRA = high right atrium.<sup>5</sup>

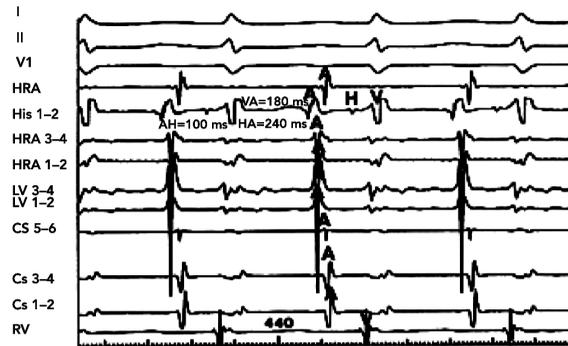
**Figure 4:** Typical Slow-Fast Atrioventricular Nodal Reentrant Tachycardia



Simultaneous mapping of the right septum (R His), left septum (L His) and the anatomic area of the Slow pathway is undertaken. Earliest retrograde atrial activation is recorded on the left septum. I to V6: 12-lead ECG leads. Abl = ablation electrode at the anatomical area of the Slow pathway; CS = coronary sinus; His = His bundle electrogram; HRA = high right atrium.<sup>5</sup>

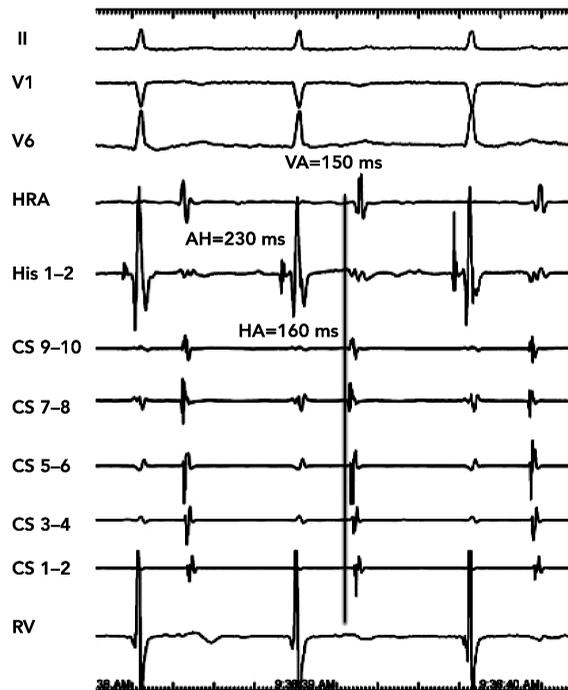
lar or different tachycardia cycle lengths. Furthermore, when a His bundle electrogram cannot be recorded during tachycardia, a diagnosis based exclusively on them is impossible.<sup>19</sup>

**Figure 5:** Atypical Atrioventricular Nodal Reentrant Tachycardia



The form is conventionally fast-slow ( $AH < HA$ ,  $HA > 70$  ms,  $AH < 200$  ms), and earliest retrograde atrial activation recorded at the His bundle electrode. I to V6: 12-lead ECG leads; CS = coronary sinus; His = His bundle electrogram; HRA = high right atrium; LV = left ventricle; RV = right ventricle.<sup>5</sup>

**Figure 6:** Atypical Atrioventricular Nodal Reentrant Tachycardia



The form is conventionally slow-slow ( $AH > HA$ ,  $HA > 60$  ms,  $AH > 200$  ms), and earliest retrograde atrial activation is recorded at the His bundle.<sup>5</sup>

**Upper and Lower Common Pathways**

Early studies have considered the possibility of additional AV nodal tissue extrinsic to the tachycardia circuit in order to explain various electro-

physiologic phenomena observed during AVNRT,<sup>20</sup> and the concepts of upper and lower common pathways have been long-standing controversies of AVNRT. The existence of an upper common pathway can now be rather easily refuted by subsequent evidence indicating that multiple atrial breakthroughs are extremely common, and retrograde activation often changes in timing and/or activation without significant alteration in tachycardia cycle, thus negating the notion of a simplistic focal atrial exit site.<sup>21-23</sup> The perinodal transitional tissue is the route to the atrium, and in this context it may be considered as a common pathway of tissue but not a discrete site. The breakthrough is whatever leads to atrial activation via transitional tissue; thus there are many possibilities (see *Figures 3-6*).

The lower common pathway, as initially considered by Mendez and Moe,<sup>24</sup> has a more sound physiological basis. The notion of a lower common pathway has been utilised in order to explain phenomena of AV block without recording of a His electrogram as well as retrograde Wenckebach periodicity during AVNRT.<sup>25-28</sup> The lower common pathway is defined as the conduction path between the distal turnaround point of the AVNRT circuit

and the His bundle. The conduction time over the lower common pathway has been usually estimated by subtracting the His to atrium interval during tachycardia (measured from the onset of the His electrogram to the onset of the atrial electrogram) from that during ventricular pacing (measured from the end of the His electrogram to the onset of the atrial electrogram) at the same cycle length and considered a measurable interval in the majority of typical AVNRT cases. Initially, a lower common pathway was demonstrated in up to 75 % of 28 patients with AVNRT who were studied,<sup>20</sup> whereas in subsequent studies with the use of para-Hisian pacing, the presence of a lower common pathway was identified in 78 % of 23 patients studied.<sup>27</sup> No evidence of a lower common pathway has been detected in typical slow-fast AVNRT.<sup>29</sup>

However, AV block during AVNRT without recording activation of the His bundle can also be explained by proximal intra-Hisian block.<sup>30</sup> In up to one-third of patients with AVNRT the lower turnaround point of the circuit is within the His bundle, thus arguing against an intranodal circuit as a universal feature of AVNRT.<sup>31</sup> Differences in the location of the lower turnaround sites of

**Table 4:** Electrophysiology Techniques for the Differential Diagnosis of Narrow QRS Tachycardias

	V Pacing in SR	V Pacing During Tachycardia	A Pacing in SR	A Pacing During Tachycardia
Easily Applicable	VA ratios during V pacing and tachycardia <sup>30,34</sup>	His-synchronous extrastimuli <sup>41</sup>	Comparison of AH during pacing and tachycardia <sup>57</sup>	
	Ventriculoatrial index <sup>35</sup>	Entrainment		
		- AAV/AAHV response <sup>42</sup>		
		- With and without stable fusion <sup>43</sup>		
		- SA-VA and cPPI-TCL intervals <sup>44-47</sup>		
		- Differential entrainment or cessation <sup>48</sup>		
Cumbersome	Delta HA during V pacing and tachycardia <sup>36</sup>	Pre-excitation index <sup>49</sup>		Differential entrainment <sup>58</sup>
		Entrainment		
	VHA pattern <sup>37</sup>	- Anterograde His capture <sup>50</sup>		
	Para-Hisian pacing <sup>38</sup>	- Progressive fusion during or after the transition zone <sup>51,52</sup>		
	Induction of retrograde RBBB <sup>39</sup>	Delta HA during entrainment and tachycardia <sup>53</sup>		
	SA <sub>int</sub> -VA and cPPI <sub>int</sub> -TCL intervals during induction of tachycardia <sup>40</sup>	- Para-Hisian entrainment <sup>54-56</sup>		

A = atrial; AH = atrio-His interval; cPPI = corrected post-pacing interval; HA = His-atrial interval; RBBB = right bundle branch block; SA = stimulus to atrium interval; SR = sinus rhythm; TCL = tachycardia cycle length; V = ventricular; VA = ventriculo-atrial interval.<sup>19</sup>

AV nodal reentry relatively to the His bundle have also been shown in experimental studies.<sup>32</sup> Thus, block during AVNRT does not necessarily define a 'lower common pathway'; it just defines longer refractory period below the circuit. This is often seen at the onset of very fast AVNRT, which may expose the His- Purkinje tissue to long-short periods and can lead to functional phase 3 block, having nothing to do with the reentrant circuit.

The electrophysiological proof of the existence of a lower common pathway depends on several assumptions that may not be valid, in a way that even if a lower common pathway exists, applied methodologies are unable to accurately detect and measure it.<sup>23</sup> Furthermore, there are certain cases in the electrophysiology laboratory where an antegrade, let alone a retrograde, His bundle electrogram may not be reproducibly and reliably recorded.<sup>19</sup> Thus, upper and lower common pathways seem to represent concepts the mechanism, relevance and practical applicability of which remain speculative.

### ***Differential Diagnosis***

Differential diagnosis of a narrow QRS tachycardia, such as AVNRT, may be difficult.<sup>17</sup> Although several ECG clues may assist differential diagnosis, this is usually accomplished at electrophysiology study and, most often, is between atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia due to a concealed accessory pathway, and atrial tachycardia. Atrial and, mainly, ventricular pacing manoeuvres during sinus rhythm or tachycardia have been used with variable success rate. In clinical practice, these techniques cannot be applied to all cases, and multiple criteria have to be used for the differential diagnosis of narrow complex tachycardias with atypical characteristics. In *Table 4* we summarise our experience with various techniques and manoeuvres for the differential diagnosis of narrow-QRS tachycardias in the electrophysiology laboratory.<sup>33-59</sup>

### ***Ablation***

Chronic administration of antiarrhythmic drugs (such as  $\beta$ -blockers, non-dihydropyridine calcium channel blockers, flecainide or propafenone) may be ineffective in up to 50 % of cases.<sup>1</sup> Thus, catheter ablation is the current treatment of choice. Slow pathway ablation or modification is effective in both typical and atypical AVNRT. Usually, a combined anatomical and mapping approach is employed with ablation lesions delivered at the inferior or mid part of the triangle of Koch.<sup>60,61</sup> Multicomponent atrial electrograms or low amplitude potentials, although not specific for identification of slow pathway conduction, are successfully used to guide ablation at these areas. Ablation should be only directed towards the anatomic position of the slow pathway. If right septal attempts are unsuccessful, the left septal side should be tried.<sup>62,63</sup>

This approach offers a success rate of 95 %, is associated with a risk of 0.5–1 % AV block and has approximately 4 % recurrence rate. There is no mortality associated with this procedure.<sup>64,65</sup> Advanced age is not a contraindication for slow pathway ablation.<sup>66</sup> The preexistence of first-degree heart block may carry a higher risk for late AV block and slow pathway modification, as opposed to complete elimination, is probably preferable in this setting.<sup>67</sup> Cryoablation may carry a lower risk of AV block, but it is negligible and this mode of therapy is associated with a significantly higher recurrence rate.<sup>67</sup>

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*Little Alex G.*

# A Little Letter for Dino Anagnostopoulos

*Alex G. Little, MD*

Dino Anagnostopoulos

It is a pleasure to submit this letter describing my relationship and friendship with Dino. Even though most of our time together was many years ago, I retain strong feelings about this remarkable man and surgeon and I am delighted to have this opportunity to share them.

I came to know Dino in 1979 when I began my Thoracic Surgery training at the University of Chicago. At that time he was in charge of the Cardiac Surgery service and, while I am no Odysseus, he quickly became an important and influential mentor to me (despite my interest in General Thoracic Surgery).

Let's start by considering Dino the technical surgeon and teacher of the art. I quickly recognized that – while all thoracic surgeons consider themselves to be above average – he was remarkably skilled. For example, in his hands the fragile tissues of a dissecting aorta remained intact and seemed to welcome his handling. He mastered all operative challenges with dexterity and gentle manipulation of tissues and was never flustered. So he could operate himself. However, while considering Dino to be unusually skilled, I know there are many capable cardiac surgeons. I doubt there are many who could combine technical expertise with the ability to teach and train young residents as successfully as Dino. He instilled confidence in the trainee and gave intraoperative direction calmly and clearly. He knew when to take over an operation himself in a way that allowed the trainee to learn and develop without losing confidence. There was no berating of the resident, only advice and demonstration of the “right way”. Speaking to both his dexterity and commitment to teaching, I well remember struggling during an operation only to have him reach across the table and put in a perfect stitch backhand while telling me why the stitch had to be in that precise location.

On a personal note, there was and is no question of his Greek nature. High energy and extreme enthusiasm mark his approach to the world and to Cardiac Surgery. He loves our specialty and this emotion is transmitted to the resident. He knew how to prevent tenseness from intruding into the operating room. There was a time for quiet and precise surgery and a time to lighten the atmosphere. It was habitual that while

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beginning an operation and going on bypass that Dino would sustain a – quite friendly – loud argument with the Anesthesiologist, typically about the wisdom of investing in gold or some other stock market opportunity. This got the room laughing and relaxed, the perfect atmosphere for high quality surgery.

Finally let me say that Dino was and is an admirable and extremely likeable human being, kind and considerate and thoughtful of others in a high-octane sort of way. I also saw him weather a personal tragedy with dignity and emotional strength, further increasing my esteem. It is an honor to have been trained by him and to be able to call him a friend. I wish him the best on this time of honor for him.

*Levett J.M.*

# A Little Letter for Dino Anagnostopoulos

*Levett J.M., M.D.*

March 8, 2017

Dear Dino and fellow Festschrift attendees:

Greetings to everyone from Iowa. I am a cardiac surgeon who trained with Dr. Anagnostopoulos (Dino) at the University of Chicago in the 70s and early 80s. I currently practice cardiac and thoracic surgery in Cedar Rapids, Iowa, and have kept in touch with Dino over the years. I have fond memories of working and socializing with Dino, and would like to share a few of these memories with you.

I first met Dino as a general surgery resident at the University of Chicago and spent a number of months on the cardiac surgery rotation during the residency years and then two full years as a cardiothoracic fellow. Dino was gregarious, fun loving, full of life, very smart, and filled with ideas for both basic research and clinical projects. Although I did not personally work on the project, fellows in Dino's lab studied the use of retrograde cardioplegia in the early 80s, many years before it became clinically accepted on a widespread basis. He was also an excellent technical surgeon with a gift for understanding complex problems we might encounter in the OR and the ability to improvise in a remarkable way when required in difficult situations. I learned from Dino that the mark of a really good surgeon is the ability to stay out of trouble initially but also to get out of trouble when things go awry. It was a pleasure to work with him and I still use a number of techniques I learned from him—the use of small needles and suture when the aorta is fragile or tearing, the use of a pulmonary artery vent in selected cases, and a unique method for the right coronary graft proximal anastomosis.

Dino loved to socialize and would regularly take his service team of residents and nurses to Greek Town in Chicago where we would eat at the Parthenon or the Plaka. We would sit at a large table and Dino would engage two or three waiters by speaking loudly in Greek, and they would soon be scrambling to get us wine and food. We drank lots of Naoussa and ate Greek salad,

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avgolemono, dolmades, spanakopita and gyros plates. This eating and lively conversation usually went on for about two hours at which time we were all stuffed, and Dino would then ask everyone what they wanted for an entree. I've been a fan of Greek food ever since.

Dino was certainly an excellent role model for his residents and fellows, and we wrote several papers together during my time with him at the University of Chicago. In recent years I've become interested in quality systems in healthcare and wrote a book several years ago on using ISO 9001 in healthcare.

Since ISO is an international standard, I wanted to include one chapter from the book as a tribute to Dino on the occasion of this international event (Chapter 8: Experience with ISO 9001 in a Multispecialty Clinic).

Many thanks to Dino for all he has taught me and for the fond memories I hold.

Sincerely,  
Jim Levett

**Levett JM**

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# Experience With ISO 9001 in a Multispecialty Clinic

*Levett JM and Burney RG*

Physicians' Clinic of Iowa (PCI) is a 55 physician multispecialty clinic in Cedar Rapids, IA with physician specialties including cardiac surgery, otolaryngology, general surgery, neurology, oncology, orthopedic surgery, plastic surgery, podiatry, rheumatology, thoracic surgery, urology, and vascular surgery. PCI employs 300 staff at an integrated single-site medical pavilion. PCI physicians manage approximately 150,000 E & M encounters and perform over 60,000 surgical procedures annually. PCI leadership elected to pursue ISO 9001 registration in the spring of 2001 and the clinic was formally registered to ISO 9001:2000 in November, 2003. This chapter describes the concept and requirements of the ISO 9001 quality management system, the PCI implementation experience and costs, and the results achieved during the first year of certification.

## **ISO 9001 Background and Requirements**

As discussed in Chapter 2, the International Organization for Standardization (ISO) was founded in Geneva in 1947 for the purpose of providing the standardization of technical specifications for products traded in the international marketplace (Ref. 1). Over the years the concept of standardization has evolved from that of specific technical

specifications to a broader concept of generic QMS standards. An organization becoming certified to ISO 9001 is essentially establishing a QMS that provides for work performance consistency, stresses the process approach, defines goals and objectives for quality, provides benchmarks to measure improvements, and requires identification and evaluation of causes of poor performance. An organization seeking ISO registration is required to describe and implement a QMS according to the requirements of the American National Standard for quality management systems (Ref. 2). This involves writing a quality policy, quality manual, and quality objectives, and then utilizing the process approach to address the other requirements of the standard. ISO 9000 is the family of standards; an entity is registered to ISO 9001:2008. ISO 9001 requirements are based on the following eight quality management principles:

- Customer focus
- Leadership
- Involvement of people
- Process approach
- Systems approach to management
- Continual improvement
- Factual approach to decision making

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- Mutually beneficial supplier relationships

The principles embedded within the eight clauses of ISO 9001:2008 comprise the quality manual for an organization, and together they describe the QMS. A QMS may thus be described as a set of processes that provide direction and control of an organization's quality.

### ISO Implementation and Costs

The experience at PCI was carefully documented over the 2.5 years during which it became ISO certified. During the first year, PCI leadership identified a local consultant experienced in ISO certification for businesses, established an ISO Steering Committee, conducted several ISO kick-off meetings and training sessions for employees, and visited local businesses that offered tours of their facilities and shared information about their ISO QMSs. A quality policy, quality objectives, and a quality manual were written and circulated to employees. Employee support for the project was obtained through active engagement in designing the QMS. In many cases employees were asked to describe their job responsibilities as ISO documents were written. This employee involvement was key, as it showed employees that the QMS was not a threat to them but rather a supporting framework to improve their clinical and business processes.

The first milestone was the development of a controlled document system using an alphanumeric numbering system. All policies and procedures were reviewed, revised, and put into a common document format. PCI had over 400 policies and procedures in place when the process began—it reduced the number of documents to 375 by the time of registration, including the addition of new policies and procedures required by ISO. Standardizing medical records among different departments and sites of care was a major work effort, but demonstrated the value of having a common document system within the organization. It also became apparent that the HIPAA requirements for healthcare providers were much easier to implement with an ISO QMS in place.

During the second year PCI selected TUV America as its registrar and developed process maps for the overall clinical patient flow process, medical patient care process, and surgical patient care process. It also conducted a quality training retreat for all interested employees. The second milestone was the internal auditor training sessions provided by the consultant. These sessions involved employees from each office and were valuable in teaching auditing principles and in clarifying the value of auditing for monitoring and improving the QMS. PCI also instituted management review meetings held every six months that are designed to oversee the QMS, monitor issues, provide follow-up to corrective and preventive actions, and measure process improvement. A Physician Quality Council was established with representatives from each specialty department; it serves as a conduit to keep physicians informed within respective departments. Furthermore, PCI established a Data Collection Committee with quality improvement representatives from each of the two community hospitals for the purpose of obtaining data for metrics residing in the hospital databases. The second year also marked the establishment of the PCI quality newsletter, "*PCIntouch*." The newsletter is written monthly and focuses on both HIPAA and ISO 9001 issues.

During the final six months of ISO certification, the PCI Chief Medical Officer wrote a series of physician newsletters focusing on basic ISO concepts, and employees participated in a practice audit conducted by the consultant and several local quality managers within the industry. PCI underwent a pre-assessment audit conducted by TUV two months prior to its formal registration audit. It became registered to ISO 9001:2000 on November 10, 2003. To our knowledge, PCI is the largest medical group in the U.S. to have attained ISO certification.

Documentation of PCI's ISO experience involved maintaining records of all meetings and attendees. Using this information, the soft costs of implementing the ISO QMS based on 142 meetings from March 2001 through September

2003 were calculated. A total of 2,345 hours of FTE time was calculated at the hourly rate for each attendee, for a soft cost total of \$81,895 (0.5% of the total payroll). The hard costs consisted of the consultant costs, pre-audit by the registrar, and formal audit by the registrar, totaling to \$26,547. Total costs were thus calculated:

- Total costs to date of certification \$ 108,443
- Cost per physician \$ 2,169
- Cost per physician per year (over 2.5 yr.) \$ 868

Although the soft costs calculation is accurate, the meetings often involved PCI business dealing with clinical issues not associated with ISO implementation. It is estimated that half of the soft costs involved time that would have been required from employees without the ISO QMS. Calculation of costs per physician per year, then, equates to \$540 rather than \$868 per physician per year.

**Cost Savings Attributed to ISO Implementation**

The major cost savings from implementing the ISO 9001 QMS result from improvements in process

management. The process approach is a fundamental principle of ISO 9001, and the clinical and support processes at PCI were defined and analyzed early during ISO implementation. This effort involved an evaluation of business processes and resulted in a reduction of days in Accounts Receivable from 66 to 46, with a one-time amount of \$72,500 of additional income (Figure 8.1).

A second area of increased income resulting from the process approach involved an analysis of actual reimbursements against payer-contracted reimbursement. This led to a careful analysis of rates, and as a result identified \$100,000 in underpayments on contracted rates during the first year.

An important aspect of ISO 9001 is the concept of standardizing purchased products and services. ISO 9001 includes Clause 7 Service Realization, with subclause 7.4 describing the purchasing process. The requirement is that organizations have methods to assure that purchased products and services conform to requirements, that suppliers are evaluated on their ability to supply products and services in accordance with the requirements, and that specific criteria are defined for the selection and evaluation of suppliers. PCI enlisted the

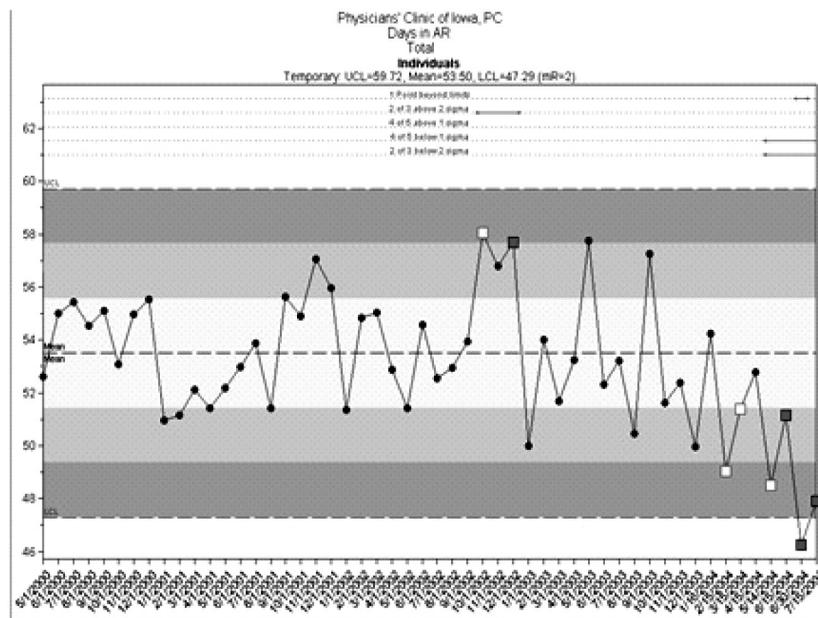


Figure 8.1 PCI Days in Accounts Receivable

help of a local industry expert in lean systems and convened a one-day *kaizen* event to evaluate the system and identify changes to implement. The process initially involved value stream mapping of the current purchasing process, shown in Figure 8.2. The next step was to develop a vision for the ideal purchasing process. The ideal state would involve economies of scale, be efficient, and include an automated purchasing order system; it would be simple, consistent, low cost, high quality, and could be monitored. The following specific objectives for developing an ideal purchasing process were identified:

- Create a standardized process
- Create a trackable process
- Create guidelines
- Identify preferred vendors
- Establish effective avenues to share information

### Purchasing Process Scope

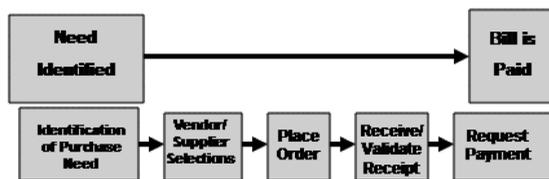


Figure 8.2 PCI Purchasing Process

Early results for PCI's redesigned purchasing process included a 42% savings in shredding costs. Additional savings in cleaning, snow removal, garage disposal, recycling, liability insurance, and medical wastes were also realized during 2005.

Another area of cost savings involved restructuring the workers' compensation program. PCI leadership initially reviewed the process and initiated an in-house nuisance claims fund of several thousand dollars to address low-level claims in a timely manner. This was combined with education of the occupational medicine staff, department directors, and employees. An "Alternate Duty Program" was initiated for employees in

areas at risk of injury, such as radiology technicians involved with lifting patients on a daily basis. An ergonomic review was conducted in clerical and clinical areas to identify potential problems and employees at risk.

Several procedures were redesigned within the workers' compensation program. Internal reporting for potential claims was changed to ensure notification of both the Director of Human Resources as well as the appropriate department director. PCI established ongoing risk management assessments in partnership with its insurance carrier and the Human Resources Department. The major change relating to the claims process itself was requiring external rather than internal clinical evaluation for an employee making a claim. This resulted in fewer nuisance claims.

As a result of using the process approach within the ISO 9001 QMS, PCI demonstrated a significant reduction in claims for worker's compensation between 2001 and 2004 (Figure 8.3). Because of this improvement, the insurance carrier agreed to reduce the annual premium for 2004 workers' compensation insurance by \$45,000. The graph below depicts the frequency of workers' compensation claims and the "mod rate". Mod rate is the experience modification factor that compares actual loss with expected loss over a period of time. If losses are lower than expected for the industry, the mod rate should be less than 1.0; if losses are higher than expected the mod rate will be greater than 1.0. The industry standard is 1.0, which represents the average amount of claims in a given industry.

- **Total**, including benefits \$ 81,895

The cost savings outlined above totaled approximately \$220,000, and were identified during the initial twelve months of ISO implementation. While some of the cost savings would have been achieved without the ISO QMS, having a QMS in place and using the concepts derived from ISO 9001 clearly improved the efficiency and efficacy of the transition. Even half of the cost savings,

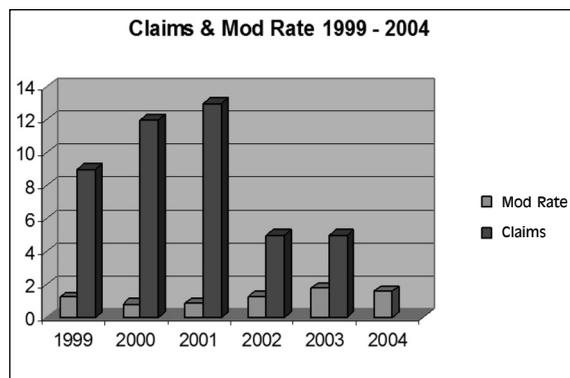


Figure 8.3 PCI Worker's Compensation Claims

\$110,000, would have paid for the total costs of implementing the QMS, \$108,443, with soft costs included.

### Community Benefits of ISO Implementation

During the ISO implementation process a PCI Quality Council was established to help develop the clinical quality program and identify key quality indicators. The council consisted of one physician from each specialty at PCI, each asked to determine metrics of value for his/her specialty. The council identified 55 indicators among 10 specialties. In evaluating the indicators, it became apparent that operational definitions were unclear, the process of data collection was difficult, and PCI was unable to collect indicators without the help of the two community hospitals. Therefore, a second quality committee, the Data Collection Committee, was established with QI representatives of both hospitals and PCI. The committee reviewed the requested data and decided to focus on data the hospitals had already collected. Many physicians expressed interest in antibiotic administration, which coincided with a project of the Iowa Foundation for Medical Care (IFMC), the quality improvement organization in Iowa. The committee chose to work together on the national Surgical Infection Prevention (SIP) project sponsored by Medicare, in the hopes that the project would be a combined effort among all three entities. The SIP indicators were:

- Antibiotic administration within one hour of the surgical incision
- Use of appropriate antibiotics

- Discontinuation of antibiotic use within 24 hours

Mercy Medical Center and St. Luke's Hospital agreed to collect the three SIP indicators, while PCI would provide the "rate of surgical-site wound infection after discharge" statistic for the hospitals. This ability to track wound infections in a clinical setting improved the overall understanding of community infection rates and was implemented by developing an ISO document for tracking wound infections, maintained by the nurses in each PCI surgical office. Initial results of the collaborative effort for orthopedic patients during 2003 are shown in Figure 8.4. A joint presentation by representatives of PCI and both hospitals was given at the annual IFMC quality conference in November 2003.

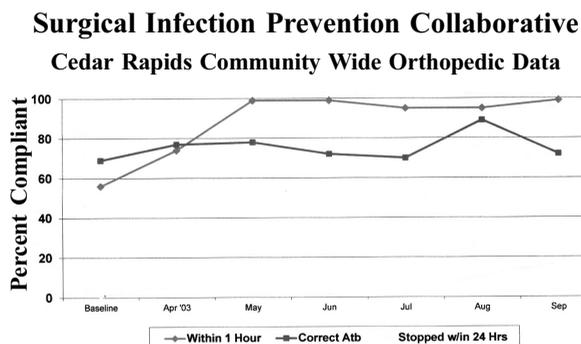


Figure 8.4 SIP Orthopedic Indicators in Cedar Rapids

### Additional Clinic Benefits of ISO Implementation

As noted above, utilization of the process management approach was the key to implementing the ISO QMS and improving both clinical and support processes at PCI. The process approach was used in initially designing the medical and surgical patient care process maps that were integrated into the ISO system during the first six months. These maps were helpful in understanding the process steps as the care processes were evaluated, improved, and incorporated into the ISO framework. Figure 8.5 illustrates several initial steps in the PCI Clinical Patient Flow Proc-

ess. The key point in this illustration is that the process map is linked to ISO documents using the standard PCI document system developed within the ISO QMS (ISO documents are underlined and numbered to the right). This method facilitates access to written policies and procedures related to and supporting the process map.

### Clinical Patient Flow Process

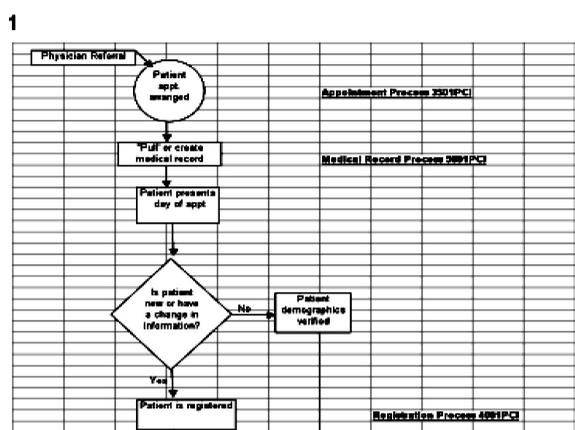


Figure 8.5 PCI Clinical Patient Flow Process

The process approach was also used in developing a balanced scorecard and strategy map for the organization. These documents, described in Chapter 7, were written as a result of the strategic planning process undertaken at PCI biannually. Although the balanced scorecard and strategy maps are not an ISO requirement, they clearly support the ISO management principles outlined above and complement the Management Review activities required by the ISO 9001 QMS.

The process approach was also used to develop a payer matrix for evaluating payments and contract language on proposed insurance contracts. Through the purchasing process discussed above, a request for proposal (RFP) process was developed and incorporated into the ISO QMS as a methodology to use in obtaining information from vendors. PCI has also used the RFP process to evaluate electronic medical record systems by querying vendors and standardizing categories of comparisons.

The auditing experience at PCI has been very positive. Both internal and external auditing are ISO

requirements. PCI has developed an internal auditing program based on training PCI employees, which has been well received and supported by PCI employees. Internal audits are conducted every three to six months and focus on selected areas based on previous audits and findings of non-conformance. The external registrar audit is required annually.

Another aspect of the ISO QMS is the corrective and preventive action procedures required by ISO 9001. This system requirement ensures that any problems identified within the clinic setting receive an adequate and timely follow-up. PCI has incorporated patient comments of significance into the corrective action plan system as well; these documents are audited and oversight is maintained through the Management Review process.

### Summary of Results of ISO 9001 Implementation

The experience of introducing an ISO 9001 QMS at Physicians' Clinic of Iowa has been very positive. PCI demonstrated that an ISO QMS provides a framework for quality improvement and for monitoring clinical and business processes. The QMS can be utilized to efficiently implement additional regulatory requirements such as HIPAA, and may serve as a framework to support community healthcare activities, as will be described in Chapter 11. Establishing an ISO QMS requires time and work effort on the parts of both employees and management. Although it was initially hoped that an ISO 9001 QMS could be implemented within a year, the process required over two years. Nevertheless, there was ample time to accomplish the task. In fact, the slower approach made employees more involved in the process, resulting in a more cooperation. Committed leadership was essential and process management was the most important learning objective gained during the implementation process.

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# Protecting the Myocardial Cell During Coronary Revascularization

*Sidney Levitsky, MD*

## Abstract

**Background**— Using the ischemic myocardial cell as a paradigm, competitive coronary revascularization technologies will be analyzed for their potential in causing additional myocardial cell damage during the course of therapeutic procedures.

**Methods and Results**— Percutaneous coronary intervention (PCI) using balloon and/or stent (bare metal or coated) approaches may be associated with myonecrosis related to atherosclerotic debris plugging the downstream coronary microcirculation as well as ischemia/reperfusion injury associated with revascularization of occluded coronary vessels. The placement of distal mechanical devices and filters during the course of PCI has not been successful in ameliorating this problem. Coronary revascularization using coronary artery bypass grafting (CABG) similarly may be associated with myocardial stunning and cell necrosis associated with ischemia/reperfusion injury. Surgically induced myocardial ischemia secondary to aortic cross clamping, results from the attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial requirements to preserve cellular membrane stability and viability. Recovery involves: (1) resumption of normal oxidative metabolism and the restoration of myocardial energy reserves; (2) reversal of ischemia induced cell swelling and loss of membrane ion gradients and the adenine nucleotide pool; (3) repair of damaged cell organelles such as the mitochondria and the sarcoplasmic reticulum. Despite meticulous adherence to presently known principles of surgical myocardial protection using advanced cardioplegic technologies, some patients require inotropic support and/or mechanical assist devices postoperatively, when none was required preoperatively.

**Conclusions**— Which method of coronary revascularization causes the least amount of myocardial cell injury and is associated with superior long-term outcomes remains an area of increasing controversy.

**Key Words:** coronary artery bypass graft (CABG), coronary revascularization, percutaneous coronary intervention

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*email slevitsk@caregroup.harvard.edu, Presented as the 17th William W.L. Glenn Lecture at the American Heart Association Scientific Sessions, Dallas, Tex, November 13-13, 2005*

I am honored to have been chosen as the seventeenth William W.L. Glenn Lecturer. This presentation has very special meaning to me, as I believe that I am the first lecturer to have been a cardiac surgical resident at Yale under Dr Glenn's supervision. First, a few words about Dr Glenn (Figure 1). Not only was he a creative cardiac surgical pioneer, devising the superior vena cava-right pulmonary artery shunt, popularly known as the Glenn shunt,<sup>1</sup> but Dr Glenn also made many other important contributions including the concept of fibrillatory arrest, the radiofrequency pacemaker, and the phrenic nerve pacemaker. Moreover, he was a superb educator and a strong supporter of his residents throughout their academic careers. Finally, Dr Glenn was the first surgeon to be elected President of the American Heart Association.



**Figure 1.** William W.L. Glenn, MD.

Although my research interests over the past 45 years have focused on intraoperative protection of the myocardium, I thought for this Lecture, I would focus on how we, as cardiac physicians, protect the vulnerable ischemic myocardial cell undergoing therapeutic coronary revascularization. Since, basically, our job in the patient with myocardial ischemia is not only to increase the coronary blood supply but to act as a "myocardial cell-saver!" Using this paradigm, I will attempt to contrast

the competitive coronary revascularization technologies for their potential in causing additional myocardial damage during the course of the therapeutic procedures and the means to avoid this injury. Obviously, a patent coronary artery perfusing a segment of myocardium with numerous areas of myonecrosis serves no useful purpose

### **Percutaneous Coronary Intervention-Induced Myonecrosis**

Most of the clinical research studies evaluating percutaneous coronary intervention (PCI) have focused on the mechanical techniques and outcomes of opening the stenosed or occluded coronary artery and maintaining vessel patency utilizing balloon angioplasty and the insertion of bare metal or coated stents. However, PCI-related injury leading to myonecrosis associated with stent-related side-branch flow impairment/occlusion or associated with atherosclerotic debris plugging the downstream coronary microcirculation as well as ischemia/reperfusion injury associated with revascularization of occluded coronary vessels has not been emphasized.

Traditionally, creatine-phosphokinase-myocardial band (CPK-MB) and electrocardiographic evidence of Q-wave or non-Q-wave myocardial infarction have been used as markers to diagnose post-procedure myonecrosis, which can occur in 16% to 39% of patients<sup>2</sup> and has been documented to be a predictor of poor late outcomes.<sup>3</sup> The concept of "CPK washout" or innocent "infarctlets" as a routine occurrence after PCI has been debunked as a myth and is associated with an increase in late mortality.<sup>4</sup> As a further demonstration of the importance of CPK-MB elevation, the investigators<sup>5</sup> in the PERSUIT (Platelet Glycoprotein 11b/111a in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial compared the myocardial damage between PCI-induced and spontaneous myocardial infarction and noted "the relative increase in 6-month mortality with each increase in peak CK-MB level was similar for PCI-related myocardial necrosis and spontaneous myocardial necrosis..."

Recent clinical application of magnetic reso-

nance imaging in measuring and reliably quantifying post-procedure irreversible myocardial injury has provided a new tool to document the extent of myocardial tissue loss. In a recent study, the investigators<sup>6</sup> have correlated post-PCI troponin elevations and its relationship to the volume of myocardial tissue destruction using delayed-enhancement magnetic resonance imaging (DE-MRI). The characteristics of the 50 patients included in this study are of note in that a single or double vessel PCI was planned, the mean ejection fraction (EF) was  $67\pm 11\%$ , and patients with an EF below 40% were excluded... a relatively low risk group of patients. Nevertheless, 28% of the patients had evidence of procedure-related myocardial necrosis resulting in a loss of  $5.0\pm 4.8\%$  of total left ventricular mass (Figure 2). Utilizing standard measures of measuring EF, there was no statistically valid adverse effect on global LV function, which raises a question about the validity of this measurement in documenting small but significant changes associated with PCI-induced myonecrosis. There were 2 distinct sites of myocardial cell injury: (1) the previously normal area of the apical myocardium in the majority patients was apparently related to embolization of particulate matter during left anterior descending coronary artery (LAD) balloon inflation and stenting; and (2) the basal or mid-ventricular myocardium adjacent to the inserted stent.

<b>PCI</b>	<b>CABG</b>
• N=50	• N=30
• Single & double PCI	• $2.9\pm 0.8$ grafts/pt.
• Mean EF = $67\pm 11\%$	• 36% myonecrosis
• 28% myonecrosis	• Loss of 2% LV mass
• Loss of $5.0\pm 4.8\%$ LV mass	• Myocardial Protection-St. Thomas's cold (4°C) crystalloid cardioplegia

**Figure 2.** Post-procedure myonecrosis quantification using delayed-enhancement magnetic resonance imaging (DE-MRI) after PCI<sup>6</sup> and CABG.<sup>13</sup>

#### PCI Myocardial Protection Devices

In an attempt to ameliorate PCI-induced myonecrosis, mechanical devices, such as the Filter Wire, which uses a polyurethane filter bag contained on a radiopaque loop to trap embolic debris, have been used. In a series of 35 patients,

the device entrapped embolic debris in 82% of the cases, although no data are provided to support a decrease in myonecrosis.<sup>7</sup> Furthermore, in patients with ST-segment elevation myocardial infarction (STEMI), thrombectomy and embolic protection devices, investigated in large, multi-center studies, have not demonstrated any clinical benefits.<sup>8</sup>

#### CABG-Induced Myonecrosis

How successful have surgeons been in protecting the ischemic myocardial cell during surgically induced myocardial ischemia secondary to aortic cross-clamping during CABG procedures? Myocardial stunning and myonecrosis associated with ischemia/reperfusion injury results from the attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial requirements to preserve cellular membrane stability and viability. Recovery involves: (1) resumption of normal oxidative metabolism and the restoration of myocardial energy reserves; (2) reversal of ischemia induced cell swelling and loss of membrane ion gradients and the adenine nucleotide pool; and (3) repair of damaged cell organelles such as the mitochondria and the sarcoplasmic reticulum.

#### Postoperative Myocardial Stunning

Despite meticulous adherence to presently known principles of surgical myocardial protection using advanced cardioplegic technologies, some patients require inotropic support and/or mechanical assist devices postoperatively, when none was required preoperatively. There is good clinical evidence to support the concept that all patients undergoing CABG have varying degrees of myocardial stunning, occasionally requiring inotropic support, which after abatement over hours or days after surgery have no objective evidence of myocardial infarction.<sup>9</sup> However, there is a significant downside to the use of inotropic agents. The classic physiological experiment on a Langendorf rat heart preparation teaches us that increasing doses of isoproterenol will cause myonecrosis as the myocardial oxygen consumption exceeds the heart's capacity to increase coronary blood flow. In ad-

dition, there is recent evidence that therapeutic levels of inotropic support in the postischemic heart increases intracellular calcium and subsequent apoptosis<sup>10</sup> resulting in cell death, which is probably accentuated in the post-CABG patient with segments of the heart that have not been adequately revascularized.

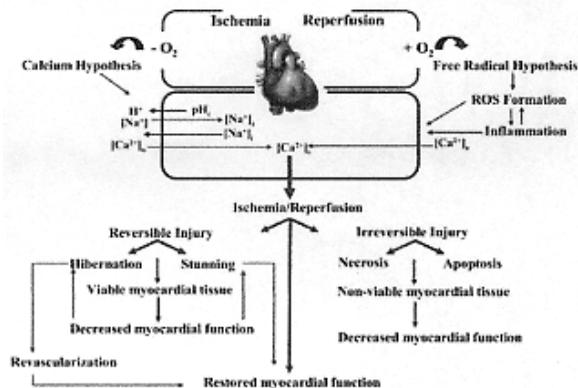
### Clinical Studies

In a study comparing PCI and CABG outcomes from the Cleveland Clinic, there was a greater incidence of CPK-MB leak from CABG patients than PCI patients.<sup>11</sup> However, when the criterion for significant myocardial injury was arbitrarily changed to 10-times normal, there was no difference and the CABG patients had a significant, but small, increase in 3-year cumulative survival. In the Arterial Revascularization Therapies Study (ARTS), there was a direct relationship between CPK-MB elevation and long-term outcomes.<sup>12</sup> At 1 year, the worst adverse outcomes as defined by the incidence of MACCE (death, myocardial infarction, repeat revascularization, as well as combined major cardiac and cerebrovascular events) occurred in patients with CPK-MB levels greater than 5-times normal. In a more recent study using troponin levels and DE-MRI, the Oxford group noted a 36% overall incidence of myonecrosis and a 2% loss of LV mass.<sup>13</sup> However, these investigators used cold crystalloid cardioplegia, which in North America is considered suboptimal compared with blood cardioplegia.

### Intraoperative Myocardial Protection

#### Biology of Ischemia/Reperfusion

The surgical perception of myocardial cell injury occurring after ischemia/reperfusion involves 2 major hypotheses: increases in intra-cellular calcium and/or the accumulation of reactive oxygen species (ROS) causing the sarcolemmal peroxidation of the cellular phospholipid layer, leading to the loss of cellular integrity and facilitating calcium entry. After the aortic cross-clamp is removed, the myocardial cell may function normally, be stunned, or become dysfunctional from either necrosis or apoptosis (Figure 3).

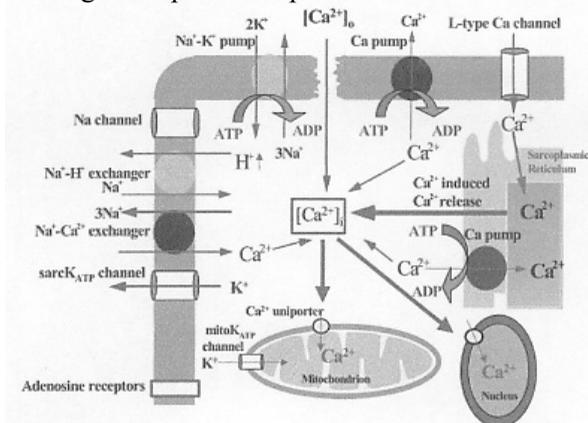


**Figure 3.** Mechanisms of ischemia/reperfusion injury. Putative mechanisms of the calcium and free radical hypotheses and inflammation in the generation of ischemia/reperfusion injury.

### Calcium Transport

Ischemia leads to the induction of metabolic acidosis and the activation of the sodium–proton exchanger, resulting in the transport of hydrogen ions to the extracellular space and the movement of sodium into the cytosol (Figure 4). As the sodium–calcium exchanger is activated, sodium is transported to extracellular space and calcium is taken up into the cytosol, increasing cytosolic calcium ( $[Ca^{2+}]_i$ ) concentration. Increased  $[Ca^{2+}]_i$  accumulation is also augmented by ischemia-induced depolarization of the membrane potential, which allows for the opening of the l-type calcium channels and further calcium entry into the myocyte. Cellular and  $[Ca^{2+}]_i$ -dependent phospholipases and proteases are, in turn, activated inducing membrane injury and the further entry of calcium into the cell. In trying to understand the clinical observation that neonates had less postoperative stunning compared with both newborns and adult patients, we measured intracellular calcium and demonstrated that at the extremes of life, there is an increased accumulation of intracellular calcium after ischemia/reperfusion.<sup>14</sup> Later studies demonstrated that the neonate's resistance to the effects of ischemia/reperfusion is related to the developmental differences in calcium transport and sequestration.<sup>15</sup> The increase in  $[Ca^{2+}]_i$  could be decreased, using a simple cardioplegia solution, consisting of potassium to achieve rapid diastolic arrest and magnesium to inhibit

calcium entry into the cell. In addition, calcium accumulation occurred in increased concentrations not only in the cytosol but also in the nucleus resulting in DNA fragmentation, which appeared to be worse in the senescent heart, and inhibited the production of reparative proteins during the reperfusion period.<sup>16</sup>



**Figure 4.** Calcium sources. The inability of the myocyte to modulate intracellular and intra-organellar calcium homeostasis during ischemia and during early reperfusion is the basis of the “Calcium Hypothesis” for ischemia/reperfusion injury. Increased intracellular calcium ( $[Ca_{2+i}]$ ) induces a cascade of events culminating in increased mitochondrial and nuclear calcium accumulation and cell injury and death.

**Basic Principles and Technical Details**

Historically, the concept of “elective cardiac arrest” was introduced in 1955, by rapidly injecting into the aortic root, after aortic cross-clamping, a 2.5% potassium citrate solution in warm blood to arrest the heart.<sup>17</sup> Thereafter, a variety of approaches evolved including normothermic ischemic arrest, intermittent aortic cross-clamping, fibrillatory arrest, continuous coronary perfusion, topical hypothermia, and, finally, the introduction of cardioplegia.<sup>18</sup> Similarly, the basic principles of myocardial protection<sup>19</sup> have evolved, which include: rapid cardiac arrest, since the myocardial oxygen stores are depleted within 6 seconds as oxidative metabolism switches from aerobic to anaerobic metabolism, hypothermia to decrease myocardial oxygen consumption and prevent the depletion of high-energy phosphate moieties, avoidance of myocardial edema, and a question whe-

ther it is necessary to add metabolic substrates to the “cardioplegic soup” As far as the ingredients are concerned, most European groups use crystalloid cardioplegia, while most US surgeons use blood cardioplegia to provide additional substrate oxygen. Most surgeons use a combination of antegrade and retrograde delivery systems. Although there have been proponents of all or some of these methodologies, and despite numerous reports in the literature, there have been no definitive prospective studies that narrow the techniques enough to allow universal adaptation of one particular methodology.

**Microplegia or Whole Blood Cardioplegia**

This technique avoids hemodilution associated with administering large volumes of the classically diluted ratio of 1:4 blood cardioplegia, uses minimal amounts of potassium and magnesium to arrest the heart and deter the influx of calcium, eliminates concerns about buffering, and avoids myocardial edema.<sup>20</sup> In a retrospective study, we<sup>21</sup> compared microplegia with whole blood and the standard 4:1 blood cardioplegia in a series of patients with severe multivessel disease and low ejection fraction below 30% and prolonged cross-clamp times. While there was no difference between the patient groups, there was a significant decrease in inotropic support favoring the micro-

**TRADITIONAL BLOOD CARDIOPLEGIA (4:1) VS. MICROPLEGIA: CABG WITH POOR LV FUNCTION**

	Traditional N=23	Micro. N=18	P	Inotropic Use				
				Traditional		Micro		p
Age	67.6	65.6	NS	Yes	No	Yes	No	
EF	27.7	30.0	NS					
Distal Anast.	4.5	4.5	NS					
CPB (min)	174	166	NS	11	12	2	16	0.01
XClamp (min)	122	120	NS	17	6	4	14	0.001
Intubation (hrs)	22.5	13.5	NS					

**Figure 5.** Comparison of 4:1 cardioplegia to microplegia.<sup>21</sup>

**Comparison of PCI and CABG**

Now let us go back to our original question, which is which method of coronary revascularization salvages the greatest number of ischemic myocardial cells and, in turn, results in superior long-term outcomes. Using the same metric by the same

investigators comparing the DE-MRI technologies, there is evidence that PCI appears to injure a greater number of myocardial cells during the procedure because, in my mind, of limitations in myocardial protection associated with PCI, as compared with CABG (Figure 2). Obviously these uncontrolled studies to address the hypothesis are provocative and by no means conclusively answer the question posed in this lecture. Nevertheless, this hypothesis may partially explain the 4-year outcome studies using the New York cardiac registry in 59 314 patients, which demonstrated a survival benefit for CABG.<sup>22</sup> An editorial commenting on the study attributes the differences to CABG's ability to bypass numerous "culprit lesions," compared with PCI.<sup>23</sup> My own thinking is related to the high incidence of repeat revascularization procedures in the PCI group (27.3% versus 4.6% in the CABG group;  $P < 0.001$ ), with each repeated PCI associated with an additive superimposed myocardial injury, may be responsible for the differences in outcome. However, a preliminary review by the investigators does not support this hypothesis "... due to a variety of factors that counterbalance the dangers of multiple PCIs...".<sup>24</sup>

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

### **Conclusion**

In closing, I understand that I have ventured into a stormy scientific sea, full of conflicting hypotheses and great difficulties in interpreting retrospective and prospective randomized trials. And, in addition, I have added to the confusion by advancing an untested hypothesis in an attempt to explain long-term outcomes. Perhaps a recent editorial, of which I have quote excerpts,<sup>25</sup> "... it is likely that most patients undergoing coronary arteriography are not told the entire story when a decision is made about undergoing a percutaneous intervention nor is there an appropriate setting for alternative viewpoints to be expressed by cardiac surgeons... our patients deserve to hear the full, unbiased story... about coronary revascularization." points the way in assisting clinicians to manage the patient with the vulnerable ischemic myocardial cell.

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### **Disclosures**

None.

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**Lozos Vasileios A. - Toumpoulis Ioannis K.**

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# Aprikalim a potassium adenosine triphosphate channel opener reduces neurologic in a rabbit model of spinal cord ischemia

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## Abstract

**Background:** Potassium adenosine triphosphate ( $K_{ATP}$ ) channel openers have been involved in the enhancement of ischemic tolerance in various tissues. The purpose of the present study is to evaluate the effects of aprikalim, a specific  $K_{ATP}$  channel opener, on spinal cord ischemic injury.

**Methods:** Fifty-four rabbits were randomly assigned to three groups: group 1 (n = 18, sham operation), group 2 (n = 18, 30 min of normothermic aortic cross-clamping) and group 3 (n = 18, aprikalim 100 mg/kg was administered 15 min before 30 min of normothermic aortic cross-clamping). Neurologic evaluation was performed according to the modified Tarlov scale. Six animals from each group were sacrificed at 24, 48 and 168 h postoperatively. The lumbar spinal cords were harvested and examined histologically. The motor neurons were counted and the histologic lesions were scored (0-3, 3: normal).

**Results:** Group 3 (aprikalim group) had better Tarlov scores compared to group 2 at all-time points ( $P < 0.025$ ). The histologic changes were proportional to the Tarlov scores and group 3 had better functional outcome as compared to group 2 at 168 h (number of neurons:  $21.2 \pm 4.9$  vs.  $8.0 \pm 2.7$ ,  $P < 0.001$  and histologic score:  $1.67 \pm 1.03$  vs.  $0.50 \pm 0.55$ ,  $P = 0.03$ ). Although aprikalim exhibited im-

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proved effect on clinical and histologic neurologic outcome when compared to normothermic spinal cord ischemia, animals in group 3 had worse Tarlov score, reduced number of motor neurons and worse histologic score when compared to group 1 (sham operation) at 168 h ( $P = 0.003$ ,  $P = 0.001$  and  $P = 0.019$  respectively).

**Conclusion:** Aprikalim reduces the severity of spinal cord ischemic injury in a rabbit model of spinal cord ischemia.

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## Introduction

Operations that require proximal aortic occlusion result in ischemia to the distal organs. The spinal cord is exquisitely vulnerable to ischemia. In contemporary published clinical series the incidence of paraplegia and/or paraparesis after operations in the thoracoabdominal aorta ranges from 5% to 14%,<sup>1,2</sup> while similar neurologic deficits can occur after endovascular interventions.<sup>3</sup> Therefore, it would be advantageous if pharmacologic agents were available that could increase the tolerance of the spinal cord to ischemia due to aortic occlusion.

Recent advances in molecular biology and pharmacology of potassium channels have enabled the investigation of potential therapeutic ef-

fects of potassium channel agonists.<sup>4</sup> There are experimental data showing that activation of potassium channels in neurons enhances protection against ischemia and reperfusion injury.<sup>5-8</sup> The purpose of the present study is to evaluate the effects of aprikalim, a specific potassium adenosine triphosphate ( $K_{ATP}$ ) channel opener, on spinal cord injury after aortic cross-clamping in a rabbit model of spinal cord ischemia after a follow-up period of 7 days in order to truly evaluate the neuroprotective efficacy of this pharmacologic agent.

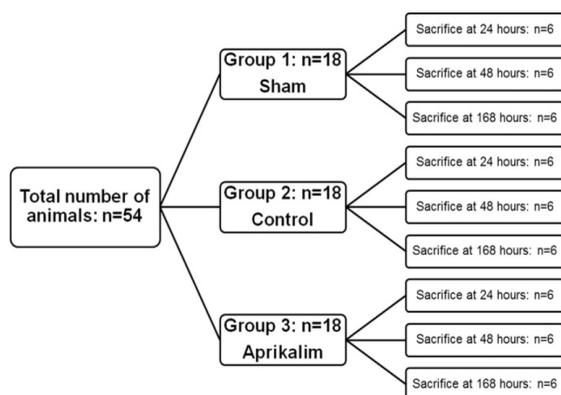
## Materials and Methods

### Animals

Fifty-four New Zealand rabbits of either sex were used in this study. All animals weighted between 3.0 and 3.5 kg and were randomly assigned to one of three groups. Group 1 ( $n = 18$ ) underwent a sham operation, group 2 ( $n = 18$ ) underwent aortic cross-clamping for 30 min, and in group 3 ( $n = 18$ ) 100 mg/kg aprikalim (Sanofi-Aventis, Germany, GmbH) was administered intravenously 15 min before aortic cross-clamping for 30 min.

### Experimental preparation

All animals were fasted for 12 h before the procedure. The rabbits were anesthetized with an intramuscular injection of xylazine (4 mg/kg) and ketamine hydrochloride (50 mg/kg). Gentamicin sulfate (1 mg/kg) was administered intramuscularly. Animals were allowed to breathe spontaneously with a face-mask device in 100% oxygen. The arterial  $PaO_2$  was maintained at greater than



**Fig. 1.** The diagram shows the distribution of animals used in this study. Eighteen animals were used in each of the three groups and 6 animals from each group were sacrificed at 24, 48 and 168 h. Comparisons were performed among the three groups at 24, 48 and 168 h in terms of the Tarlov score, the number of motor neurons and the histologic score using 6 different animals from each group at the three time points. Therefore, these observations were not correlated in an attempt to avoid producing biased results.

100 mmHg, PaCO<sub>2</sub> maintained at 35-45 mmHg and pH at normal levels, as confirmed by means of arterial blood gas analysis. Tracheas were not intubated throughout experiments and anesthesia was maintained with intravenous xylazine (2.5 mg/kg) when necessary. A rectal probe was inserted to monitor body temperature, which was maintained at 39 °C (baseline value in our animals) using a heating pad. A marginal ear vein was cannulated for intravenous fluid and drug administration. The median ear artery and the right femoral artery were cannulated to monitor proximal and distal aortic blood pressure respectively. Electrocardiograms and pulse oximetry were continuously recorded.

Under sterile conditions, following intravenous administration of heparin (100 UI/kg), a midline laparotomy was made and the viscera reflected to the right. After opening the retroperitoneum the abdominal aorta was dissected distal to the left renal artery and proximal to the aortoiliac bifurcation, where Satinsky clamps were used to occlude the abdominal aorta. After 30 min of normothermic spinal cord ischemia Satinsky clamps were removed and all animals were fully resuscitated with intravenous fluids and phenylephrine hydrochloride to restore blood pressure. After 60 min of reperfusion, all animals were hemodynamically stable (mean arterial blood pressure >70 mmHg), without the need of fluid or drug administration. All catheters were removed and all wounds were closed. Finally, the animals were placed in their cages for postoperative care and follow-up.

**Neurologic evaluation**

Six animals from each group (Fig. 1) were evaluated by an independent observer at 24, 48

and 168 h after the end of the experiment according to the modified Tarlov<sup>9</sup> scoring system (0: atony, 1: slight movement, 2: sits with assistance, 3: sits alone, 4: weak hop, and 5: normal gait/hopping).

**Histologic study**

Six animals from each group (Fig. 1) were randomly chosen and were sacrificed at 24, 48 and 168 h after the end of the experiment with an overdose injection of sodium pentobarbital (50 mg/kg), whereas lumbar spinal cords specimens were harvested immediately for histologic study by means of light microscopy. The lumbar spinal cords were fixed in 10% formalin solution for 120 h before being set in paraffin blocks for sectioning. Representative glass slices having 5-mm-thick sections were obtained from each animal at L<sub>4</sub>-L<sub>5</sub> and stained with hematoxylin-and-eosin. Images of the stained sections were captured with a Nikon DS-2MW colour CCD digital camera mounted on a Nikon Eclipse 80i microscope (Nikon Co., Tokyo, Japan) under 200 original magnification and stored as high quality JPG files. Images were then analyzed with Image-Pro Plus 5.1 software (Media Cybernetics, SilverSpring, MD). Size threshold settings of stained pixels were set manually prior to analysis in order to avoid counting inflammatory or glial cells and left unchanged throughout. Through the interactive message screen, cells that should not be included in the analysis were eliminated, concentrating the counting on motor neurons. The microscope slide-mounted tissue sections were coded, and the pathologist performing the computerized image analysis was blinded to the experimental data. In addition, a histologic score was created ranging from 0 to 3 (score 0: high grade of inflammation

**Table 1**  
Proximal and distal mean arterial blood pressure, rectal temperature and heart rate at baseline, during aortic cross-clamping and during reperfusion. Statistical analysis was by means of one-way analysis of variance.

	Baseline				Aortic cross-clamping				Reperfusion			
	Prox MAP	Distal MAP	Temp °C	Heart rate	Prox MAP	Distal MAP	Temp °C	Heart rate	Prox MAP	Distal MAP	Temp °C	Heart rate
Group 1 (n = 18) (sham operation)	79 ± 4	80 ± 4	39.0 ± 0.2	193 ± 17	79 ± 1	80 ± 2	38.9 ± 0.2	192 ± 17	79 ± 2	80 ± 3	39.0 ± 0.2	190 ± 15
Group 2 (n = 18) (30 min SCI)	78 ± 4	79 ± 3	39.0 ± 0.2	191 ± 15	80 ± 2	10 ± 1	39.0 ± 0.1	192 ± 16	78 ± 3	78 ± 3	39.0 ± 0.2	191 ± 19
Group 3 (n = 18) (30 min SCI + Aprikalim)	78 ± 3	79 ± 3	39.0 ± 0.2	184 ± 13	79 ± 3	10 ± 1	38.9 ± 0.2	189 ± 14	78 ± 3	78 ± 3	39.0 ± 0.2	187 ± 18
P-value	P = 0.651	P = 0.484	P = 0.487	P = 0.198	P = 0.321	P < 0.001	P = 0.213	P = 0.770	P = 0.352	P = 0.318	P = 0.291	P = 0.754

MAP, mean arterial blood pressure; SCI, spinal cord ischemia.

with high grade of interstitial edema and low viability of motor neurons, score 1: moderate grade of inflammation with moderate grade of interstitial edema and moderate viability of motor neurons, score 2: low grade of inflammation with low grade of interstitial edema and high viability of motor neurons, and score 3: no inflammation, no interstitial edema and very high viability of motor neurons).

### **Statistical analysis**

Comparisons were performed among the three groups at 24, 48 and 168 h in terms of the Tarlov score, the number of motor neurons and the histologic score using 6 different animals from each group at the three time points. Therefore, these observations were not correlated in an attempt to avoid producing biased results. Data are presented as means  $\pm$  SD and as median and interquartile range (IQR). Statistical evaluation was performed by means of One-way analysis of variance test with the post hoc Tukey honestly significant difference test for comparison of experimental variables between groups. The difference among groups in terms of the Tarlov scores and the histologic score was determined by means of nonparametric statistical analysis with the Kruskal-Wallis test with the post hoc Mann-Whitney U test for comparison between two groups, while significant level was corrected using Bonferroni method. P values  $<0.05$  were considered significant as determined with IBM SPSS Statistics 20.0 software for all comparisons, while P values  $<0.025$  were considered significant for post hoc Mann-Whitney U tests (the number of comparisons was 2 at each time point).

## **Results**

### **Hemodynamic measurements**

The animals in the three groups did not differ with respect to weight and blood gas analysis. There was no significant difference among groups 1, 2, and 3 with regard to mean arterial pressure proximal and distal to aortic cross-clamping, rectal temperature and heart rate at baseline and

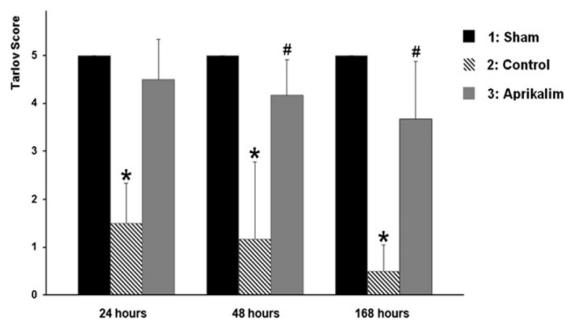
during reperfusion. During aortic cross-clamping only distal mean arterial pressure was statistically reduced in groups 2 and 3 as compared to group 1 (Table 1).

### **3.2. Neurologic outcome**

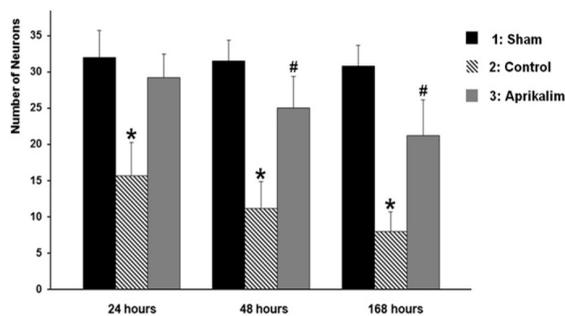
Neurologic outcome is shown in Fig. 2. All animals in group 1 had normal neurologic outcome (Tarlov score 5) at 24, 48 and 168 h (median Tarlov score 5 IQR = 0). In group 2 the mean Tarlov score was  $1.50 \pm 0.84$ ,  $1.17 \pm 1.60$  and  $0.50 \pm 0.55$  at 24, 48 and 168 h respectively (median 2 IQR = 2, median 0.5 IQR = 4 and median 0.5 IQR = 1 at 24, 48 and 168 h respectively). In group 3 the mean Tarlov score was  $4.50 \pm 0.84$ ,  $4.17 \pm 0.75$  and  $3.67 \pm 1.21$  at 24, 48 and 168 h respectively (median 5 IQR = 2, median 4 IQR = 2 and median 3.5 IQR = 3 at 24, 48 and 168 h respectively). The differences among the three groups were statistically significant at all-time points ( $P < 0.001$ , Kruskal-Wallis test). Animals in group 3 (aprikalim) had statistically significant better neurologic outcome compared to group 2 (30 min of normothermic spinal cord ischemia) at all-time points ( $P = 0.003$ ,  $P = 0.011$  and  $P = 0.003$ , at 24, 48 and 168 h respectively; Mann-Whitney U test corrected with Bonferroni method). Animals in group 3 (aprikalim) had statistically significant worse neurologic outcome compared to group 1 (sham operation) at 48 and 168 h ( $P = 0.140$ ,  $P = 0.021$  and  $P = 0.022$  at 24, 48 and 168 h respectively; Mann-Whitney U test corrected with Bonferroni method). There was an aggravation of the mean Tarlov scores in groups 2 and 3 comparing the results at 24 and 168 h, but this aggravation was not statistically significant ( $P = 0.065$  and  $P = 0.240$  respectively; Mann-Whitney U test corrected with Bonferroni method).

### **Histologic evaluation**

The results of motor neurons counting and histologic score are shown in Figs. 3 and 4 respectively. Animals in group 1 had the higher number of motor neurons at all-time points ( $32 \pm 3.7$  at 24 h,  $31.5 \pm 2.9$  at 48 h and  $30.8 \pm 2.9$  at 168 h) (median 31 IQR = 9 at 24 h, median 31.5 IQR



**Fig. 2.** It is shown the mean Tarlov scores in groups 1, 2 and 3 at 24, 48 and 168 h (\* $P < 0.025$  vs. group 2 and # $P < 0.025$  vs. group 1; Manne-Whitney U test corrected with Bonferroni method).



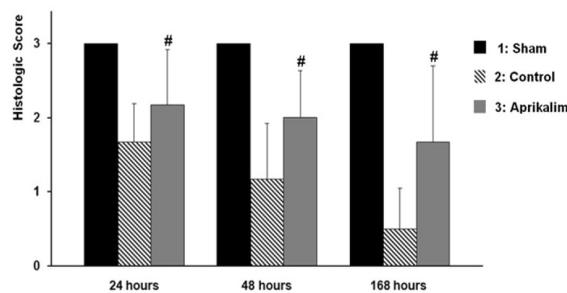
**Fig. 3.** It is shown the mean number of motor neurons in groups 1, 2 and 3 at 24, 48 and 168 h (\* $P < 0.05$  vs. group 3 and # $P < 0.05$  vs. group 1; Tukey honestly significant difference test).

= 8 at 48 h and median 30.5 IQR = 8 at 168 h) compared to group 2 ( $15.7 \pm 4.6$  at 24 h,  $11.2 \pm 3.7$  at 48 h and  $8.2.7$  at 168 h) (median 16 IQR= 11 at 24 h, median 11 IQR = 10 at 48 h and median 8.5 IQR = 8 at 168 h) and 3 ( $29.2 \pm 3.3$  at 24 h,  $25.0 \pm 4.4$  at 48 h and  $21.2 \pm 4.9$  at 168 h) (median 29.5 IQR = 9 at 24 h, median 24 IQR = 12 at 48 h and median 19.5 IQR = 13 at 168 h) ( $P < 0.001$ , at all-time points, One-way analysis of variance test). Animals in group 3 (aprikalim) had statistically significant higher number of motor neurons compared to group 2 (30 min of normothermic spinal cord ischemia) at all-time points ( $P < 0.001$  for all, Tukey honestly significant difference test).

Animals in group 3 (aprikalim) had statistically significant lower number of motor neurons compared to group 1 (sham operation) at 48 and 168 h ( $P = 0.439$ ,  $P = 0.021$  and  $P = 0.001$  at 24, 48 and 168 h respectively; Tukey honestly significant difference test). There was an aggravation of the mean motor neuron number in groups 2 and 3

comparing the results at 24 and 168 h after the end of experiment, and this aggravation was statistically significant ( $P = 0.007$  and  $P = 0.014$  respectively; Tukey honestly significant difference test).

All animals in group 1 had normal histologic scores (score 3) at 24, 48 and 168 h (median 3 IQR = 0). In group 2 the mean histologic score was  $1.67 \pm 0.52$ ,  $1.17 \pm 0.75$  and  $0.50 \pm 0.55$  at 24, 48 and 168 h respectively (median 2 IQR = 1, median 1 IQR = 2 and median 0.5 IQR = 1 at 24, 48 and 168 h respectively). In group 3 the mean histologic score was  $2.17 \pm 0.75$ ,  $2.00 \pm 0.63$  and  $1.67 \pm 1.03$  at 24, 48 and 168 h respectively (median 2 IQR = 2, median 2 IQR = 2 and median 1 IQR = 2 at 24, 48 and 168 h respectively). The differences among the three groups were statistically significant at all-time points ( $P < 0.001$ , Kruskale-Wallis test). Animals in group 3 (aprikalim) had better histologic score compared to group 2 (30 min of normothermic spinal cord ischemia) but this difference was not statistically significant ( $P = 0.206$ ,  $P = 0.067$  and  $P = 0.030$  at 24, 48 and 168 h respectively; Manne-Whitney U test corrected with Bonferroni method). Animals in group 3 (aprikalim) had statistically significant worse histologic score compared to group 1 (sham operation) at all-time points ( $P = 0.021$ ,  $P = 0.006$  and  $P = 0.019$  at 24, 48 and 168 h respectively; ManneWhitney U test corrected with Bonferroni method). There was an aggravation of the mean histologic scores in groups 2 and 3 comparing the results at 24 and 168 h, and this aggravation was statistically significant only in group 2 ( $P = 0.011$ ,



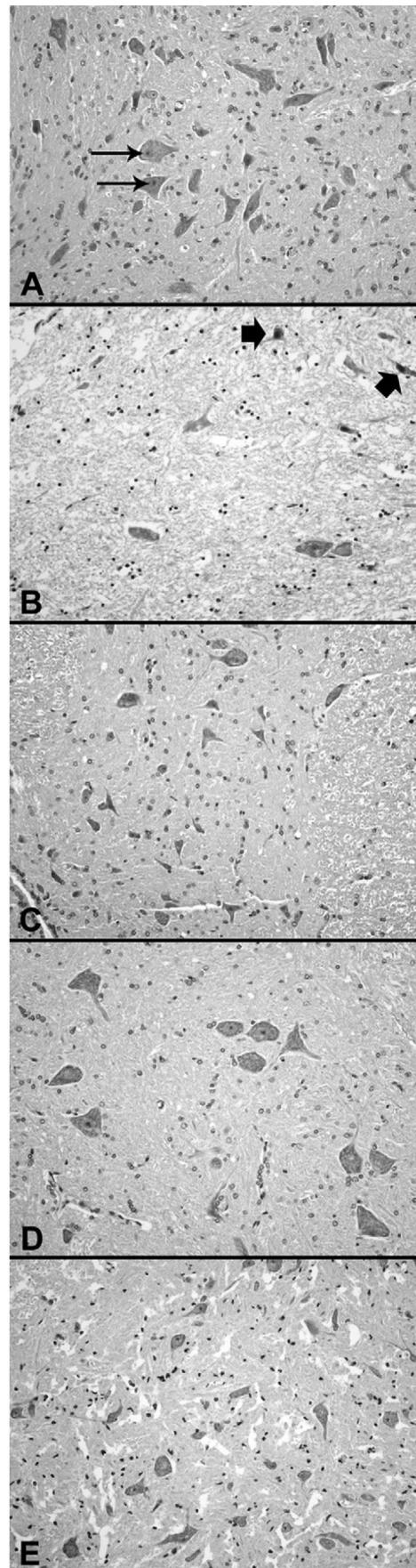
**Fig. 4.** It is shown the mean histologic scores in groups 1, 2 and 3 at 24, 48 and 168 h (# $P < 0.025$  vs. group 1; ManneWhitney U test corrected with Bonferroni method).

Manne-Whitney U test, corrected with Bonferroni method). Representative photographs of spinal cord sections are shown in Fig. 5.

## Discussion

Spinal cord ischemic injury following a successful operation or endovascular repair of the thoracoabdominal aorta in the modern era remains a potentially devastating and unpredictable complication and it has grave social, economic and psychosocial implications. Several protective strategies have been developed either to preserve the blood supply of the spinal cord or to increase its ischemic tolerance, but no method has totally prevented the development of paraplegia. There are accumulating experimental data showing that early and late ischemic preconditioning protect spinal cord injury after aortic occlusion.<sup>10e13</sup> However, in the clinical setting ischemic preconditioning may be difficult to apply for many practical reasons including the need for additional aortic occlusions in diseased aneurysmal aortas, increased surgical time, emergent operations etc. Therefore, the elucidation of the molecular mechanisms and pathways, which are activated by ischemic preconditioning, may be the key element in developing pharmacologic preconditioning for a successful use in patients undergoing surgery in the thoracic and thoracoabdominal aorta.

One of the molecular mechanisms of neuroprotection against ischemia afforded by means of ischemic preconditioning is the activation of  $K_{ATP}$



**Fig. 5.** Representative histologic images from lumbar spinal cord sections from group 1 at 168 h (A), group 2 at 168 h (B), and group 3 at 24 (C), 48 (D) and 168 h (E) stained with hematoxylin-and-eosin. Panel (A) demonstrates very high viability of motor neurons, with remarkable Nissl substance and prominent nucleoli (thin arrows). Panel (B) shows less cellularity, reduced number and low viability of motor neurons, while there are pycnotic motor neurons (thick arrows) and interstitial edema. In group 3, where aprikalim administered, 24 (C), 48 (D) and 168 h after 30 min of normothermic spinal cord ischemia it is shown preservation in the number of motor neurons with moderate interstitial edema. Original magnification 200.

channels.<sup>14</sup> The purpose of the present study was to evaluate the possible neuroprotective effects of aprikalim, a specific  $K_{ATP}$  channel opener, on spinal cord ischemic injury in the rabbit animal model of 30-min abdominal aortic cross-clamping. The results of the present study showed that intravenous administration of aprikalim in a bolus dose of 100 mg/kg 15 min before aortic occlusion had a protective effect on the rabbit spinal cord motor neurons and motor function and reduced the incidence and severity of paraplegia.

More specifically, group 3 (aprikalim) had a mean Tarlov score of 3.67 at 168 h postoperatively and we observed only one animal with a Tarlov score <3. A Tarlov score of 3 on clinical observation means that the animal is able to sit alone, while a Tarlov score of 2 means that the animal needs assistance to sit, and this represents a fundamental clinical difference compared to group 2 (normothermic spinal cord ischemia) with a mean Tarlov score of 0.50 at 168 h. In accordance with the above clinical findings, histologic assessment in our experiment indicated that 74% of motor neurons in group 2 were lost at 168 h and this percentage was only 31% in the aprikalim group at the same time point ( $P < 0.05$ ). Of course, complete protection from ischemic spinal cord injury by aprikalim was not achieved in this experimental model. However, the ischemic duration of 30 min in this experimental setting represents an extreme ischemic insult as confirmed by animals in group 2, in which all animals showed paraplegia at 168 h (Tarlov scores of 0 or 1).

The beneficial effect of other  $K_{ATP}$  channel openers on spinal cord protection after aortic occlusion has been confirmed by other investigators. Wakamatsu et al. were the first to demonstrate the protective effect of nicorandil, a specific  $K_{ATP}$  channel opener, on motor function in the rabbit model of spinal cord ischemia.<sup>15</sup> They performed abdominal aortic occlusion with a balloon catheter for 15 min, nicorandil was administered in a dose of 100 mg/kg 10 min before aortic occlusion and the follow-up was 48 h. Caparrelli et al. compared the effects of diazoxide, a potent mitochondrial  $K_{ATP}$  channel opener, with ischemic preconditioning on spinal cord injury in the rabbit

model.<sup>16</sup> They performed aortic crossclamping for 20 min, diazoxide was administered in a dose of 5 mg/kg 15 min before aortic occlusion and the follow-up was 48 h. Finally, Kim et al. evaluated the delayed effect of diazoxide on spinal cord injury in a dose of 5 mg/kg 48 h before infrarenal aortic occlusion with a balloon catheter for 20 min in the rabbit model and the follow-up was 72 h<sup>17</sup> All these published studies have shown a statistically significant better neurologic outcome in the groups of  $K_{ATP}$  channel openers in comparison to controls. The rabbit model was chosen in many studies because of the similarity with the human vascular system mechanisms.<sup>18</sup> Moreover the attempts to neuromodulate the blood flow in the central nervous system by electrical stimulation beside the biochemical stimulation has to be underlined according to the literature.<sup>19,20</sup> However, to our knowledge the present study is the first to demonstrate the protective effect of aprikalim on motor function in the rabbit model of spinal cord ischemia. In contrast, to the other three studies mentioned above, the duration of aortic cross-clamping was longer in our study (30 min vs. 20 and 15 min), indicating a stronger ischemic insult. Moreover, the follow-up in the present study was 168 h (7 days) in an attempt to rule out the effect of delayed paraplegia and to obtain more reliable results. Papakostas et al. showed that neuronal cell death in spinal cord after aortic occlusion occurs in two phases; one during the first 10 h of reperfusion and a second between 48 and 120 h of reperfusion, even after extreme ischemic insult leading to only necrosis of motor neurons.<sup>21</sup> Indeed, in the present study an aggravation in the Tarlov score as well as in the number of motor neurons and histologic score from 24 to 168 h in groups 2 and 3 were observed indicating the possible role of delayed paraplegia. We also ruled out the effects of hypothermia and hypotension,<sup>22,23</sup> because all groups had similar rectal temperatures and mean arterial blood pressures throughout the experiment.

The specific mechanism underlying the beneficial effect of  $K_{ATP}$  channel openers on ischemic spinal cord remains to be elucidated. Regarding the possible neuroprotection of  $K_{ATP}$  channel

openers, published studies suggest that, in general, opening of  $K_{ATP}$  channels leads to hyperpolarization of excitable cells by increasing the efflux of potassium ions from the relatively negatively charged intracellular compartment into the extracellular space.<sup>5-8</sup> On the other hand, current concepts of ischemia/reperfusion neuronal damage include the deleterious effects of excessive secretion of neurotoxic excitatory neurotransmitters and the intracellular accumulation of calcium.<sup>24</sup>  $K_{ATP}$  channel openers may counteract these effects by hyperpolarizing presynaptic and postsynaptic neurons.  $K_{ATP}$  channel openers may also inhibit the release of calcium from intracellular stores. This may result to decreased glutamate secretion, slowing of the depolarization rate, diminished intracellular calcium accumulation, lower energy consumption and reduced production of reactive oxygen species.<sup>5-8</sup> Given the fact that neurons contain two distinct  $K_{ATP}$  channels, one in the cell membrane (surface  $K_{ATP}$  channel) and another in the mitochondrial inner membrane (mito  $K_{ATP}$  channel),<sup>5e7</sup> it is obvious that further detailed molecular biology studies are needed in order to clarify the specific effects of different  $K_{ATP}$  channel openers in these channels, but this was not the purpose of the present study.

We acknowledge that the present study has limitations. First, regarding the administration of aprikalim we evaluated only one time interval (15 min before ischemia) and one dosage (100 mg/kg). Further studies are needed in order to reveal the optimum time interval and dosage of administration as well as the delayed effect of aprikalim on spinal cord protection. We have chosen this time interval of administration and dosage based on previous published reports with the use of  $K_{ATP}$  channel openers for spinal cord protection.<sup>15-17</sup> Second, we used ketamine as anesthetic agent and ketamine is a noncompetitive N-methyl-D-aspartate antagonist and has been reported to enhance a protective effect on spinal cord.<sup>25</sup> Although the results of the present study may have been influenced by the effect of ketamine, we used the same dose of ketamine in all three groups of the study and we speculate that this had equal effect in all groups. Third, we did not evaluate the

effects of any  $K_{ATP}$  channel antagonist in simultaneous administration with aprikalim. Finally, the present study is the first step in understanding the role of aprikalim on the amelioration of spinal cord injury after aortic occlusion. Ongoing studies in our laboratory are evaluating the protein synthesis levels of various proteins in order to provide a better understanding regarding the activation of molecular pathways afforded by aprikalim leading to neuroprotection.

In conclusion, the present study showed for the first time that aprikalim has the ability to reduce ischemic spinal cord injury after aortic cross-clamping in the rabbit model. However, it may be necessary to use further combined therapeutic strategies to totally prevent the ischemic neuronal injury. In the clinical setting further studies to evaluate the clinical benefit of aprikalim seem warranted.

#### **Ethical approval**

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health 5377-3, (Washington: National Academy Press; 1996) and the animal protocol was approved by the Institutional Animal Care and Use Committee at Attikon University Hospital Center.

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**Author contribution**

Lozos VA: study design, data collections, data analysis, writing.

Toumpoulis IK: study design, data collections, data analysis, writing, proof read.

Agrogiannis G: data analysis, writing.

Giamarellos-Bourboulis EJ: data collections, writing.

Chamogeorgakis TP: data collections, data analysis.

Rizos IK: data analysis, writing, proof read.

Patsouris ES: data analysis, writing, proof read.

Anagnostopoulos CE: study design, data analysis, writing, proof read.

Rokkas CK: study design, writing, proof read.

Conflict of interest

The authors report no conflicts of interest.

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# Postoperative jaundice after cardiac surgery

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## ABSTRACT

**BACKGROUND:** The frequency and pattern of hyperbilirubinemia after open-heart surgery and its severe perioperative complications are not well clarified. The purpose of this study was to investigate the incidence and nature of postoperative jaundice in patients undergoing cardiac operation, to analyze the determinants, and to identify the clinical significance of this complication with regard to the associated morbidity and mortality.

**METHODS:** A prospective observational study was made during the period of 2003-2004 in a Surgical Intensive Care Unit of a Cardiac Surgery Center, Athens. One hundred twenty-eight adult patients for open heart surgery were divided into three groups. Group A included 50 patients who underwent coronary artery bypass grafting (CABG), group B 31 patients who were subjected to aortic valve replacement (AVR)+CABG and group C 47 patients who underwent mitral valve replacement (MVR)+CABG. Aminotransferases, alkaline phosphatase, gamma-glutamyltranspeptidase and both types of bilirubin were determined at admission, 24 hours after the operation and thereafter according to clinical evolution. The presence of jaundice was associated with elevated serum bilirubin above 3 mg/dl.

**RESULTS:** Hyperbilirubinemia developed in 34 patients (26.5%). The incidence of postoperative jaundice was higher in patients who were subjected to MVR+CABG than to CABG and AVR+CABG. Hyperbilirubinemia was correlated with prolonged cardiopulmonary by-pass time ( $P<0.001$ ), aortic cross-clamping time ( $P<0.001$ ), the use of intra aortic balloon pumping ( $P<0.001$ ), the administration of inotropes and the number of blood and plasma transfusions. Postoperative jaundice resulted mainly from an increase in conjugated bilirubin.

**CONCLUSIONS:** Although hyperbilirubinemia seems to be multifactorial, the type

of operation, the preoperative hepatic dysfunction due to advanced heart failure (NYHA II-III) and the decreased hepatic flow during the operation seem to determine the incidence of jaundice.

**KEY WORDS:** jaundice; conjugated bilirubin; cardiac surgery; prognosis

## Introduction

In the early studies hyperbilirubinemia and serum transferase changes were reported to occur in a small number of patients who were subjected to open heart surgery for a variety of cardiac lesions. However, in more recent retrospective studies it became apparent that postoperative jaundice occurred in a substantial number of cases and its incidence is estimated to be more than 20%. In addition, the frequency and pattern of these biochemical shifts as well as their severe perioperative complications are not clarified. The appearance of postoperative hyperbilirubinemia is associated with serious morbidity and carries a mortality rate of 25%.<sup>1,2</sup> Other studies reported no association between elevated conjugated bilirubin and mortality.<sup>3</sup> Retrospective studies suggested many possible risk factors underlying the development of jaundice, which included the type of surgical procedure, the age of the patient, the bypass time, the aortic cross-clamping time, the number of blood and plasma transfusions, the preoperative hepatic dysfunction and heart failure, and the development of hypoxemia during the operation.<sup>4</sup> The purpose of this study was to investigate the incidence and nature of postoperative jaundice in patients undergoing cardiac operations, to analyze the determinants, and to identify the clinical significance of this complication with regard to the morbidity.

## Methods

Into this prospective study were consecutively enrolled 128 patients older than 18 years who were subjected to open heart surgery with the use of extracorporeal circulation from December 1, 2003 to January 30, 2004. The patients were not selected with any predetermined criteria. They were all treated at the intensive care unit (ICU) of our institution, and were divided into three groups in accordance with the type of cardiac operation.

Group A included 50 patients who underwent coronary artery bypass grafting (CABG), group B 31 patients who were subjected to aortic valve replacement (AVR)+CABG, and group C 47 patients who underwent mitral valve replacement (MVR)+CABG. Patients undergoing CABG or valve replacement that was incidental to multiple valve repair, resection of a ventricular or aortic aneurysm, transplantation or another surgical procedure were not included. The majority of patients received a mechanical valve (n:12). In addition, patients with preoperative liver dysfunction and hyperbilirubinemia, defined as total bilirubin concentration of more than 3 mg/dl were excluded from this study. Hepatic dysfunction was determined as prolonged prothrombin time (PT), decreased serum protein and increased gamma globulin combined with elevated liver enzymes.

All operations were performed by a group of surgeons, while giving anesthesia according to a standard protocol. Cardiopulmonary bypass was initiated after ascending aorta-to-right atrial or bicaval cannulation. Myocardial protection was achieved with cold, intermittent, antegrade cardioplegia or a combination of antegrade and retrograde cardioplegia. During the operation, electrocardiographic values, pulse, radial arterial line, nasopharyngeal and rectal temperature and urine output (via Foley catheter) were determined. All patients received a central venous catheter, but only the high-risk patients a pulmonary artery (Swan-Ganz) line. Moderate hypothermia with the lowest nasopharyngeal temperature of around 28 °C was instituted with a roller pump. At the induction of anesthesia all patients who were subjected to CABG received intravenous cefuroxime as a single dose (3 g), while patients who underwent valvular replacement were given a combination of a single dose of 400 mg teicoplanin and 3 doses of 2 g

ceftazidime in combination for 24 hours.

Blood samples were collected for biochemical analysis of hepatobiliary function were within 2 days before the operation. The levels of serum creatinine, urea, globulin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma glutamyl-transpeptidase ( $\gamma$ -GT), alkaline phosphatase (ALP), total bilirubin, unconjugated and conjugated bilirubin were determined at admission, 24 hours and after the operation. The presence of jaundice was associated with elevated level of serum bilirubin (above 3 mg/dl).

In each patient important preoperative, perioperative and immediate postoperative parameters were thought to influence the liver function. Right atrial pressure and pulmonary artery pressure were obtained from the record of preoperative cardiac catheterization. Demographic data including age, sex, presence of any disease, preoperative left ventricular ejection fraction as assessed by angiography and New York Heart Association (NYHA) class were recorded in each patient. Furthermore, type of the operation, bypass time, aortic cross-clamping time, administration of inotropes, number of blood and plasma transfusions, use of intra-aortic balloon counterpulsation (IABP), duration of mechanical ventilation, days of hospitalization in the ICU, and outcome were observed. Dobutamine and noradrenaline were used in the rewarming phase and dopamine was used at a low dose in case of reduced urine output. In this study clinical and laboratory examinations were performed prospectively. The study was considered as a quality control study, and ethical approval was not necessary.

### Statistical analysis

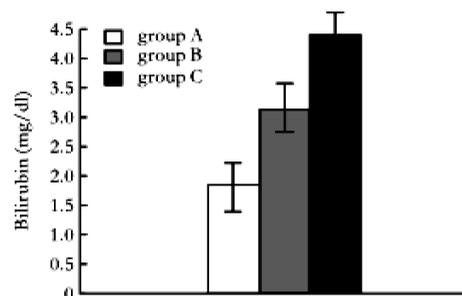
All variables were tested for homogeneity and normal distribution before statistical analysis. The data were expressed as mean $\pm$ standard deviation unless they were stated specifically and a *P* value <0.05 was regarded as statistically significant. The Chi-square test was used to compare qualitative characteristics. Analysis of variance was performed to detect differences between the groups. The post-hoc Bonferroni-test was applied for multiple com-

parisons. Pearson's linear, as well as, stepwise multiple regression analysis was used in order to assess correlations between the variables. Statistical analysis was performed using SPSS 11.5 for Windows.

**Table 1.** Demographic data and operative times among the three groups of patients

Variables	CABG	AVR+CABG	MVR+CABG
Age	69.7 $\pm$ 6.4	71 $\pm$ 8	66.3 $\pm$ 11.5
M/F	45/5	20/11	18/29
Off-pump	6	0	0
On-pump	44	31	47
Bypass time (min)	17.8 $\pm$ 54.7	140.2 $\pm$ 61.1	176.0 $\pm$ 78.4
Aortic CC time (min)	83.9 $\pm$ 39.4	104.8 $\pm$ 51.7	133.3 $\pm$ 56.8

CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MVR: mitral valve replacement; M/F: male/female; CC: cross-clamping.



**Fig.** Postoperative jaundice levels between groups. Group A: CABG, group B: AVR+CABG, group C: MVR+CABG; CABG: coronary artery bypass grafting, AVR: aortic valve replacement, MVR: mitral valve replacement.

**Table 2.** Variance of conjugated bilirubin among the three groups of patients

	CABG	AVR+CABG	MVR+CABG
Conjugated bilirubin (mg/dl)	1.86 $\pm$ 2.71	3.09 $\pm$ 4.56	4.39 $\pm$ 3.61

### Results

Demographic data for patients of different disease categories are shown in Table 1. There was no statistically significant difference between the ages of patients who underwent different types of surgical procedures (0.092). Group A had 5 women, group B 11 women and group C 29 women. Extracorporeal circulation was avoided only in 6 patients of group A. Hyperbilirubinemia developed in 34 patients. The overall incidence of postoperative jaundice was 26.5%, and it remained higher in patients who were subjected to MVR+CABG than in those who were subjected to CABG and AVR+CABG

(Fig.). The elevated level of serum bilirubin was correlated with bypass time ( $r:0.32$ - $P<0.001$ ), aortic cross-clamping time ( $r:0.33$ - $P<0.001$ ), use of IABP ( $r:0.37$ - $P<0.0001$ ), injection of inotropic agents ( $r:0.18$ - $P<0.04$ ), and number of blood ( $r:0.239$ - $P<0.008$ ) and plasma transfusions ( $r:0.30$ - $P<0.001$ ). There was a difference between bypass time and aortic crossclamping time among the three groups of patients (Table 1).

Furthermore, there was a difference between the morbidity of patients who developed low cardiac output syndrome (NYHA Functional Class II-III) and those who were subjected to valve replacement. Stepwise multiple regression analysis showed that aortic cross-clamping time ( $P:0.001$ ), use of IABP ( $P:0.001$ ) and number of plasma transfusions ( $P:0.000$ ) were independent determinants of the elevated level of bilirubin.

As to the nature of hyperbilirubinemia, postoperative jaundice results mainly from an increased level of conjugated bilirubin and is associated with a higher mortality, especially in patients in whom the highest level of total bilirubin occurred late after operation. On the first postoperative day, the levels of total and unconjugated bilirubin increased in patients with postoperative hyperbilirubinemia and those with nonpostoperative hyperbilirubinemia compared with the preoperative levels. In the majority of patients, the levels of bilirubin normalized within 7-21 days after operation (Table 2). There was a statistically significant difference between different groups of patients ( $P=0.003$ ). The difference between groups A and C was more significant ( $P=0.002$ ). Five patients developed hepatic dysfunction during sepsis, multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) and died eventually from a bilirubin level over 21 mg/dl. Three of them had Staph epidermidis positive blood cultures. In addition, 2 patients died after AVR as hyperbilirubinemia was one of the severe perioperative complications such as low cardiac output syndrome.

## Discussion

This prospective study has shown that despite demonstrable improvements in all aspects of opera-

tive and perioperative care over the last decade, hepatic dysfunction remains a serious postoperative complication with unknown pathogenesis. The incidence of postoperative hyperbilirubinemia is 26.5%, which is similar to the data reported by Chu et al,<sup>3</sup> Collins et al,<sup>1</sup> and Wang et al.<sup>4</sup> It is more common than others suggested by retrospective studies.<sup>13</sup> Successful outcome depends on prompt diagnosis and supportive therapeutic intervention.

Many factors may contribute to the development of jaundice after open heart surgery. Before operation the most important contributing factor is high right atrial pressure reflecting the degree of liver congestion. It is obvious that severe heart failure predisposes the patient to the development of clinical jaundice after cardiopulmonary bypass. Chu et al<sup>3</sup> suggest that among patients whose livers had been congested, as a result either of right heart failure or tricuspid insufficiency, the incidence of postoperative jaundice was significantly higher. Wang et al<sup>4</sup> support the idea that patients with severe pre-operative cardiac failure may have higher right atrial pressure and, with their liver in a "congested" state, its capacity to dispose of the bilirubin load may be impaired.<sup>5,6</sup>

Analysis of the degree of perioperative hypotension and hypoxia has enabled us to confirm the previously suggested hypothesis that either, or both, of these factors are important in the development of postoperative jaundice. Chu et al<sup>3</sup> suggest that hypotension in the early postoperative period would reduce hepatic perfusion and hypoxemia further decrease hepatic oxygen supply. Although the pathogenesis of hepatic lesions is complex and multifactorial, the major factor implicated in cardiac surgery is reduced systemic blood flow, which leads to inappropriate oxygen delivery and energy deficit.<sup>7</sup> D'Ancona et al<sup>8</sup> believe that during the intraoperative phases, hypovolemia, prolonged bypass and aortic cross-clamping time and administration of inotropes can cause hypoperfusion. Hypoxia of intestinal cells leads to activation of hepatic macrophages (Kupffer cells) with consecutive release of mediators. Surgical patients may suffer from ischemia followed by a reperfusion injury in those organs that are less perfused during shock, particularly the gut.<sup>9</sup> A low tissue ATP content due to

ischemia contributes to a disturbed function of the intestinal epithelial barrier. An impaired function of the small intestinal mucosal endothelial and epithelial barrier integrity results in the translocation of bacteria, their DNA, and their toxins into the portal vein. Hepatic macrophages and monocytes are activated and release inflammatory mediators that lead to the development of jaundice and multiple organ failure. In most of the cases, jaundice is reversible with no harm results. However, the more hyperbilirubinemia persists and ascends the more frequent the mortality is Michalopoulos et al<sup>10</sup> support that hepatic dysfunction follows other perioperative complications, such as low cardiac output syndrome necessitating administration of inotropic agents and usage of IABP, as well as perioperative shock or arrest. In our study 10 patients required intraoperative cardiac support with IABP.

Another factor in the development of severe hepatic dysfunction is the number of blood transfusions. Postoperative jaundice is believed to occur because the liver, “shocked” by hypotension, hypoxia, or hypothermia or chronically congested by right heart failure, can not handle the bilirubin load presented after massive transfusions. On the other hand, high preoperative alcohol consumption or HBsAg positivity ( $n=3$ ) does not predispose to the appearance of hyperbilirubinemia, although they may aggravate the already developed hepatic dysfunction. Mathie<sup>11</sup> suggests that microembolism, free radicals and derangements in hepatic blood supply may contribute to liver damage. Thousands of gaseous microemboli return from the pump to the patient during cardiopulmonary bypass. In addition, platelet aggregates from the bypass tubing may contribute to these emboli.

As for the nature of jaundice, the elevated level of serum bilirubin is mainly conjugated. Only a small number of jaundiced patients have abnormal liver enzymes. The decreased hepatic capacity for bi-

lirubin disposal in combination with the increased level of unconjugated bilirubin level as a result of hemolysis from cardiopulmonary bypass, cardiomy suction, and mechanical prosthesis is responsible for a higher incidence and greater severity of postoperative hyperbilirubinemia.<sup>12,13</sup> Furthermore, there is a clear relationship between the development of jaundice and the type of operation as severe hepatic dysfunction may occur far more frequently in patients undergoing MVR or multiple valve surgery requiring more time and blood than in those receiving coronary bypass graft procedures.<sup>14</sup> In addition, these patients have a higher rate of postoperative infection, and hyperbilirubinemia is associated with prolonged mechanical ventilation and ICU stay.

In summary, these data suggest that the overall incidence of postoperative hyperbilirubinemia, which results mainly from conjugated bilirubin, is approximately 26.5% in patients who have undergone cardiac operations and its origin remains multifactorial. Nevertheless the mortality rate is 5.5%. The type of surgical procedure including the specific technique during the performance of mitral valve replacement (cannulation of both venae cavae), a possible preoperative hepatic dysfunction due to advanced heart failure (NYHA II-III) and the decreased hepatic flow during open heart surgery could determine the incidence of postoperative jaundice.

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**Competing interest:** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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# A Pulmonary valve replacement in patients with corrected tetralogy of Fallot

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## Abstract

**Introduction:** Development of pulmonary insufficiency in patients with surgically corrected tetralogy of Fallot (TOF) may lead to severe right heart failure with serious consequences. We herein present our experience with pulmonary valve replacement (PVR) in these patients.

**Methods:** From 2005-2013, 99 consecutive patients (71 males/28 females, mean age 38±8 years), underwent PVR after 7 to 40 (mean 29 ± 8) years from the initial correction. Seventy nine of the symptomatic patients presented in NYHA II, 14 in III and 2 in IV. All underwent PVR with a stented bioprosthetic valve, employing a beating heart technique with normothermic extracorporeal circulation support. Concomitant procedures included resection of aneurysmal outflow tract patches (n = 37), tricuspid valve annuloplasty (n = 36), augmentation of stenotic pulmonary arteries (n = 9), maze procedure (n = 2) and pulmonary artery stenting (n = 4).

**Results:** There were 2 perioperative deaths (2%). One patient developed sternal dehiscence requiring rewiring. Median ICU and hospital stay was 1 and 7 days respectively. Postoperative echocardiography at 6 and 12 months showed excellent bioprosthetic valve performance, significant decrease in size of the right cardiac chambers and reduction of tricuspid regurgitation (TR) in the majority of the patients. At mean follow-up of 3.6 ± 2 years, all surviving patients remain in excellent clinical condition.

**Conclusion:** Probability of reoperation for pulmonary insufficiency in patients with surgically corrected TOF increases with time and timely PVR by preventing the development of right heart failure is crucial for long-term survival. Current bioprosthetic valve technology in combination with the beating heart technique provides excellent immediate and short-term results. Further follow-up is necessary to evaluate long-term outcome.

**Keywords:** Adult Congenital Heart Disease, Congenital Heart Surgery, Pulmonary Valve **Reoperation**

## Introduction

Tetralogy of Fallot (TOF) is one of the commonest cyanotic congenital heart defects (CHD) and its treatment is considered as one of the success stories of modern medicine and surgery.<sup>1</sup> Nevertheless, this is hampered by long-term morbidity due to right ventricular (RV) dysfunction secondary to pulmonary regurgitation (PR).<sup>2</sup> Therefore, pulmonary valve replacement (PVR) is employed to prevent the detrimental effects of PR.<sup>3</sup> Timely management although essential for optimal long-term functional and hemodynamic results, remains undetermined.<sup>4</sup> We herein present our experience with PVR in patients with surgically corrected TOF using stented bioprosthetic valves.

## Patients and Methods

From September 2005 to December 2013, 99 consecutive patients, mean age  $38 \pm 8$  (range 17-51) years, 71 males and 28 females with surgically corrected TOF underwent PVR after a mean time of  $29 \pm 8$  (7-40) years from the initial surgical repair. All patients had undergone surgical correction of TOF with the transannular patch technique. Seventy-nine symptomatic patients presented in NYHA II, 14 in NYHA III and 2 in NYHA IV. Eighty-five patients underwent re-operation for the first time, while 9, 3 and 2 patients were re-operated for the second, third and fourth time respectively (Table 1).

Patient referral and therefore study inclusion criteria were those set by Davlourous and colleagues: (a) asymptomatic patients with severe PR, progressive RV dilatation, and dysfunction and/or deterioration in exercise tolerance. (b) Symptomatic patients with established severe PR and RV dilatation regardless of RV function. (c) Patients with moderate to severe PR and associated lesions with significant hemodynamic impact requiring surgical intervention. (d) Patients with severe ventricular arrhythmias, associated with severe PR and RV dilatation irrespective of ventricular function.<sup>5</sup> The only exclusion criteria applied were those conditions, which would diverge the procedure from the beating heart technique (e.g. performing a left side valve procedure

or a residual VSD requiring cardioplegic arrest).

In all cases, the procedure was performed using the beating heart technique with extracorporeal circulatory support. Thorough preoperative echocardiographic evaluations determined RV dimensions and function and excluded the presence of intracardiac communications. Findings were confirmed by cardiac magnetic resonance imaging (MRI). Stented, oversized, third generation bioprosthetic valves (Aortic Magna -Edwards Life sciences, Soprano Armonia-Sorin and Mosaic - Medtronic Inc.) were implanted based on surgeon's preference and availability. In addition, resection of aneurysmal outflow tract patches ( $n = 37$ ), tricuspid valve annuloplasty ( $n = 36$ ), augmentation of stenotic pulmonary arteries ( $n = 9$ ), modified maze procedure ( $n = 2$ ) and intraoperative pulmonary artery stenting ( $n = 4$ ) were also performed (Table 1).

## Operative approach

After induction of general anesthesia, redo mid-line sternotomy incision was performed with an oscillating saw. Cautiously all adhesions were meticulously removed by sharp dissection and electrocautery to achieve a dry field prior to heparinization. Standard bicaval or in some cases single right atrial to aorta cannulation was established and on occasion, arteriovenous (AV) femoral cannulation as necessary. Normothermic cardiopulmonary bypass was then established and the operation was accomplished using beating heart technique.<sup>6</sup> The main pulmonary artery (MPA) was incised longitudinally and the old patch excised. A soft metal tip sucker was placed into the confluence of the branch pulmonary arteries and occasionally another one in the RV through the RV outflow tract (RVOT) to create a relatively dry operative field. Rudimentary pulmonary leaflets were excised. RV aneurysms or remaining subpulmonary muscle bands were resected as well. The MPA was thereafter reconstructed with a large piece of Dacron, where the valve would also be sewn on anteriorly, with the patch covering like a hood the MPA and the newly created RVOT. If necessary, the branch pulmonary arteries were enlarged with the use of autologous or

bovine pericardium and occasionally with the aid of an intraoperatively inserted pulmonary artery stent. The largest suitable and available bioprosthetic valve was then sutured to the pulmonary annulus with a continuous polypropylene suture technique (Figure 1). Whenever appropriate, i.e. in any patient with 2+ or greater tricuspid regurgitation (TR), the TV was also repaired using various annuloplasty techniques.

Table 1. Enrolled patients' data

Parameters	Value
No of patients	99
Gender	
Male	71
Female	28
Mortality	2/99 (2%)
Mean age (y)	38±8
Pre-operative NYHA status	
I	4
II	79
III	14
IV	2
No of reoperations	
1 <sup>st</sup>	85
2 <sup>nd</sup>	9
3 <sup>rd</sup>	3
4 <sup>th</sup>	2
Concomitant procedures	
Resection of aneurysmal RVOT patches	37
Tricuspid valve annuloplasty	36
Augmentation of stenotic PAs	9
Modified Maze procedure	2
Intraoperative PA stenting	4
CPB time (min)	47.5±12
Median stay (d)	
ICU	1
Hospital	7
Mean follow-up (y)	3.6±2

Abbreviations: NYHA, New York Heart Association; RVOT, right ventricular outflow tract; PA, pulmonary artery; ICU, intensive care unit; CPB, cardio-pulmonary bypass,

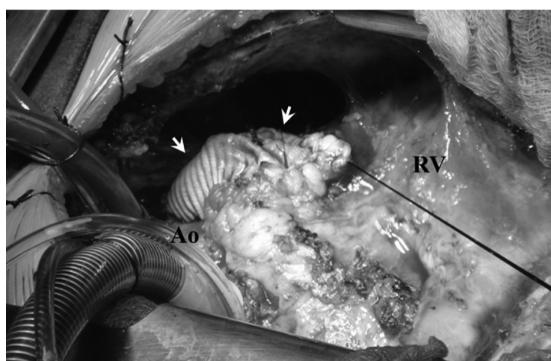


Figure 1. Arrows signify RVOT Dacron patch (surgeon's view).

## Patient follow-up

All patients were placed postoperatively on anti-platelet therapy with aspirin for 6 months. Periodic follow-up included clinical assessment, electrocardiography and transthoracic echocardiography at 6-month intervals. None of the patients required postoperative cardiac catheterization. Clinical assessment involved exercise capacity and detection of symptoms and signs of right heart failure. ECG study included QRS complex duration values. MRI was reserved for those patients with evidence of RV function deterioration.

At echocardiography, RV dimensions were assessed both qualitatively and quantitatively. Qualitative assessment of RV size was accomplished by calculation of RV area and mid-cavity diameter at end diastole, from the apical four chamber view wherein they should normally be smaller than those of the LV. In case of moderate RV enlargement, the ventricular cavity area matches that of the LV and shares the apex of the heart. Progression, however, of RV dilatation results in further increase of the cavity area surpassing therefore that of the LV and dominating the formation of the apex.<sup>7</sup> RV function was assessed by means of tricuspid annular plane systolic excursion (TAPSE), measuring the level of systolic excursion of the lateral tricuspid valve annulus towards the apex in a four chamber view. In addition, tissue Doppler imaging (TDI) was used as a quantitative assessment of RV systolic and diastolic function by calculating myocardial velocities.<sup>8</sup> TR was evaluated in a semi-quantitative manner by means of proximal isovelocity surface area (PISA) radius and vena contracta width. A vena contracta width =7 mm suggests severe TR, whereas a diameter <6 mm refers to mild or moderate TR.<sup>9,10</sup> PR was assessed by jet size, deceleration rate and regurgitant fraction.<sup>9,10</sup>

## Statistical analysis

Preoperative and postoperative continuous variables were compared by paired t test. The significance of differences between two groups was assessed by Student's t test. All results were expressed as mean ± standard deviation and a P value

of  $<0.05$  was considered statistically significant.

### Results

Total cardiopulmonary bypass time was  $47.5 \pm 12$  minutes. There were two early deaths (2%). Both patients were in NYHA IV status preoperatively with severe RV dilatation and dysfunction. This was their fourth re-operation and they eventually died from multiple organ dysfunction syndrome (MODS). In particular, the first patient developed septic shock and died 45 days after surgery while the second severe coagulopathy due to hepatic failure and died 30 days postoperatively.

Of the surviving patients ( $n = 97$ ), 5 had a cardioverter defibrillator implanted for sustained severe ventricular arrhythmias. Both patients who underwent the modified Maze procedure remained in sinus rhythm. One patient required re-wiring for sternal dehiscence. Median ICU and hospital stay was 1 and 7 days respectively.

Follow-up period ranged from 6 months to 8 ( $3.6 \pm 2$ ) years during which none of these patients required re-operation. All of them experienced significant clinical improvement and remain in excellent clinical condition.

### ECG assessment

QRS complex duration was significantly reduced from  $147.3 \pm 13.6$  ms preoperatively to  $139.5 \pm 13$  ms postoperatively ( $p < 0.05$ ). Especially, in NYHA II patients, QRS duration significantly decreased postoperatively from  $144.1 \pm 11.4$  ms to  $137.3 \pm 10.5$  ms ( $P < 0.05$ ) and in NYHA III from  $161.3 \pm 8.9$  ms to  $149.5 \pm 9.7$  ms ( $P < 0.05$ ) respectively (Figure 2).

### Functional class

Significant improvement in NYHA status was achieved in the vast majority of the surviving patients. In particular, 92 patients are in NYHA I and 5 in NYHA II (Figure 3).

### Right ventricle

#### RV dimensions

At qualitative assessment, RV dilatation was found to improve from severe in 17 patients to moderate in 10 and mild in 7 patients respectively (Figure

4). The other 82 patients improved from moderate to mild dilatation.

Quantitative study showed a significant decrease in RV end diastolic diameter (RVEDD) from  $37.5 \pm 2.8$  mm to  $30.9 \pm 2.8$  mm postoperatively ( $P < 0.05$ ). More specifically, in patients who preoperatively were in NYHA II and III status, RVEDD decreased significantly ( $P < 0.05$ ) from  $36.7 \pm 1.3$  mm to  $30.2 \pm 1.3$  mm and from  $40.6 \pm 1.7$  mm to  $33.0 \pm 3.1$  mm respectively (Figure 5). It should be noted that RV dilation remained severe in the two patients who finally died.

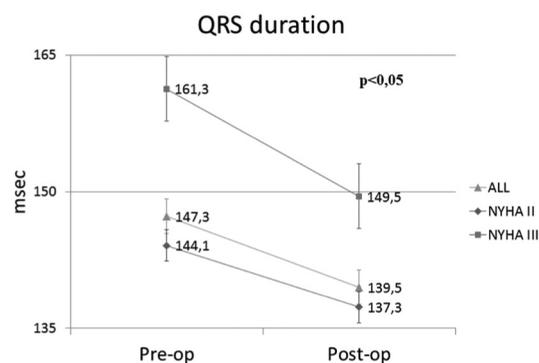


Figure 2. Significant postoperative reduction in QRS duration ( $P < 0.05$ ).

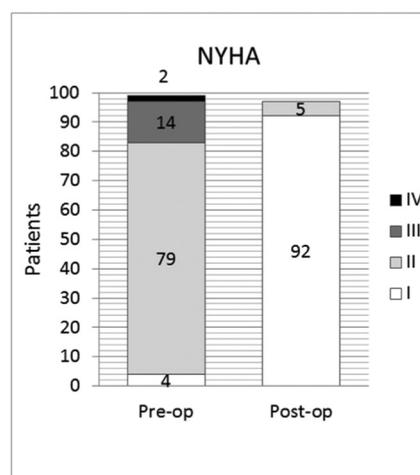


Figure 3. Dramatic clinical improvement in the vast majority of patients.

### RV dysfunction

RV dysfunction was present in 12 patients preoperatively, 2 of which eventually died. Of the 10 surviving patients, 7 persisted with RV dysfunction (preoperative: TAPSE  $8.14 \pm 2.67$  mm,  $TDI < 11.5$  cm/s, postoperative: TAPSE  $10.85 \pm 4.22$

mm, TDI <11.5 cm/s) yet with improved (moderate) RV dilatation. Of these, 6 patients in preoperative NYHA III status are now in NYHA II, whereas 1 patient remained in NYHA II status (Figure 6).

Three patients, however, recovered RV function (preoperative: TAPSE 14.66 ± 0.58 mm, TDI <11.5 cm/s, postoperative: TAPSE 17.0 ± 1.0 mm, TDI >11.5 cm/s) 6 months after the operation. All of them were in NYHA III with severe RV dilation preoperatively and improved to NYHA I status in spite of, moderate, although improved, RV dilatation (Figure 7).

### Tricuspid regurgitation

Preoperative TR was evaluated as severe, moderate and mild in 30, 35 and 34 patients respectively. The tricuspid valve was repaired using various annuloplasty techniques (Kay, pericardial strip, Kalangos ring, conventional rings) in 36 patients, all 30 with severe and selected 6 with moderate regurgitation. All patients had mild or less TR at follow-up (Figure 8).

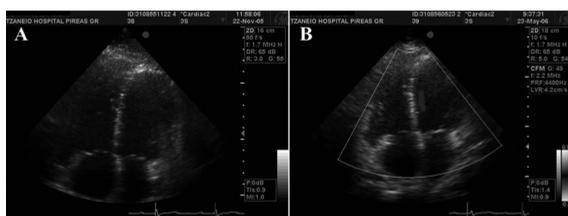


Figure 4. Comparison of preoperative (A) and postoperative (B) echocardiogram in a patient with RV dilatation depicting the postoperative decrease in RV dimensions.

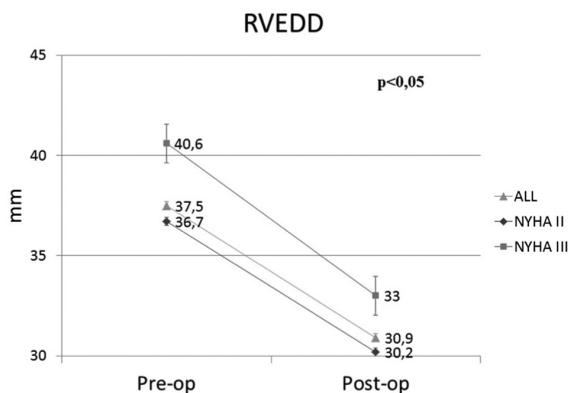


Figure 5. Significant postoperative reduction in RV end diastolic diameter ( $P < 0.05$ ).

### Pulmonary regurgitation

All patients (n = 99) had severe PR prior to operation. Following PVR, all surviving patients showed excellent prosthetic pulmonary valve function with only 11 of them having mild regurgitation, while the remaining 88 an absolutely competent prosthesis. Postoperative mean pulmonary valve gradient was 9 ± 2 mm Hg.

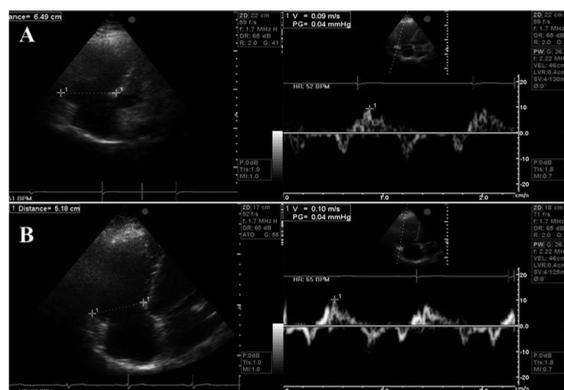


Figure 6. Echocardiographic study in a patient with preoperative RV dysfunction (A): RV dysfunction remains unchanged after PV replacement with reduced, nevertheless, RV dilatation (B).

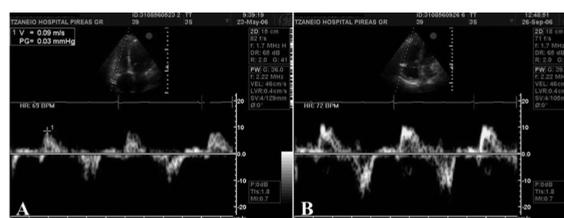


Figure 7. Echocardiographic study in a patient with preoperative RV dysfunction (A) who recovered RV function 6 months after the operation (B).

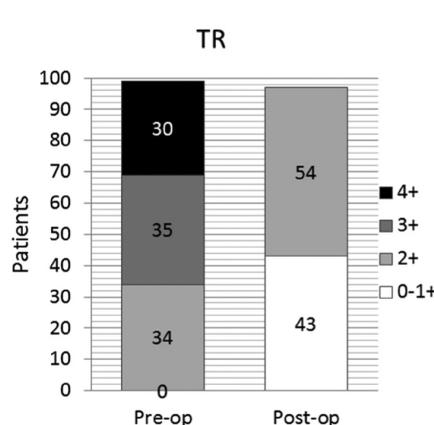


Figure 8. Postoperative reduction in tricuspid regurgitation.

## Discussion

Longstanding PR has been recognized to have deleterious effects on RV function. Indeed, progressive RV volume overload results in severe late complications. Exercise limitation, right and left ventricular dysfunction, electrocardiographic abnormalities and most importantly, development of life threatening atrial and ventricular arrhythmias are the most common.<sup>11</sup> It seems that the main cause of sudden death in these patients is fatal arrhythmias resulting from RV dysfunction and therefore preservation or restoration of RV function may reduce the risk.<sup>2,11-13</sup> Nevertheless, in the case of established supraventricular arrhythmias, a combined procedure with cryoablation seems beneficial.<sup>5</sup>

Some degree of PR is almost always present in patients following anatomical correction of TOF. Pulmonary regurgitation is well tolerated for years, yet the chronic effects on RV function may be, dramatic.<sup>14</sup> Patients often are unaware of any symptoms, until RV dysfunction becomes severe. In addition, for undetermined reasons, a right to left ventricular interaction ensues with subsequent left ventricular dysfunction.<sup>14</sup> Pulmonary regurgitation is frequently underestimated on physical examination, since the anticipated diastolic murmur is often soft and short due to rapid equalization of the diastolic pressures in pulmonary artery and right ventricle. The regurgitant jet is also often missed on two-dimensional echocardiography due to low velocity and laminar flow pattern. Therefore, all patients with previous surgical repair of TOF should undergo routine monitoring to determine changes in cardiothoracic index followed by a comprehensive echocardiographic examination.<sup>14</sup>

Currently, PR secondary to valve commissurotomy, transannular enlargement and patching presents as the most common finding and subsequent indication for reoperation in patients with repaired TOF. PVR is consequently considered for preservation of the jeopardized RV function. Yet, although the importance of chronic RV volume overload is well recognized, the ideal time for PVR remains a debatable issue.<sup>15</sup>

Appropriate and timely management of post-operative PR remains essential for beneficial long-term functional and hemodynamic results. Follow-

ing PVR, subjective clinical improvement has been reported in several studies. Objective improvement in RV function and reduction in RV size, subsequent to PVR, has also been shown.<sup>15-22</sup> Bove and colleagues reported, in a group of 11 patients, favourable change in RV size by demonstrating significant reduction in cardiothoracic index as also diminished echocardiographic right to left ventricular end diastolic dimensions ratio.<sup>18</sup> Ilbawi et al displayed a significant reduction of the cardiothoracic index in 42 and a decrease in angiographically determined RV end systolic volumes in 18 patients.<sup>19</sup> Warner and colleagues reported a 30% reduction in echocardiographic RV end diastolic diameter (RVEDD) in 16 patients after PV replacement for PR.<sup>11</sup> All the aforementioned studies also documented improvement in exercise tolerance.

Pulmonary valve replacement should be considered before the development of irreversible RV dysfunction and can be performed with low operative risk (1%-2%).<sup>2,11,12</sup> Evidence suggests that delayed intervention leads to disastrous consequences.<sup>14</sup> Although subjective improvement in clinical symptoms may occur after delayed reoperation, RV function and volumes often remain unchanged as chronic myocardial exposure to severe PR results in irreversible contractile impairment.<sup>17</sup>

Early detection of TR may signify and prove reliable indicator of the appropriate timing for PVR and subsequent RV function preservation.<sup>2,15</sup> Davlouros and colleagues classified the indications for PV replacement based on clinical and PR and RV dilatation assessment criteria.<sup>5</sup> These constitute our current surgical indications; patients undergoing surgery in extension of these criteria exhibited varied outcomes, with some of them, nonetheless, experiencing significant clinical improvement. Therrien et al concluded that PVR should be undertaken before RV end-diastolic volume reaches 170 mL/m<sup>2</sup> or RV end-systolic volume reaches 85 mL/m<sup>2</sup> to increase the chances of normal RV volume restoration after repair.<sup>17</sup> In a recent study, Dave and colleagues showed that timely insertion of a PV substitute in young patients, when RV end-diastolic volume exceeds 150 mL/m<sup>2</sup>, is directly associated with improvement

in RV dimension and function, in a 6 month period.<sup>21</sup> The duration of the QRS complex is directly proportional to RV dimensions and right bundle branch block is anticipated in almost 95% of patients. Therefore, QRS duration may also designate the time of re-operation, although clear limits are yet to be defined.<sup>2,14</sup>

The ideal valve for the pulmonary position is yet to be found. Selected PV prostheses should demonstrate optimal hemodynamics, durability, easy implantation and, not the least, at a relatively low cost. A variety of valves have been used over the years for PVR and include mechanical, xenografts (stented or stentless), homografts, autologous pericardial valves and more recently bovine jugular valves (stented or stentless). The use of mechanical valves in the pulmonary position has been reported, but has significant drawbacks, largely due to the frequent occurrence of thromboembolic phenomena and valve failure.<sup>15,22</sup>

Earlier results with stented xenografts were disappointing due to premature deterioration and calcification and reported freedom from reoperation of only 37% at 5 years.<sup>24</sup> Fortunately, homografts came around and became the 'conduit of choice' for the pulmonary position. However, they also deteriorate with time and actuarial freedom from reoperation at 5 and 10 year varies from 74%-85% and 54%-69% respectively.<sup>25,26</sup> During the last decade bioprosthetic valve technology has made some distinct advances. Third generation valves share some unique characteristics that include glutaraldehyde zero pressure fixation and treatment with alpha amino oleic acid (AOA), an anti-mineralization agent that has been shown to reduce leaflet calcification in animal models.<sup>27</sup> These techniques have significantly increased the durability of these valves. Over the years, in an effort to achieve optimal hemodynamics with long-term durability, our approach to patients requiring PVR has evolved into the following strategy: employment of third generation, stented, oversized bioprosthetic valves.

Although Kanter and colleagues have reported excellent short-term results with the use of a stentless aortic valve we prefer the stented counterpart since with oversizing the stented framework

minimizes the compression from the sternum after closure.<sup>28</sup> This is supported by the low incidence of postoperative insufficiency or stenosis in our group of patients who received oversized valves. The other theoretical advantage of using oversized valves is to minimize the RV to pulmonary artery gradient (albeit functioning in a low pressure system) and the high pressure effect that cause long-term structural dysfunction. With reduced diastolic trans-prosthetic pressure gradient and low closing stress in the pulmonic position the, in any case, limited mechanical destruction is even further minimized.<sup>29</sup> Also, we have placed these patients on antiplatelet therapy with aspirin for 6 months until endothelialization has occurred, extrapolating from the existing data with the use of these valves in adults with acquired valve disease. Although, the use of percutaneously implanted bovine jugular valves is still in its infancy and long term studies are warranted to determine its efficacy, safety and durability, the stented valves we have used provide the necessary setting for a possible future intervention of this kind.<sup>15,30</sup>

## Conclusion

Although the beating heart approach is technically more demanding, it has the significant advantage of avoiding myocardial ischemia/reperfusion syndrome which occur during cardiac arrest. As a result we did not observe any patients with low cardiac output syndrome postoperatively. A word of caution though for the beating heart technique; preoperative work up should exclude any intracardiac communication to avoid the complication of air embolism, which can be devastating. The incidence of serious postoperative complications in our series was low and none of these patients had clinical evidence of infective endocarditis during the study period.

Patients with surgically corrected TOF require clinical and echocardiographic evaluation on a regular basis in order to detect and follow the progression of PR. Optimal timing of PVR remains a subject of debate. It is highly important to identify the time span that the RV can endure PR before irreversible damage develops (not too late)

and avoiding an untimely re-operation (not too early).

In experienced centers, PVR is achieved with low morbidity and mortality (especially with the beating heart technique) and should be accompanied by a surgical strategy to optimize hemodynamic performance and extend durability of the valve. Our findings suggest that currently available bioprosthetic valves in the pulmonary position provide excellent immediate and intermedi-

ate results. Longer follow-up is necessary to determine the long-term performance of these valves.

**Limitations**

As a retrospective study bears its well-known limitations.

**Ethical issues**

Not applicable.

**Competing interests**

The authors declare no conflict of interest regarding this study.

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# Cardiovascular Tumors in Childhood

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**Keywords:** Cardiac tumors, Childhood, Metastatic cardiac tumors, Classification, Epidemiology, Diagnosis, Treatment, Tubular Sclerosis, Gorlin syndrome, Carney complex, Multiple Hemangiomas

**Abbreviations:** Cardiovascular tumors(CVT), Echocardiography (Echo- 2/3D), cardiac Computing Tomography (c-CT),cardiac Magnetic Resonance Imaging (c-MRI), Inflammatory myofibroblast tumor (IMFT), twelve lead electrocardiogram (12L-ECG), Tubular Sclerosis (TS), sudden cardiac death(SCD), Wolff–Parkinson–White syndrome(WPW Syndrome), Left Atrium(LA),Right Atrium(RA), Right Ventricular (RV), Left Ventricular (LV), main pulmonary artery(mPA), Ascending Aorta (AAo), congestive heart failure(CHF), Superior Vena Cava (SVC), Inferior Vena Cava (IVC),Pericardial effusion(PE),First pass myocardial perfusion (FPP), Myocardial delayed enhancement(MDE), multiple hemangiomas, Acute Lymphoblastic Leukemia (ALL), pericardial Effusion(PE)

## ABSTRACT

Cardiac tumors, either primary or metastatic are rare in adults. These became even rarer in childhood. More, they consist of a variety of lesions, some of which, do not fit into the usual concept of tumor or neoplasm. This creates difficulties to classify them<sup>1</sup>. This review, aims to: 1)Present an update on the topic of cardiovascular tumors (CVT) in childhood, emphasizing on epidemiology, clinical assessment, diagnostic approach, treatment strategies and outcomes. 2) Address concerns on the current accepted classifications of CVT based on the accumulated biological analyses and clinical data of the reported literature. They include also, other lesions such as: ectopic hyperplasia / ectopic, tumors/others, and tumors of great vessels, with reference to the series of Atlas of tumor pathology of the Armed Forces Institute of Pathology and the recent World Health Organization classification of cardiac tumors issued in 2004. We suggest a pediatric

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subdivision on CVT of the existing two most used and accepted Histological classifications is needed for simplifying every day clinical practice (Table1).

## INTRODUCTION

Tumors of the cardiovascular system, benign or malignant, are very rare disease, in any age group<sup>1</sup>. Albers first published these rare entities in 1835<sup>2</sup>. It was only in the 20<sup>th</sup> century in which we have information about an accurate diagnosis of an intracardiac tumor, imaged by angiography in 1952, following a successful surgical removal on by pass circulatory arrest, in 1955<sup>3</sup>. Primary CVT are rare in pediatric practice with a prevalence of 0.0017 to 0.33% in autopsy series<sup>1</sup>. In contrast, the incidence of CVT during fetal life has been reported to be approximately 0.14%<sup>2,3</sup>. The existence of many disorders, which do not fit the definition of neither a tumor nor a neoplasm, creates a difficulty in their classification<sup>1</sup>. As tumors involved with an organ, CVT are classified as primary tumors originated from the heart and great vessels, as primary metastatic that originate in distal organs and secondary/metastatic tumors that invade nearby organs such as lungs or other organs. Additional to this classical approach, tumors originating from the heart are classified by the site of tumor location such as tumor of the heart muscle, cardiac septum, pericardium, or great vessels, and classified by cell type constituting the tumor such as hyperplasia, hamartoma, cyst, or benign or malignant, and classified by histological features such as mesenchymal, epithelial, and serous membrane (mesothelium). However, there is no established standard method of classification of tumors of the heart and great vessels up to now. In this review, we present the most adopted classification for tumors of the cardiovascular, in clinical use<sup>1</sup>.

Most primary cardiac tumors in children are benign, whilst approximately 10% are malignant. Secondary malignant tumors are 10–20 times more prevalent than primary malignant tumors. Rhabdomyoma is the most common cardiac tumor during fetal life and childhood. It accounts for more than 60% of all primary cardiac tumors. The

frequency and type of cardiac tumors in adults differ from those in children with 75% being benign and 25% being malignant. Myxomas are the most common primary tumors in adults constituting 40% of benign tumors. Sarcomas make up 75% of malignant cardiac masses<sup>1,2,3</sup>. Echocardiography (Echo- 2/3D), cardiac Computing Tomography (c-CT) and cardiac Magnetic Resonance Imaging (c-MRI) of the heart are the main non-invasive diagnostic tools. Cardiac catheterization is seldom if never necessary<sup>3</sup>. Tumor biopsy with histological assessment remains the gold standard for confirmation of the diagnosis<sup>2</sup>. Surgical resection of primary cardiac tumors should be considered to relieve symptoms and mechanical obstruction to blood flow. The outcome of surgical resection in symptomatic, non-myxomatous benign cardiac tumors is favorable. Patients with primary cardiac malignancies may benefit from palliative surgery but this approach should not be recommended for patients with metastatic cardiac tumors. Surgery, chemotherapy and radiotherapy may prolong survival. The prognosis for malignant primary cardiac tumors is generally extremely poor<sup>2</sup>.

## EPIDEMIOLOGY

Due to their minor impact on the total prevalence of malignant diseases and the difficulty to diagnose up to present, where recent developments of imaging techniques (Echo-3/4D, cardiac CT/MRI) have improved their diagnosis, CVT were rarely included in studies. The few of them that did received data, came from incidental autopsy reports<sup>1,6,7</sup> and case reports. All reported both their rarity and histological variety.

Taking in consideration USA data regarding autopsy series, published in 1993, the frequency of primary CVT was estimated to 0.0017-0.33%. Historically, in the earlier known reports, Pollia and Gogol reported in 1936, the highest incidence of CVT to be 0.33 % (154 cases) in autopsy of

46,072 cases<sup>1,9</sup>. Straus and Merliss a few years later, in 1945, reported in the lowest incidence as 0.0017 % (8 cases) in autopsy of 480,000 cases by summarizing the autopsy statistics of six hospitals<sup>1,10</sup>. In one of the first attempts to meta analyze data existing data from 22 published papers on the subject, Reynen in 1996 reported the incidence as 0.021 % following 731,309 autopsy cases<sup>1,11</sup>. It is interesting to observe the variation in the incidence of CVT reported during 1915–1931 as 0.047 % and rising to 0.17 % in the years 1954–1979 from the report of Mayo Clinic series<sup>1,12,13</sup>. In Japan, Mukai et al. in 1988, using data from the National Cancer Center reported that CVT was found only in 1 case (0.038 %) among 2,649 autopsy cases who died of cancer, during the period of 1976 to 1985. On the other hand, reports for CVT in children are showing a near tenfold increase since Nadas and Ellison reported in 1968, an incidence of CVT of 0.01 % at autopsy findings in childhood<sup>15</sup>. Since the era of the new imaging techniques our understanding on the incidence of CVT has moved from autopsy series and case reports to large series from pediatric reference centers<sup>2,3,16</sup>. From the published up to date data, in infants and children, the most common cardiac tumors are Rhabdomyomas and Fibromas, which are benign primary cardiac tumors, accounting for up to 80% of cases of all CVT. In adult populations, thrombus is the most common cardiac mass and myxoma is the most common primary CVT. Second most common Teratomas, Fibromas and Hemangiomas, are reported<sup>17</sup>. Myxomas is exceedingly rare in fetuses and neonates<sup>18</sup>. Although, Fibromas and intracardiac Teratomas are exceptionally rare in adults they are more commonly seen in early infancy and during childhood. Rhabdomyomas and pericardial Teratomas make up more than 70% of the primary CVT in fetuses, neonates, and infants<sup>2,3</sup>. Finally, Sarcomas are the most common primary malignant cardiac tumors in both children and adults. Metastatic cardiac tumors which occur via either direct extension or hematogenous spread, occur less often in children than in adults and include Sarcomas, Lymphoma, Testicular Cancer, and Wilms tumor<sup>1,2,3</sup>. Table 1 summarizes the fre-

quency and basic biological behavior of the CVT in childhood.

## HISTOLOGY

The most common used classification for CVT, is the well-known classification of “Tumors of the heart and great vessels” (Armed Forces Institute of Pathology: AFIP) published in 1996.<sup>7</sup> In this, cardiac tumors and pericardial tumors are classified into benign or malignant cardiac tumors. Sarcomas of the aorta (AAo) and pulmonary artery (mPA), sarcomas of the inferior vena cava (IVC), and leiomyomatosis of veins are classified in different categories. Benign cardiac tumors are further classified as tumors of unknown histogenesis, tumors of cardiac muscle, tumor of fibrous tissue, vascular tumors and tumor-like lesions, tumors and proliferations of fat, tumors and tumor-like lesions of mesothelial cells, tumors of neural tissue, tumors of smooth muscle, heterotopias, and tumors of ectopic tissue. And malignant cardiac tumors are classified as sarcomas, malignant germ cell tumors, hematologic tumors, granulocytic sarcoma, mesothelial malignancies, and metastatic tumors to the heart<sup>1,7</sup>.

In the classification of WHO 2004, tumor of the heart is divided into three categories: benign tumors and tumor-like lesions, malignant tumors, and pericardial tumors. In benign tumors, tumor was classified as tumor showing differentiation into muscle cells such as rhabdomyoma, adult cellular rhabdomyoma, hamartoma of mature cardiac myocytes, and histiocytoid cardiomyopathy. Cardiac myxoma and papillary fibroelastoma are classified as pluripotent mesenchymal origin, and cardiac fibroma and inflammatory myofibroblastic tumor were classified as tumor showing differentiation into myofibroblastic cell. Other benign tumors are vascular tissue origin as hemangioma, fat tissue origin as lipoma, and congenital cystic lesions in the atrioventricular node as cystic tumor of atrioventricular node.

Most prominent differences of WHO classification from AFIP classification are classification of malignant tumors. First, epithelioid hemangioendothelioma, formerly classified as benign tumor has been classified as malignant tumor, and sec-

ond, undifferentiated sarcoma, which has been classified as tumor of unknown origin, is united to form one disease as malignant pleomorphic fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma subtype. Other features of WHO classification are malignant mesenchymomas, osteosarcoma, chondrosarcoma, and many other sarcomas were not included as an independent sarcoma, but included in MFH/undifferentiated pleomorphic sarcoma, and tumor that had been referred to as myxosarcomas specific for heart was classified as a subtype of myxoid fibrosarcoma<sup>1</sup>.

Both these two classifications, although include the histological types of the CVT seen in childhood do not focus on the specific CVT of fetal, child and adolescence era of human development. Further studies have showed that approximately 90% of primary cardiac tumors in children are benign, mostly consisting of non-neoplastic hamartomatous lesions such as Rhabdomyoma and fibroma. Hemangioma, teratoma, myxoma, and histiocytoid cardiomyopathy, also known as Purkinje cell hamartoma are less common benign cardiac tumors<sup>19</sup>. Inflammatory myofibroblast tumor (IMFT) is an uncommon tumor that can occur anywhere in the body, including originating from the endocardium, and should be considered in the differential diagnosis for a CVT<sup>20</sup>. Fetal heart tumors are like those occurring in children, with a higher proportion of germ cell tumors<sup>19,21</sup>. Mesenchymal proliferations of the myocardium, other than fibroma, are extremely rare in the pediatric age range. Most sarcomas are undifferentiated, like their adult counterparts. However, embryonal rhabdomyosarcoma primary in the heart is a tumor of children and young adults; alveolar rhabdomyosarcoma may occur in the heart as a metastatic lesion. Recently, IMFTs have been described as originating from the endocardium. The precise nature (reactive/neoplastic) of cardiac IMFT remains undetermined<sup>19</sup>. The need of a pediatric subdivision on CVT of the existing two most used and accepted A summary of the different types of CVT in childhood is suggested in Table. 1. It focuses on the most common CVT of childhood, summarizing the type, frequency, location and histology.

## CLINICAL ASPECTS-DIAGNOSIS-TREATMENT

### RHABDOMYOMAS

The most common primary CVT in infants and children is rhabdomyoma. It accounts for more than 60% of all primary cardiac tumors<sup>1,2,19</sup>. They are usually located within the ventricles but not infrequently they may also originate in the atriums. When located in the atrioventricular junction may have a rather peculiar effect where tumor may act like an accessory pathway with resultant pre-excitation on twelve lead electrocardiogram (ECG). Fetal diagnosis of cardiac rhabdomyoma is most commonly made on a 20-week anomaly scan after incidental detection of multiple intracardiac masses or be noted coincidentally during evaluation for fetal cardiac arrhythmias<sup>2,19</sup>. The manifestations of a cardiac tumor in fetal life include arrhythmia, congestive heart failure, hydrops, and not infrequently stillbirth<sup>2</sup>.

Histologically, they are well-demarcated nodules of enlarged cardiac myocytes with cleared cytoplasm. In some cells, strands of eosinophilic cytoplasm stretch from a central nucleus to the cell membrane, giving rise to cells that resemble a spider (“spider cells”). Most cells show vacuolization with sparse myofilaments (Photo 1).

Both sporadic and single lesion cases as well as linked to Tubular Sclerosis (TS) observed. In cases of a solitary tumor a careful examination of cardiac chambers should be made in order not to miss smaller lesions elsewhere. Multiple cardiac rhabdomyomas in fetal life can contribute in the early diagnosis of TS well before the other features of the disease, such as skin signs or seizures, emerge in infancy<sup>23</sup>. The incidence of TS in patients with rhabdomyoma has been reported to be between 60–80%<sup>2,19</sup>. More, than 50% of patients with TS have rhabdomyomas<sup>3</sup>.

Postnatally, in addition to the TS specific symptoms and signs, rhabdomyomas may present with commonly related to obstruction of inflow or outflow tracts, followed by cyanosis, murmur, respiratory distress, myocardial dysfunction, valvular insufficiency, arrhythmias, and sudden cardiac death(SCD)<sup>2</sup>. The incidental finding in fetal

life or the clinical presentation and the physical examination will follow imaging. The echo-2/3D and c-MRI will establish the diagnosis. Rhabdomyomas appear as hyperechoic solid masses at echocardiography (Fig 1). They are isointense to slightly hyperintense relative to myocardium on T1-weighted images and hyper-intense on T2-weighted images (Images 1). They may enhance less than myocardium after administration of intravenous contrast material. 12L-ECG can detect arrhythmias that are frequent. They have been reported to occur in 16 - 47% of cases. Atrial or ventricular arrhythmias frequently occur. Since the tumor cells are structurally like Purkinje cells they can function like accessory pathways<sup>24</sup>. This explains the higher incidence of Wolff-Parkinson-White syndrome (WPW Syndrome) has been noted in patients with TS (1.5%) compared to the general population (0.15%)<sup>2</sup>.

The unique nature of this CVT, postnatally, loses the ability to divide and regression of the tumor in infancy is an expected outcome, regardless of size of the tumor<sup>24</sup>. Following birth, regression is a rule rather than an exception. Complete resolution of more than 80% of the tumors may occur during early childhood. As a high rate of spontaneous regression, after birth, seems to be the rule, we can be managed conservatively these patients with echo-2/3D and 12L-ECG monitoring.

Surgical intervention should be preserved only for sick patients with symptoms of severe obstruction with hemodynamic compromise or hemodynamically significant and intractable<sup>2,3,29</sup>. arrhythmias that are unresponsive to antiarrhythmic drugs. Recent reports have shown that everolimus, a mammalian target of rapamycin (mTOR) inhibitor, can act as a potential new therapeutic option for treating clinically significant cardiac rhabdomyoma<sup>27</sup>.

## FIBROMAS

Fibroma, derived from connective tissue fibroblasts, is the second most common benign primary CVT<sup>1,2,3,19</sup>. Most fibromas are found in infants younger than 1 year. Their size may vary from 1 to 10 cm. About 3%–5% of patients with

Gorlin syndrome have cardiac fibroma<sup>3</sup>. Gorlin syndrome is an autosomal dominant disease deriving from germline mutations in the PTC gene, which maps to chromosome 9q22.3 and is characterized by basal cell carcinomas, odontogenic keratocysts, skeletal abnormalities, palmar or plantar pits, and ectopic calcifications of the central nervous system<sup>28</sup>. Approximately 1/3 of patients with cardiac fibroma are asymptomatic, and tumors are detected incidentally. However, symptomatic patients may present with arrhythmias, heart failure, or SCD. Fibromas often are single lesions that do not regress, unlike rhabdomyomas. Fibromas are commonly located in the ventricular septum or RV, LV free wall.

Histologically, they resemble fibromatoses, with infiltrating margins. There are usually abundant elastic fibers

(Photo 2). Cellularity may be quite marked in young infants but usually decreases with age. On echo-2/3D, they appear as a large, noncontractile, heterogeneous solid mass (Image 3). Calcification is a relatively common feature histologically in about 25% of cardiac fibromas<sup>19</sup> and can be seen on c-CT. Central calcification results from poor blood supply to the mass and is a pathognomonic finding that helps distinguish fibromas from Rhabdomyomas. Fibromas are generally well-defined masses that are hypo- to isointense relative to myocardium on T1-weighted images and hypo-intense on T2-weighted images of c-MRI scans (Figs 3,4). At imaging, these tumors may demonstrate slow progressive diffuse or heterogeneous enhancement after administration of intravenous contrast material (Gadolinium), with a hypo-intense core due to decreased blood supply that is discernible from the surrounding myocardium<sup>29</sup>. Fibromas generally are surgically resected<sup>2,3</sup>. Cardiac transplantation is reserved for patients with large tumors that cause progressive heart failure<sup>2,3</sup>. Pacemaker placement may be required for life threatening arrhythmias.

## TERATOMAS

Teratomas are the second most common tumor in the fetus and neonate after rhabdomyomas, affecting the heart and pericardium. Most com-

monly, these tumors are detected in the pericardial cavity attached to the pulmonary artery and aorta<sup>2,3,29</sup> (Image3). The tumor size within the heart varies from 2 - 9 cm in diameter, and intrapericardial tumors as large as 15 cm have been reported<sup>30</sup>. The intracardiac tumors are rare from the extracardiac ones and arise from the atrial or ventricular wall as nodular masses protruding into the cardiac chambers. Cardiac and pericardial teratomas are easily detected in the fetus and neonate by echo-2/3D as heterogeneous and encapsulated cystic masses. Characteristic imaging features include an intrapericardial multilocular mass with cystic and solid components that is adjacent to the AAO and mPA. The mass may cause compression of the superior vena cava (SVC) and right atrium (Image 4). Teratomas may appear in c-MRI scans as iso- or hypo-intense on T1-weighted images and hyperintense on T2-weighted images. Teratomas are hypo-intense at early myocardial perfusion imaging, a finding that differentiates them from hemangiomas. The main clinical findings in the fetus or neonate relate to the mass effect of the tumor and to the accumulation of fluid in the pericardial space (Image4.) Fetal hydrops and stillbirth may occur. Respiratory distress, cyanosis and congestive heart failure(CHF), are predominant signs in the neonate. Pericardial effusion (PE) may lead to cardiac compression and tamponade. The pericardial effusion is usually serous and contains small numbers of mesothelial cells. Macroscopically teratomas have a typical cystic and multilobulated appearance (Photo 3). Most intrapericardial germ cell tumors occur within the pericardium and represent pericardial teratoma<sup>30</sup>. The intracardiac teratomas seem to have a different histology, containing multiple immature elements including: epithelium, neuroglial tissue, thyroid, pancreas, smooth and skeletal muscle, cartilage and bone tissues.

Although teratomas have thought to be benign, tumor recurrence after resection or rare malignant differentiation has been reported. Surgical excision is the only effective treatment for cardiac teratoma. Most intrapericardial teratomas can be easily dissected off from the great vessels; on the contrary, surgical removal of intracardiac ones is

technically more difficult<sup>32,33</sup>. Since the blood supply is usually from the root of the AAO, the surgeon must perform a careful dissection and ligation of these vessels to prevent massive hemorrhage. Intracardiac teratomas, because of their location in the interventricular septum, are more difficult to remove than pericardial teratomas. Malignant germ cell tumors require chemotherapy as for gonadal tumors<sup>29</sup>.

### MYXOMAS

Myxoma is the most common primary cardiac tumor in adults (65%) with predilection to females.

The left atrium is the most common location (90%) but they can be seen on the right atrium as well<sup>1,2,3,19</sup>. In 90% of cases the myxomas is solitary. Myxomas usually do not cause murmurs, but present with breathlessness, syncope, embolus, CHF, arrhythmias and constitutional symptoms. As the presenting symptoms may not suggest a cardiac cause, myxomas may present late in the disease and at this stage cardiac signs may then also ensue. Sometimes, left sided myxomas may cause diastolic murmurs or added sounds (“diastolic plop”) due to inflow obstruction. Right-sided myxomas are rare and they may lead to tricuspid or pulmonary artery obstruction or pulmonary embolism. Familial occurrence of myxomas has been reported, usually seen in younger patients<sup>1,2</sup>. These myxomas are associated with multiple endocrine syndromes including LAMB (lentiginos, atrial myxoma, mucocutaneous myxoma, and blue naevi) and NAME (naevi, atrial myxoma, myxoid neuro-fibromata, and ephelides). Familial tumors are predominantly multiple but the sporadic cases are mostly solitary. Screening of first-degree relatives is suggested. Approximately 7% of cardiac myxomas are found in association with Carney complex, an autosomal dominant disease characterized by spotty skin pigmentation, myxomas, testicular Sertoli cell tumors, and psammomatous melanotic schwannomas.

Macroscopically, myxomas are pedunculated with a short, broad-based attachment to the atrial wall. They are gelatinous consistency. Micro-

scopically, they are consisted by complex structures resembling cords, nests, rings or poorly formed glands, often surrounding blood vessels. They are composed of stellate or globular myxoma cells with abundant eosinophilic cytoplasm, indistinct cell borders, oval nucleus with open chromatin and indistinct nuclei. Abundant mucopolysaccharide (myxoid) ground substance contains chondroitin sulfate and hyaluronic acid. Frequently they include inflammation reactions and intratumor hemorrhage. More cellular and mitotic activity takes place near their surface. Finally, variable amounts of fibrosis (41%), calcification (20%), Gamna-Gandy bodies (17%, identical to those in spleen of sickle cell anemia patients), ossification (8%), extramedullary hematopoiesis (7%, more common in children), mucin-forming glands (3%), atypia (3%), thymic rests (1%), characterize the histology of the myxomas<sup>37</sup>

The echocardiographic appearance of a myxoma is highly suggestive of the diagnosis: it has a pedicle, with irregular, non-homogenous small lucencies or calcifications on it and the location is characteristically to the atrial septum, around foramen ovale<sup>2</sup>. In contrast, an intracardiac thrombus is usually homogenous in appearance (Image 5). On c-MRI imaging, myxomas are pedunculated mobile masses with irregular borders and are hypo-intense on T1-weighted images and hyperintense on T2-weighted images because of their high-water content. They may contain foci of fibrosis or hemorrhage. Myxomas typically demonstrate heterogeneous enhancement after administration of intravenous contrast material, although homogeneous enhancement has also been reported. On cine c-MRI scans, prolapse through the mitral valve may also be seen<sup>3,29</sup> (Image 6).

The treatment of choice is complete surgical excision of the myxoma with removal of substantial portion of healthy adjacent endocardial tissue. If the surrounding tissue along with the myxoma is not resected completely, the tumor is likely to recur. Prognosis following surgery is quite good, albeit with a recurrence rate of up to a 5% if there has been inadequate resection,

intraoperative implantation, tumor embolization, or unrecognized multiple lesions<sup>2</sup>. Survival after surgery has been reported to be excellent with no late deaths attributable to surgery or to myxoma recurrence during 16 years of follow-up<sup>35</sup>.

### HEMANGIOMAS

CVT/hemangiomas are being an exceedingly rare tumor that can be located anywhere within the cardiac layers with slight predilection to the ventricular septum and right atrium<sup>21</sup>. Macroscopically, hemangiomas are subendocardial nodules measuring 2–4 cm in diameter.

Two basic types regarding their histological features are described: those that are endocardial based and have histologic features of capillary or cavernous hemangiomas and those that are intramyocardial and have histologic features like intramuscular hemangiomas<sup>36</sup>. Fewer than 25% of cardiac hemangiomas occur in the pediatric age range. In neonates, there appears to be a predilection for the right atrium. Minorities of children with cardiac hemangioma have extracardiac hemangiomas and rarely diffuse neonatal hemangiomatosis, involving at least three-organ systems<sup>21</sup>. During investigation with c-MRI the points of interest are, 1) clearly positive (iso- or hyperintense) FPP sequence; 2) variable, often weak enhancement (iso- or mildly hyperintense) on MDE imaging; and 3) variable location. Note that imaging sequences currently available by c-MRI might not allow distinction among benign vascular tumors (e.g., hemangioma), malignant vascular tumors (e.g., angiosarcoma), vascular malformations, and tumors with ample vascular supply (e.g., paraganglioma) (Image 7)<sup>29</sup>.

Although, undergo spontaneous regression with a good prognosis. However, their clinical course may be unfavorable in infant's due to high-output cardiac failure, hemorrhage from ruptured vessels, and thrombocytopenia. Ventricular tachycardia and cardiac tamponade are not uncommon<sup>2,3</sup>. Complete surgical excision may be difficult because of the vascular nature of the tumor<sup>38</sup>. Although over the last 12 years many studies have proved the beneficial role of  $\beta$ -blockers (and most propranolol)<sup>39</sup> in treatment of hemangiomas, we

still have no report on the use of these safe drugs in the treatment of hemangiomas as CVT.

### **HISTIOCYTOID NODULE – ONCOCYTIC CARDIOMYOPATHY – PURKINJE CELL TUMOR**

Histiocytoid cardiomyopathy is a rare, arrhythmogenic disorder caused by multifocal hamartomatous proliferation of cardiac cells with oncocyctic features. Synonyms include: infantile histiocytic cardiomyopathy, oncocyctic cardiomyopathy, histiocytoid cardiomyopathy, Purkinje cell tumor, focal lipid cardiomyopathy, idiopathic infantile cardiomyopathy, unclassified cardiac hamartomas<sup>1,2,19,21,40</sup>. Female: Male ratio is 3:1. Approximately 5% of reported cases have occurred in families. The most common clinical presentation is refractory arrhythmias such as paroxysmal atrial tachycardia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, premature atrial contractions, premature ventricular contractions, WPW Syndrome, and right or left bundle branch block<sup>41</sup>. Oncocyctic cardiomyopathy is an important cause of sudden unexpected death in infancy<sup>41</sup>. In up to one-third of patients the tumors may be associated with cardiac or extracardiac anomalies such as atrial and ventricular septal defects; hypoplastic left heart syndrome, cleft palate, and anomalies of the eyes, skin and central nervous system<sup>42</sup>. The most common locations are conduction system and the LV. Macroscopically; they look like typically subendocardial yellow-tan nodules or plaques. Their size varies from 1 to 2 mm in diameter. They can also be seen in the inner myocardium and sub-epicardial areas. The lesions may be grossly difficult to identify, but there is generally a subtle color difference separating the lesion from a normal myocardium (Photo 4.) The histologic findings are pathognomonic, with nests of foamy-appearing myocytes resembling macrophages<sup>19,21</sup>. The cytoplasm of the myocytes is filled with bizarre looking mitochondria. The term oncocyctic cardiomyopathy describes the process of the granules (mitochondria) replacing the working myofibrils (Photo 5). Additional to the above, Infants with oncocyctic cardiomyopathy may show similar oncocyctic cells

in other organs including the trachea, adrenal, thyroid, anterior pituitary, and salivary glands<sup>43</sup>. On echo-2D, we can reveal nodular deposits on the ventricular endocardium or valves<sup>15,16</sup>. If left untreated, oncocyctic cardiomyopathy may have a fatal course in infants. In infants with intractable arrhythmias, electrophysiological mapping is indicated if antiarrhythmics are ineffective in ablating arrhythmias and allowing regression of the lesions. Treatment includes surgical excision or direct-vision cryoablation of the multiple small nodular tumors. Surgical intervention, electrophysiological mapping, and ablation of the arrhythmogenic foci result in a survival rate of approximately 80%. Rare patients have been heart transplanted<sup>21</sup>.

### **INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMFT)**

A rare neoplasm of mesenchymal cells composed of differentiated myofibroblasts and numerous inflammatory cells. In children and adolescents, this tumor mainly occurs in the lungs but can be seen in the head and neck, genitourinary and gastrointestinal tracts, retroperitoneum, and soft tissues of the trunk and extremities<sup>3,45</sup>(Photo 6.). There are only a few reports of cardiac IMFT<sup>1,3,19,21,46</sup>. Patients with cardiac IMFT may present with shortness of breath, syncope, chest pain, transient ischemic attacks, embolic events, or fever with myalgia<sup>45,46</sup>. Most cardiac IMFTs are benign, with no reported cases of metastasis. However, a few cases of local invasion and recurrence after resection have been reported<sup>45,46,47</sup>. Several pediatric heart tumors, reported in the medical literature as sarcomas, are likely IMFTs, given good prognosis, location on valves, and available histologic descriptions<sup>48</sup>. This is one more example that underlines the need of an up to date clinic-histological classification<sup>1</sup>.

Surgical resection can be performed in symptomatic patients. CVT/IMFT generally arises from the endocardium and may involve the valve leaflets, with a typically broad-based attachment and lobulated contour. The RA, RV are the most common sites of involvement<sup>3,45</sup>. On echo-2D, a CVT/IMFT may appear as a vascular mass arising from

the endothelium (Image 8). At c-CT, it may manifest as a lobulated broad-based mass with patchy areas of contrast enhancement that persist at delayed phase imaging<sup>49</sup> (Image 9). On c-MR imaging appearance varies depending on the cellular and myxoid composition and is not well described in cardiac cases. However, IMFTs are generally isointense relative to myocardium on T1-weighted images and hypo-intense on T2-weighted images (depending on their fibrous component) and may demonstrate intense delayed enhancement<sup>50</sup> (Image 10).

### LYMPHAGIOMAS

Cardiac lymphangioma is a very rare CVT, first reported in 1911 by Armstrong and Monckeberg<sup>51</sup>. Only nine cases of cardiac lymphangioma have been reported in the medical literature. A review of reported cases shows that the tumor is mostly located extracardiac in 95.5% of cases. CVT/Lymphangiomas are commonly revealed during CHF, syncopal or embolic pathology, arrhythmias, palpitations, or cardiac tamponade<sup>52</sup>. It is atypical multiloculate lesion with cystic cavities divided by septa of variable thickness. Macroscopically, CVT/Lymphangiomas may be either soft and spongy or firm and fibrous. The size of these tumors varies, and the largest one reported was 9 cm in diameter. The tumors most commonly occur in the pericardial space, but other unusual primary sites include the myocardium, the posterior wall of the LA, and the AV node regions. Histopathology shows sinterconnecting channels lined by flat endothelial cells beneath which are bundles of smooth muscle and lymphoid nodules. The absence of red blood cells in the cyst contents eliminates hemangioma or lymphangiohemangioma<sup>53</sup> (Photo 6). The diagnosis must be thought when masses are detected by echo-2/3D in clinical settings of CHF, arrhythmias or syncopal events. Further imaging with c-CT and c-MRI is necessary for the differential diagnosis (Image 11.). Surgical removal of the CVT is the treatment of choice<sup>51</sup>.

### INTRAPERICARDIAL PHAEOCHROMOCYTOMA

These CVT's are soft, vascular and originate from the paraganglia of the autonomic nervous system. They may be found within the atrium, in the atrial septum, in coronary, pulmonary, or aortic locations. If the tumor can be resected, the prognosis is favorable<sup>63</sup>.

### MALIGNANT CARDIAC TUMORS

#### Primary malignant cardiac tumors

Up to 25% of all cardiac tumors may exhibit some features of malignancy. 95% of these primary malignancies are sarcomas<sup>29,54</sup>. The remaining 5% are Lymphomas. Due to their rarity, up to date, a few case reports are only published<sup>19</sup>. When present in fetal life and childhood, although can be located as a single mass anywhere in the heart, most commonly they are found in the LA. In childhood, most patients suffering from primary malignant CVT's are male and the clinical presentation can vary. It includes recurrent pericardial effusion, respiratory distress, pulmonary emboli, shortness of breath, arrhythmia, chest pain, and CHF<sup>19</sup>. Imaging with echo-2/3D and c-CT/c-MRI, is the initial investigation process and biopsy establishes the diagnosis.

These mesenchymal tumors show various morphologies. Most commonly are sarcomas, followed by angiosarcomas, rhabdomyosarcomas, and other rare CVT's such as osteosarcomas. The clinical outcome is usually aggressive with extensive local infiltration, intracavity obstruction and poor prognosis with reported survival, up to 13 months<sup>19</sup>.

#### PRIMARY CARDIAC SARCOMAS

Sarcomas are mesenchymal neoplasms of various histologic morphologies and are more common in adults<sup>2</sup>. Their most common location in adulthood is RA, but in childhood when seen, the originate from the LA<sup>2,19</sup>. Angiosarcomas are founded more common in male sex. These CVT in 80% of the cases originate in the RA or pericardium<sup>55</sup>. Echo-2D shows a broad based atrial

mass close to the IVC with frequent epicardial, endocardial or intracavity extensions (Image12.). Further imaging with c-CT(Image13.) and c-MRI verifies the diagnosis. Specifically, in c-MRI imaging, sarcomas are infiltrative masses that cross tissue planes and extend through vessels, with variable appearances at T1-weighted, T2-weighted, and contrast-enhanced imaging (Image14.)<sup>3,29</sup>. Pulmonary, pleural and mediastinal metastases are frequent.

Clinical findings include right-sided heart failure, pericardial disease, pleuritic chest pain, dyspnea, and pericardial effusion. Some patients (10%) may present with nonspecific symptoms such as fever, weight loss, and malaise. The outlook is poor, for most of the patients, shortly after the onset of symptoms<sup>2,3</sup>.

Rhabdomyosarcomas are the second most common primary malignancy of the heart. Their origin is of striated muscle. These malignancies are most common in adult males<sup>1</sup> and can occur in any heart chamber. The most common presenting symptoms are nonspecific including fever, anorexia, malaise, and weight loss. The symptoms associated with pericardial disease, pleural effusion, and embolic phenomena are also common. As compared to angiosarcoma, diffuse pericardial involvement is not common and the tumor rarely invades beyond the parietal pericardium. The prognosis is poor<sup>54,56</sup>.

Fibrosarcomas are mesenchymal tumors with fibroblastic origin. These tumors can be seen within the left or right heart chambers<sup>54,56</sup>. At post-mortem, they are usually found in multiple intracardiac sites as firm, greyish-white small nodules. The clinical findings include heart murmurs, nonspecific ECG changes, chest pain, fever, and malaise. They may spread to surrounding structures<sup>57</sup>. The outlook is poor with death ensuing within a year of diagnosis<sup>2</sup>.

## LYMPHOMAS

Primary cardiac lymphoma is extremely rare in childhood and is defined as lymphoma involving only the heart or the heart and pericardium<sup>58</sup>. Primary CVT/Lymphomas are typically non-Hodgkin lymphoma<sup>59</sup>. Secondary cardiac involve-

ment by lymphomas, either through direct extension or via hematogenous spread, is more common. However, most cases of secondary cardiac lymphoma are often reported as an autopsy finding<sup>60</sup>. Patients may present with shortness of breath, arrhythmia, or symptoms related to SVC obstruction. Chemotherapy with or without surgical resection is the main treatment. Primary cardiac lymphoma typically involves the right heart and more than one cardiac chamber<sup>59</sup>. Atrial involvement is more common than ventricular in the setting of secondary cardiac lymphomas<sup>61</sup> (Images 15-16). On echo-2D, cardiac lymphomas may present as a single or multiple mass. However, if the involvement is primarily myocardial infiltration, a definitive mass may not be present. Images by c-CT demonstrate low-attenuation masses with heterogeneous enhancement.

At c-MRI imaging, the masses are hypointense relative to myocardium on T1-weighted images and isointense relative to myocardium on T2-weighted images, with heterogeneous enhancement<sup>62</sup>.

## Secondary malignant (metastatic) cardiac tumors

The incidence of cardiac metastases from malignant CVT's is estimated to be approximately 1% and 20 times higher than primary malignant CVT's<sup>64</sup>. In childhood, cardiovascular metastases can occur with lymphomas, sarcomas, testicular carcinomas, and Wilms tumors<sup>65</sup>. A rarer malignant tumor that has also been reported to produce metastasis and can be found commonly with congenital heart diseases is neuroblastoma<sup>65,66</sup>. All these tumors create metastasis, by either direct extension or hematogenous spread. Melanomas show a special affinity to spread to heart with equal distribution to all four chambers of the heart<sup>64</sup>. In adults, most commonly we see metastatic disease from primary lung tumors in men and breast tumors in women<sup>1,2</sup>. They are mostly located in the epicardial surface of the heart<sup>1,2</sup>. Macroscopically metastatic tumors are multiple

small, discrete, and firm nodules. Patients may be asymptomatic or may present with chest pain, CHF, arrhythmias and pericardial effusions. In cases of Leukemias and lymphomas, intramyocardial infiltration, hemorrhagic pericardial effusion are mostly seen, although occasionally they can remain asymptomatic<sup>2</sup>. In imaging, they present as a single atrial mass and may enhance with intravenous contrast material<sup>29,70</sup>.

The tumor may extend directly from the IVC, or from adjacent extracardiac structures, such as the lung.

Treatment is targeted at the primary malignancy. Surgical resection is typically reserved for patients with tumors that are resistant to chemotherapy or radiation therapy and who exhibit cardiovascular compromise. The prognosis is usually poor with the diagnosis of cardiac metastatic disease<sup>65</sup>.

## MIMICING CARDIAC TUMORS

### THROMBUS

Intracardiac thrombus is the most common mimic of a CVT. Cardiac thrombus is rare in children in comparing with adults, due to the low prevalence of myocardial infarction in children, although thrombus may occur in the setting of myocardial infarction in patients with homozygous familial hyperlipidemia or Kawasaki disease<sup>68</sup>. Cardiac thrombi in children are more commonly associated with indwelling central venous catheters. They have been reported to be a frequent clinical problem in children suffering from Wilms's tumors<sup>68</sup>. Finally, can also be seen in patients with congenital heart disease or dilated cardiomyopathy. Treatments include thrombolytic therapy, anticoagulation therapy, and thrombectomy<sup>69</sup>. In imaging, on echo-2D an intracardiac thrombus can appear as a laminar and adherent mural mass or a pedunculated and mobile intraluminal mass<sup>70</sup>(Image17.). Using c-CT, it may appear as a filling defect and may contain calcification if chronic. The signal intensity of a thrombus varies at c-MRI imaging, depending on the age of the thrombus<sup>70</sup>. Acute thrombus can be T1 and T2 hyperintense, as opposed to subacute thrombus, which typically is hyperintense on T1-weighted

images and hypointense on T2-weighted images. Chronic organized thrombus is generally both T1 and T2 hypointense because of low water content and possible calcification. Organized thrombus does not enhance after administration of intravenous contrast material, compared with neoplasms, which typically enhance<sup>29</sup>. However, some surface enhancement has been reported in chronic thrombi<sup>29</sup>.

## DISCUSSION

CVT's are a unique disease in childhood. In contrast to the adult population: 1) most of the tumors present very early, in fetal life<sup>2,3,19,21</sup> 2) the histology of some of them has not still been clarified and an acceptable easy to use in everyday clinical practice classification still is pending<sup>1,2,19</sup> 3) most primary cardiac tumors in children are benign, whilst approximately 10% are malignant. Secondary malignant tumors are 10–20 times more prevalent than primary malignant tumors<sup>19,21</sup> 4) additional to that a significant amount of them can show automatic regression is a rule rather than an exception<sup>1,19,21</sup> 5) primary CVT/Lymphomas are typically non-Hodgkin lymphomas<sup>59</sup>. Secondary cardiac involvement by lymphomas, either through direct extension or via hematogenous spread, is more common. In cases of Leukemias and lymphomas, intramyocardial infiltration, hemorrhagic pericardial effusion are mostly seen, although occasionally they can remain asymptomatic<sup>2</sup>. However, most cases of secondary cardiac lymphoma are often reported as an autopsy finding<sup>60</sup>. Other unique features of CVT's in childhood include: a. A variety in their clinical presentation that can range from asymptomatic, to general symptoms of malaise, unexplained low-grade fever and weight loss to a variety of cardiovascular symptoms and signs seen both in structural-congenital heart defects as well as acquired as cardiomyopathies<sup>2,3</sup>; b. Their existence as a part of rare syndromes and conditions such as: Gorlin syndrome, Carney complex, multiple hemangiomas, or the most common TS<sup>23,26,28</sup>; c. They can present as syncope, near or even SCD and for this they must be a part of the differential diagnosis and imaging (initially echo-2D) as well as a 12LECG must be of

ferred in the initial investigation of any episode of loss of conscience<sup>2,15,16</sup>; d. Often, primary or secondary thrombus in the cardiovascular system, can mimic CVT's<sup>68,69</sup>. Imaging can differentiate this condition<sup>29,69</sup>.

Regarding the diagnostical approach. echo-2D must always follow a thorough medical history and physical examination<sup>2,3,29,70</sup>. The use of c-CT or c-MRI is important to determine the possible histology of the CVT's. In contrary cardiac catheterization is limited if ever used. As the incidence of these defects is so low, diagnostic approach by imaging must be done in centers of excellence<sup>3,24,29</sup>. Open surgical or endomyocardial biopsy is only utilized to reveal the histology of the lesion before surgical resection. A thorough metastatic check and classification of the stage of the disease, should be carried out with CT or MRI imaging before removal of malignant cardiac tumors. A bone marrow biopsy or bone scan may be necessary<sup>2,19,21</sup>.

Treatment is targeted at the primary malignancy. Surgical resection is typically reserved for patients with tumors that are resistant to chemotherapy or radiation therapy and who exhibit cardiovascular compromise<sup>33,71</sup>.

The outcome of surgical resection in symptomatic, non-myxomatous benign cardiac tumors is favorable. Myxomas should be excised completely along with a small rim of surrounding healthy myocardium. In view of their potential for embolization or valvular obstruction, early resection of myxomas is recommended<sup>33,71</sup>.

Primary cardiac malignancies may benefit from palliative surgery but this approach cannot be recommended for patients with metastatic cardiac tumors. Surgery, chemotherapy and radiotherapy may prolong survival. The prognosis for malignant primary cardiac tumors is generally extremely poor<sup>65</sup> If the resection of the tumor is not achievable in severely symptomatic patients, orthotopic cardiac transplantation may be considered. This treatment modality is only an option for patients with unresectable cardiac tumors with no evidence of metastatic involvement of the heart<sup>2,33</sup>.

## CONCLUSIONS

CVT's are rare in childhood. In infants and children, the most common cardiac tumors are rhabdomyomas and fibromas, which are benign but can compromise cardiac function depending on their size and location. Myxomas and thrombus uncommonly occur in children, but they are the most common primary CVT and cardiac mass, respectively, in adults. As in adults, malignant pediatric CVT's include sarcoma and metastatic disease. Newest Imaging techniques as echo-2/3D, c-CT and c-MRI, plays an important role in characterization and diagnosis of these CVT's. They can be used to assess disease extent, cardiac function. Finally, they can guide patient management. A combination of chemotherapy, radiotherapy and surgical excision can be offered. The prognosis of the being tumors that do not impose on cardiac function or can be abolished, is excellent. In malignant CVT's, despite our current efforts, prognosis is still pour.

## CONFLICT OF INTEREST

None of the authors have any conflict of interest, regarding any of the information presented.

## ACKNOWLEDGEMENT

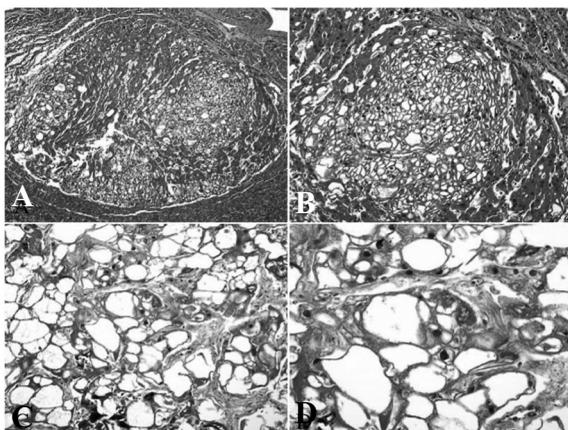
With this review, the authors are contributing to the long-life commitment of Professor Emeritus Konstantinos E. Anagnostopoulos, MD ; founder and first Director of the Department of Cardiac Surgery of the Medical School of the National and Kapodistrian University of Athens, Greece EU

<b>Primary Benign</b>	<b>FREQUENCY (%)</b>	<b>LOCATION</b>	<b>HISTOLOGY</b>
Rhabdomyomas *1	40-60%	Intramyocardial or intracavitary mostly Ventricles and less Atria's	Alternated cardiomyocyte cells: pathognomonic spider cells with centrally placed cytoplasm containing the nucleus and myofibrils radiating to the cell wall. ALSO look like Purkinje cells. Can function like accessory pathways
Teratoma	15-19%	Pericardial cavity attached: mPA, AAo (common) and intracardiac, atrial or ventricular (rare)	Germ-cell tumors intra pericardial and/or multiple immature elements: epithelium, neuroglial tissue, thyroid, pancreas, smooth and skeletal muscle, cartilage and bone
Fibroma	3-5%	Ventricles free walls of LV, RV are Common. Atrial fibromas are rare	Connective tissue fibroblasts / abundant elastic fibers
Haemangioma	5%	Endocardial origin, mostly from RA and Intramyocardial origin	Endocardial: have histologic features of capillary or cavernous hemangiomas Intramyocardial: histologic features like intramuscular hemangiomas
Histiocytoid cardiomyopathy	Rare (<1%)	Conduction system, LV	Cytoplasm of the myocytes are filled with bizarre looking mitochondria
Inflammatory myofibroblastic tumor	Rare (<1%)	RA, LA Endocardium; may involve valves	Mesenchymal cells composed of differentiated myofibroblasts and many inflammatory cells.
Lymphangioma	Very rare	Pericardial space (common), myocardium, the posterior wall of the LA, AV nod (less common)	Sinterconnecting channels lined with flat endothelial cells beneath which are bundles of smooth muscle and lymphoid nodules
Rhabdomyosarcomas - Angiosarcomas	2	Any cardiac chamber-Mostly in RA	Mesenchymal neoplasms of various histologic morphologies

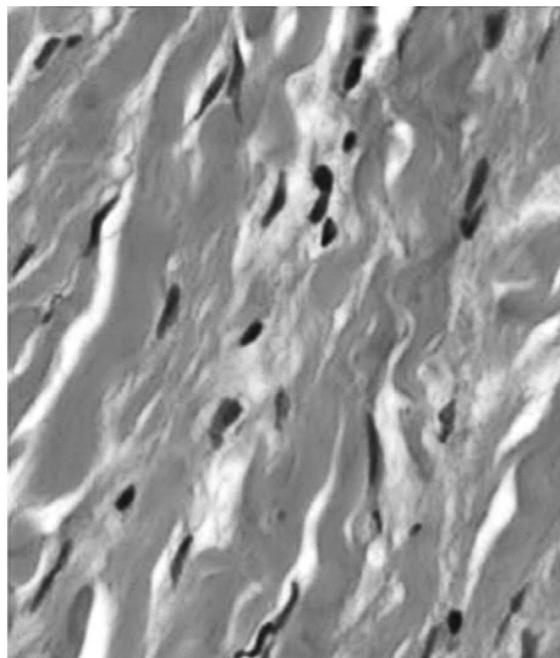
<b>Primary Benign</b>	<b>FREQUENCY (%)</b>	<b>LOCATION</b>	<b>HISTOLOGY</b>
Fibrosarcoma	2	Multiple intra cardiac sites	Mesenchymal tumors with fibroblastic origin
<b>Secondary Metastatic</b>			
Neuroblastoma	Very rare	IVC and any cardiac chambers	Neuroblastic tumors deriving from cells of the neural crest
Leukemias	Very rare	Endomyocardial infiltration, persistent PE	All
Lymphomas	Very rare	Mostly atria's then ventricles	Non-Hodgkin lymphomas <sup>59</sup>
Melanomas	Very rare	Equal distribution to all heart cavities	Aggregation of atypical melanocytes <sup>72</sup>
Sarcomas	Very rare	Endomyocardial infiltration with equal distribution to all heart cavities	Heterogeneous group of malignant mesenchymal cells originating from soft tissue (80%) and bone (20%) <sup>1, 73</sup>
Testicular Cancer	Very rare	Mostly atria's, then ventricles	Pure seminomas account for about 50% of all germinal cell tumors of the testis. The other tumor types are embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), choriocarcinoma, or teratoma <sup>74</sup>
Wilms tumor	Very rare	IVC, RA Any cardiac chamber-Mostly in RA	Mixed tumor containing metanephric blastema, stromal and epithelial derivatives <sup>75</sup>
<b>OTHERS</b>			
Thrombus	Rare	Any cardiac chambers, preferable RA, RV, SVC, IVC	Mixed (Red+White) Thrombus with fibroblasts and collagen tissue <sup>1</sup>

**(Table 1) Revised from:** Uzun Or, Wilson D G, Vujanic G M, Parsons Jon. M, De Giovanni Jos V. Cardiac tumors in children. Orphanet Journal of Rare Diseases 2007, 2:11

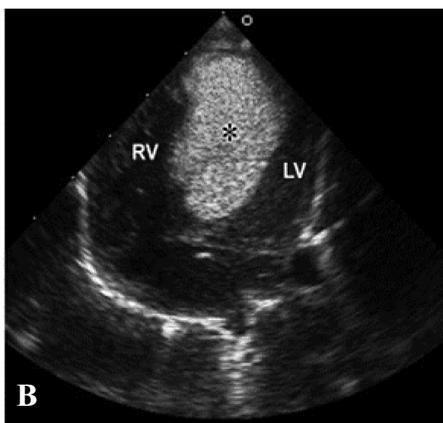
1\*Rhabdomyomas are not considered to be true tumors and many authors would describe them as hamartomas of striated muscular fibres occurring solely in the heart



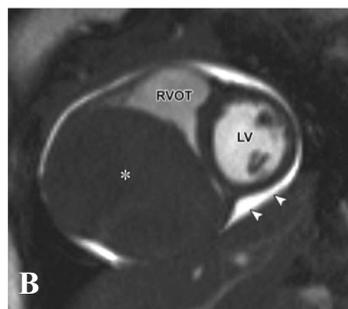
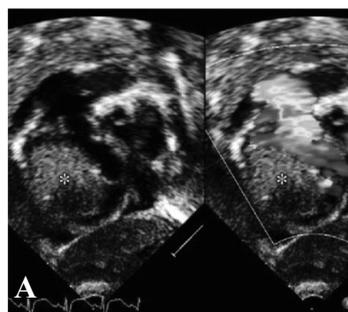
(Photo 1) Rhabdomyoma: intrauterine fetal demise, 20 weeks. The left ventricle was markedly hypertrophied with a slit like luminal cavity. There were multiple satellite nodules, with higher magnifications demonstrating vacuolated myocytes with spider cells. [Adopted from Allen Burke, Renu Virmani; Cardiovascular Pathology 17 (2008) 193–198]



(Photo 2.) Cardiac fibroma. Histologic section demonstrates bland spindled cells in a fibrous background. [Adopted from Allen Burke, Renu Virmani; Cardiovascular Pathology (2008)]



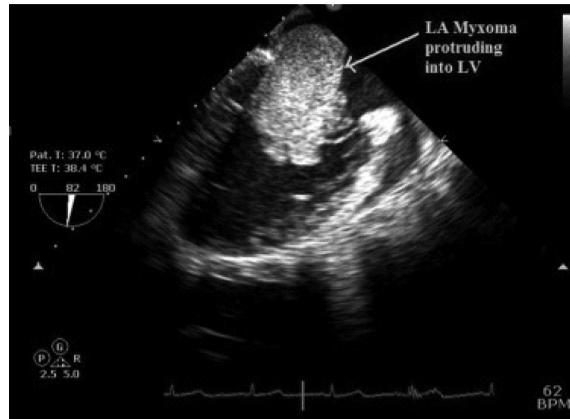
(Image1) Rhabdomyoma. (A) Transverse Echo-2D image obtained in a fetus at 22/40 weeks of gestation shows a hyperechoic mass (\*) in the interventricular septum. (L = lung). (B) Fetal MR images obtained at 34/40 weeks of gestation in the same patient as in (A) show a large mass (\*) arising from the interventricular septum, consistent with a rhabdomyoma. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



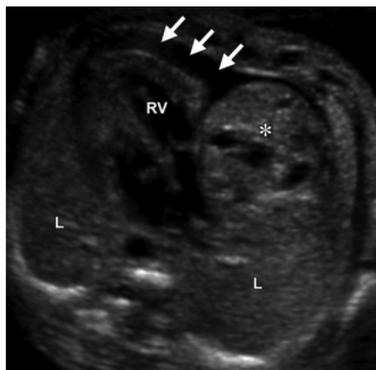
(Image 2) Fibroma in a 4-month-old female infant with a heart murmur. c-MRI(a-c) Trans-axial black blood (A) show a large isointense and slightly hypointense mass (\*) centered in the RV free wall. It exerts mass effect on the right ventricular outflow tract (RVOT),(LV = left ventricle). Echo-2D and color flow map shows this large RV mass (\*) filling the RV and causing flow obstruction through the tricuspid valve. The patient underwent surgical resection, and pathologic analysis confirmed cardiac fibroma. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



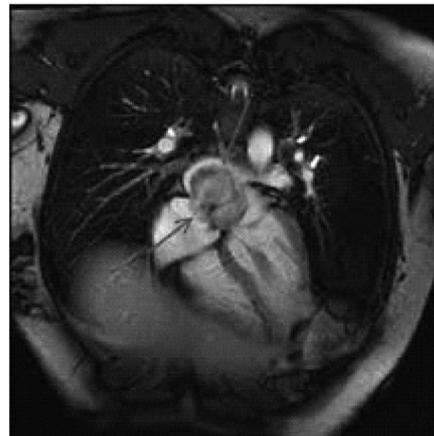
(Image 3) Cystic teratoma (\*) Echo-2D : the tumor is attached to the aortic root [Adopted from Uzun Or, Wilson D G, Vujanic G M , Parsons Jon. M, De Giovanni Jos V.; Orphanet Journal of Rare Diseases 2007, 2:11]



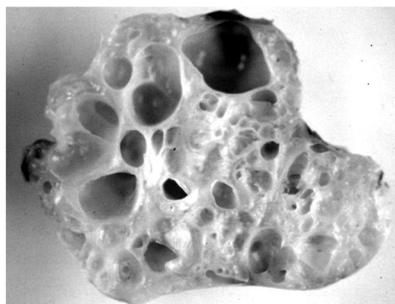
(Image5) TO Echo-2D: modified Long parasternal axis that shows a large myxoma protruding through the Mitral valve.



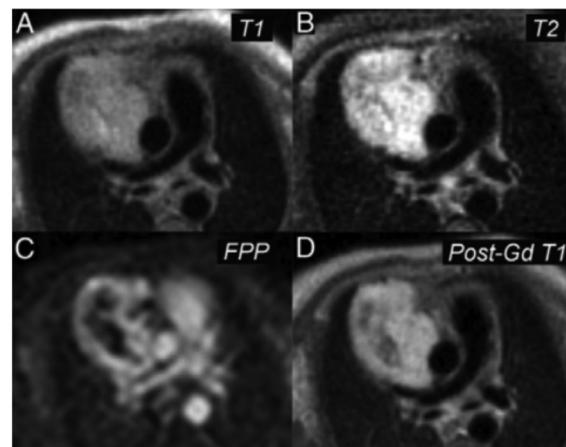
(Image 4) Intrapericardial teratoma. Echo-2D, Long-axis four-chamber image of a fetus at 23/40 weeks of gestation showing a predominantly solid heterogeneous mass (\*) arising at the base of the heart, with a pericardial effusion (arrows). (L = lung) (Courtesy of Beverly G. Coleman, MD, Children's Hospital of Philadelphia, Philadelphia, Pa.), [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



(Image 6.) c-MRI: Myxoma advancing from the Interatrial area and obstructing the LA in flow.



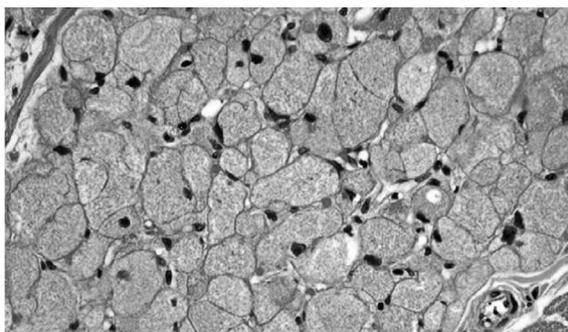
(Photo 3) Typical cystic and multi-lobular appearance of a teratoma excised from heart [Adopted from Uzun Or, Wilson D G, Vujanic G M , Parsons Jon. M, De Giovanni Jos V.; Orphanet Journal of Rare Diseases 2007, 2:11]



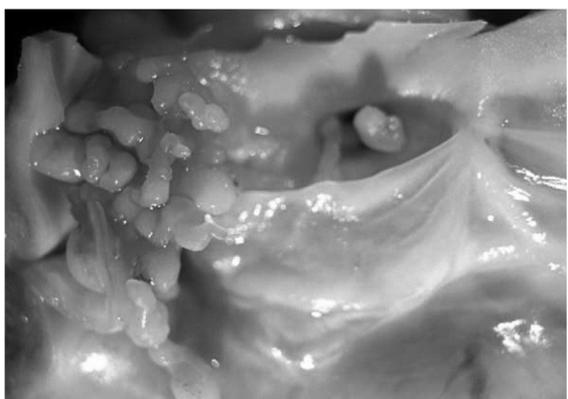
(Image 7) (A) Iso- to slightly hyperintense signal on T1-TSE; (B) strongly hyperintense signal on T2-TSE; (C) inhomogeneous, strongly hyperintense signal on FPP with avid perfusion of the tumor; and (D) hyperintense signal on post-contrast T1-TSE.



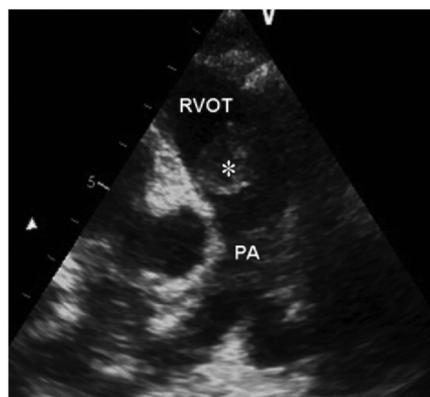
(Photo 4) Histiocytoid cardiomyopathy: Endocardial nodules are visible under the mitral valve anterior leaflet. [Adopted from Allen Burke, Renu Virmani; Cardiovascular Pathology (2008)]



(Photo 5) Histiocytoid cardiomyopathy: Histologic section demonstrating vacuolated oncocytic cells. [Adopted from Allen Burke, Renu Virmani; Cardiovascular Pathology (2008)]



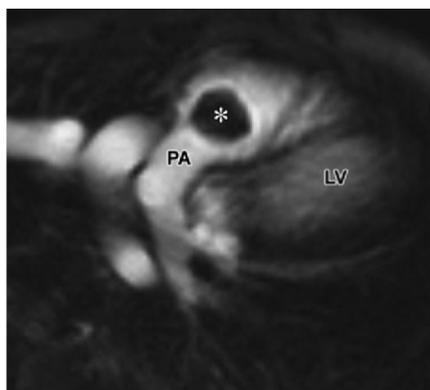
(Photo 6) IMFT. Gross appearance. There are multiple polypoid tumors arising from the aortic valve surface, one of which extended into a coronary ostium causing CSD [Adopted from Allen Burke, Renu Virmani; Cardiovascular Pathology (2008)]



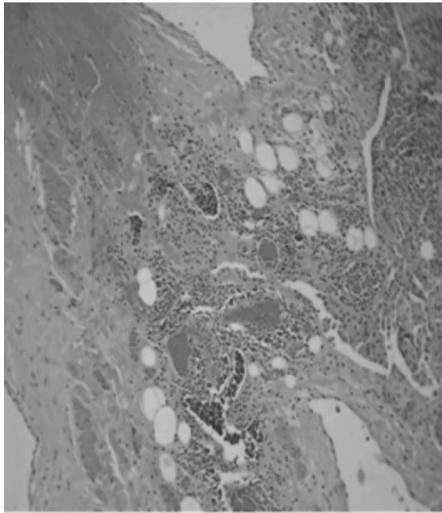
(Image 8) IMFT in a 7-year-old boy with a heart murmur. Echo-2D shows a mass (\*) attached to the pulmonary valve in the right ventricular outflow tract (RVOT) causing flow obstruction. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



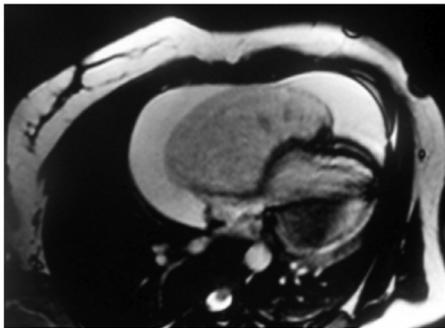
(Image 9) IMFT in a 7-year-old boy with a heart murmur. Trans axial c-CT image shows a predominantly low-attenuation lesion (\*) centered in the right ventricular outflow tract and main pulmonary artery. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



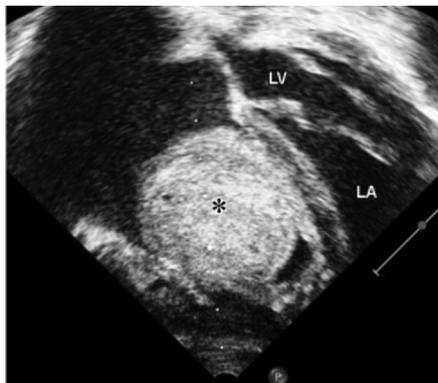
(Image 10) IMFT in a 7-year-old boy with a heart murmur. MR images show the nonenhancing mass(\*), which is likely attached to the undersurface of the pulmonic valve. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4):1031-46]



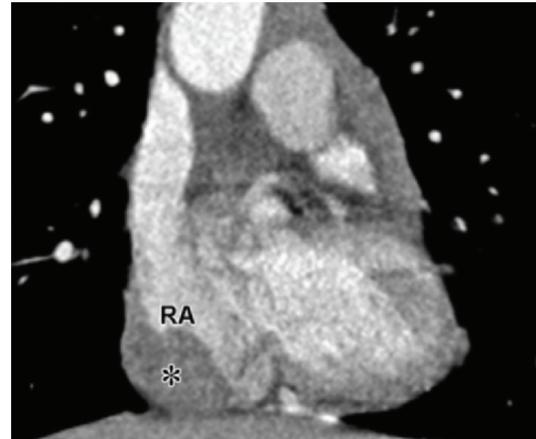
(Photo 6) CVT/Lymphangioma: Myocardial tissues is infiltrated by tiny lymphatic spaces filled with Lymphocytes. Adopted from [Naz I, Lone I. Cystic lymphangioma of heart. The Internet Journal of Pathology. 2008 Volume 10 Number 1]



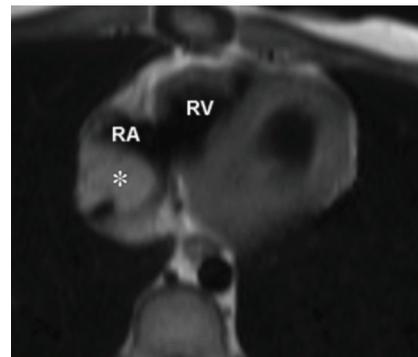
(Image 11) c-CT: CVT/Lymphangioma: a 14x8,25 cm<sup>2</sup> mass is covering most of the area of the RA and RV. Adopted from [Naz I, Lone I. Cystic lymphangioma of heart. The Internet Journal of Pathology. 2008 Volume 10 Number 1]



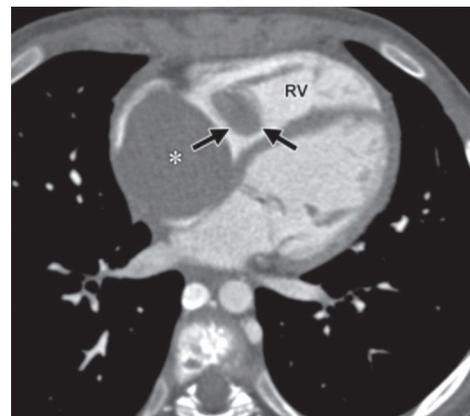
(Image 12) A 14 year old symptomatic (Right Heart Failure), boy: Echo-2D shows a large echogenic mass (\*) infiltrating the RA. Biopsy results confirmed recurrent synovial cell sarcoma at the IVC. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]



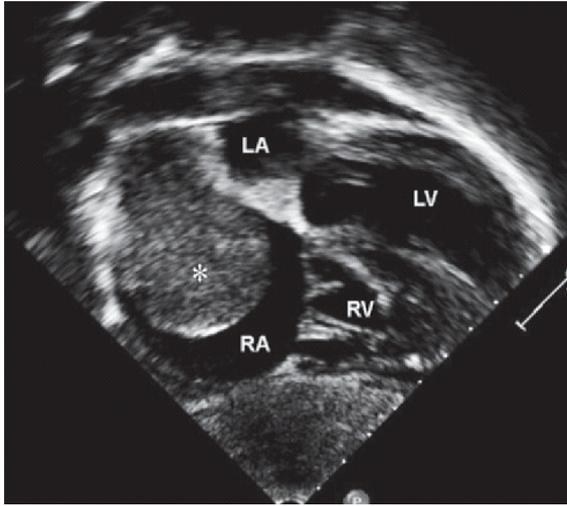
(Image 13) Coronal c-CT of the same patient, shows a mass (\*) in the RA [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]



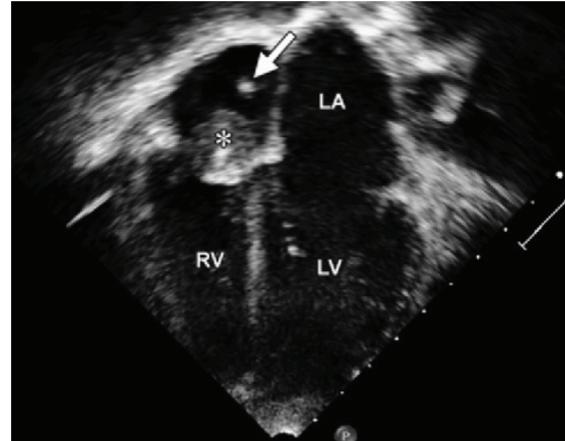
(Image 14) Same patient from above. Trans axial black blood c-MRI images demonstrate an enhancing lobulated soft-tissue mass (\*) at the inferior cavo-atrial junction that extends into the RA, a finding consistent with tumor recurrence. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]



(Image 15) B-cell lymphoma in a 9-year-old girl with worsening SVC Syndrome; c-CT Trans axial shows a large intracardiac mass (\*) predominantly in the RA. A portion of the mass extends into the r (RV) (arrows). [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]



(Image 16) (Same patient as above) B-cell lymphoma in a 9-year-old girl with worsening SVC Syndrome Echo-2D shows the large mass (\*) extending from the SVC and filling almost the RA. [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]



(Image 17) Echo-2D Thrombus in a 7-year-old girl with Sickle Cell disease and a long line. A mass is seen in the RA attached to the tricuspid valve. The tip of a central venous catheter (arrow) is seen within the RA [Adopted from Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S.; Radiographi2014 Jul-Aug. 34 (4)]

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*Natan Shaw R.*

# Constantine (Dino) Anagnostopoulos MD

*One hundred of the finest Persian Weavers would surrender if tasked with creating the rich tapestry that is Dino Anagnostopoulos. As his son in law, admiring this tapestry of a man, I will try to point out the threads that stood out most to me.*

**DINO KNOWS WHAT HE WANTS AND GETS IT**<sup>ψ</sup> My first memory of meeting Dino was a lovely spring weekend lunch in Rittenhouse Square with Anne-Marie when we first started dating. I remember the cringe –worthy 15-minute dialogue between the waiter and Dino on how to serve his beer in a Merlot glass and his Malbec in a white wine glass, naturally. This dialogue between the waiter and Dino persisted, despite the increasingly less subtle protestations of his daughter. This was one of many requests, which the waiter dutifully executed. My first impression was that Dino knows what he wants and will not rest until he gets it. Dino appears undeterred by a sense of embarrassment or insecurity that would fetter most people's attempts at achieving exactly what they want.

My second impression formed after multiple beer/red wine «shandy» mixers<sup>ΦΦ</sup> At the conclusion of the meal, Dino decided he was ready to go and stood up and I watched him walk into the kitchen to pay the first wait staff, bus boy or chef he happened to meet. He paid promptly and with a very generous tip. When I happened on the same wait staff in that restaurant weeks later, there was a palpable sigh of disappointment when he learned my father in law would not be joining me<sup>X</sup> «GREEKLISH» / «CONSTANTANISH» If you are engaged with Dino on anything more than a cursory conversation and you are paying attention, you will observe that Dino speaks neither Greek nor English lets call it Greeklish. I remember my early befuddlement in speaking with him as if the subject of most sentences appeared implied and I was having a difficult time placing the subject as a person, place or thing. I felt that my 4 years of private school Latin would place me at some type of advantage for understanding this new dialect, but it did not. Sometimes, I would just lean back at the dinner table, head in hands, and watch him have a seamless conversation back and forth with his daughter. Anne-Marie, not only understood him but she anticipated his next thought.

If Anne-Marie and I were contestants on Name That Tune the topic was «Dino's Musings» (set to song)<sup>Σ</sup> and she would be able to nail that musing in one note and I

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Ψ. One of Dino's brighter threads is his penchant for CAPITAL LETTERS with most email, and text correspondence.

ΦΦ. Scholars will point out that Dino determined this was ultimately served best in a Brandy Glass.

X. I feel I am entitled to a modicum of artistic license.

Σ. If Amazon ever takes me up on this deal, I want you to know I am filing a copyright.

would have to hear the whole song followed by announcement of the song's singer and a phonetic depiction of the subject matter and I still would not get it. I asked Anne-Marie if there was mail-a-way decoder ring that I could obtain from the Greek embassy or a crackerjack box to decode Greeklisch? Anne-Marie informed me this ring I sought was named «Time» and she had a 24 year head start. I am proud to say that now after over 13 years, I am proficient in **conversational** Greeklisch, but I still have difficulty with **email and text** Greeklisch. Another linguistic feature of Greeklisch is when discussing a multi step conclusion many steps along the way may be casually omitted, as they should be inherently obvious to the engaged listener. The conclusion he reaches is ultimately - correct and like Fermat's Last Theorem, «The proof of which is too large to fit within these margins»<sup>A</sup>. To understand Dino's language is to gain insight in the rapid and focused thought process that defines him. Upon closing this section, I realize that I am not satisfied by the name I have assigned this new language as linguists can find parallels but not direct connections to either English or Greek lineage. In fact many linguists would argue it has a unique origin<sup>o</sup>. Henceforth, I would like to rename **Greeklisch to Constantanish**.<sup>M</sup>

**CLOSET MACGYVER** It did not take me long to realize that a solidly constructed conglomeration of 15 different high-end perfumed hotel soaps could be an item of want or need. How naive I was. Limiting his artistic or creative genius to the realm of personal hygiene would be a grave disservice to the wealth of contributions he has made to culinary, organizational and storage solutions. His unique almost surgically constructed coffee bag «rapid access site» has prevented pounds of wasted coffee – grounds from being served to my floor instead of me.<sup>o</sup> The real genius of this design: is it is perfectly re-sealable and has reduced coffee spillage and waste. I soon came to realize there are few problems that Dino could not fix with the following supplies: rubber band, plastic bag, needle and thread<sup>l</sup>. His bread storage system typically employed surgically altered plastic bags and rubber bands and has subsequently been shown to extend the survival of a half-eaten baguette from one to almost four days. Arguably more impressive than his various creative inventions was his uncanny ability to know when he was above his pay grade and needed to page the specialist: STAT. It would likely be simultaneously tedious for you and embarrassing for me, to enumerate the house projects that have been stalled in contemplative purgatory, only to be promptly executed in one afternoon by Dino. His ability to summon the people you need to fix the problem you have<sup>r</sup> could be compared to the Pied Piper.<sup>Ω</sup>

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A. While I am enough of an erudite to make this reference I feel compelled to tell you I did fact check it on Wikipedia prior to publishing. IN FACT the proof was first published in 1995 a mere 358 years after the theorem was proposed. I fear I do not have that much time to prove all of Dino's Theorems.

o. A bit more of that Artistic license as referenced above.

M. Yet another copyright, I am yet to file. Used in a sentence «I cannot verify what saying but it sounds correct». I think he is speaking Constantanish. Roman Emperor Constantius, victorious but buried there after the battle of York, England ca 300 AO, was succeeded by his son Emperor Constantine, after whom my father-in-law is named.

O. Put it on the list of pending patents...

l. I would advise outsourcing electrical work...

r. Whether or not you realize you even had said problem.

Ω. The author intends to draw the parallel that Dino's charisma is much like the irresistible music of the piper drawing everyone in his path. The author would like to tamp down the aspect of the analogy comparing tradesmen to rats.

**PEARLS OF WISDOM** Some stories which I am sure he told elsewhere but I feel compelled to repeat harken back to a time: Before Shaw.<sup>Z,I,K</sup> I remember hearing that Dino would always make time to drive from Long Island to Philipps Academy to pick up or drop off Anne-Marie. This may be in the middle of a busy week of operating or in the midst of a once in a five-year blizzard. Dino realized that in a pre lpod world, spending 3 hours with the most precious person in your life was a time worth reorganizing your hectic schedule. His ability to cover large distances in vanishingly small amounts of time with remarkably little forewarning is unparalleled. While few would confuse Dino's silhouette with that of a lithe **Sub-Saharan Cheetah**, his ability to cover ground is uncannily similar. Historians will point to the time when calls were simultaneously placed to my parents in Philadelphia and Dino in Greece just minutes after we were informed that Anne-Marie would be delivering Alexandra at just over 26 weeks in about 48 hours. It was Dino who arrived first (and it was not even close) with a very nice gift for his brave daughter and my brave wife.<sup>Δ,X</sup>

His attention to our children and continued focus on their development and growth has been phenomenal. Dino for a long time was concerned that our mutual passion and busy professional lives in our chosen discipline of Cardiology would prevent us from having children. He openly lamented that he feared he would be greeted in his later years simply by «little EKGs running around our house.» I am proud instead to share two amazing children with him. They appear to be picking up Constanstanish much faster than I remember picking it up. His loving dedication to his family is a part of the Constanstanish dialect that can be quickly appreciated by those new to the language.

**ACKNOWLEDGEMENTS AND THANKS** I would like to thank Dino for the infinite number of times he has bought, cooked<sup>Δ</sup> various fine fish and steak which have apparently been sold in my immediate neighborhood for years. I thank him for not only expanding my waistline but also my views of what is possible in life including those in my immediate neighborhood. I would also like to thank him in advance for all future gifts and meals he will give and prepare for us whether stateside or in the paradise we know as SPETSES.

Lastly, I would like to point out to Dino and I ask all those reading to bear witness that this work shall serve as my long awaited academic contribution<sup>∞</sup>. I state confidently that this submission has many more references than any other work I have authored and for good reason given the complex, brilliant and clearly stated **SUBJECT** of the work.

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Z,I. Unfortunately historians refer to this as the time period of Before Shaw as: BS. Interestingly, the term BS when taken in the literal context of most sentences in which it is used, is typically correct. According to Maebey Funke of «Arrested Development» fame, everyone has BS these days.

K. BS is often thought of as a rather dismal time for humanity.

Δ. A gift giving custom to the mother that I have since learned should also apply to the father of the child. See also: push gift (I have since learned there is no statute of limitations on this tradition. NB for young husbands.)

X. I would like to state for the record there was an alleged flat tire that occurred in NJ or NY according to various accounts from my parents, which subsequently severely hampered their time.

Δ. The classic preparation of these dishes is accomplished with the little used «broil» function of your conventional Toaster Oven.

∞. Estimated Impact Factor of this work to the scientific and medical community.



*Natan Shaw R. - Michael V. Orlov*

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# First experience of 3D rotational angiography fusion with NavX electroanatomical mapping to guide catheter ablation of atrial fibrillation

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**BACKGROUND** Rotational angiography of the Left atrium with 3-dimensional reconstruction (3DATG) is a new imaging tool to guide atrial fibrillation (AF) ablation. Its role as part of a complex imaging strategy with NavX has not yet been evaluated.

**OBJECTIVE** To determine the feasibility of using 3DATG fusion with NavX in guiding AF ablation.

**METHODS** 3DATG was performed in 24 consecutive patients undergoing AF ablation by using the Philips AlluraXper FD 10 system. The 3DATG anatomical shell was fused with NavX data (fusion group). Procedural characteristics of the fusion group were compared to 12 patients (control group) who underwent AF ablation guided by NavX only during the preceding 6 months.

**RESULTS** 3DATG/NavX fusion was successful in all patients and required  $12 \pm 2$  fiducial points. Total radiation dose, fluoroscopy, and procedural times were significantly lower in the fusion group despite additional time and radiation exposure from 3DATG (total radiation dose of 20.4 mSv in the fusion group vs 34.0 mSv in the control group;  $P = .04$ ; fluoroscopy time 50.5 minutes vs 69.7 minutes; procedural time 4.3 hours vs 5.1 hours). Ablation was successful acutely in 35 of 36 patients. At follow-up, 14 of 24 (58.3%) patients in the fusion group and 6 of 12 (50%) patients in the control group were in sinus rhythm. There was 1 complication in each group.

**CONCLUSIONS** AF ablation guided by 3DATG/NavX fusion is associated with reduced procedural time and radiation exposure and similar clinical outcomes when compared with NavX mapping only. 3DATG/NavX fusion may provide a lower radiation alternative to NavX only or preprocedural cardiac computed tomography as part of complex imaging strategies.

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**KEYWORDS** Left atrium; Pulmonary veins; Fusion; 3-dimensional rotational angiography; 3-dimensional atriography; Reconstruction; Imaging; Atrial fibrillation; Catheter ablation

**ABBREVIATIONS** **3D** = 3-dimensional; **3DATG** = rotational angiography with 3-dimensional reconstruction or 3-dimensional rotational atriography; **AF** = atrial fibrillation; **CT** = computer tomography; **EAM** = electroanatomical mapping; **LA** = left atrium/ left atrial; **MRI** = magnetic resonance imaging; **PV** = pulmonary vein; **RF** = radiofrequency

## Introduction

Catheter ablation of atrial fibrillation (AF) has emerged as a powerful tool to restore and maintain sinus rhythm in many subgroups of patients.<sup>1</sup> This invasive strategy needs to be guided by imaging in order to deliver and track the ablation lesions in precise anatomical locations. Earlier approaches involved separate anatomical and electroanatomical methods to provide the needed imagery.

Two electroanatomical mapping (EAM) systems—CARTO (Biosense Webster, Diamond Bar, CA) and NavX (St Jude Medical, St Paul, MN)—are commonly used to guide AF ablation.<sup>2</sup> They provide virtual anatomy of the chamber of interest derived from electromagnetic principles. Knowledge of the true left atrial (LA) anatomy in individual patients is key to performing a safe and successful AF ablation. This true anatomical information can be provided by computed tomography (CT), magnetic resonance imaging (MRI), or rotational atriography with 3-dimensional reconstruction (3DATG). These 3-dimensional (3D) imaging modalities have been proven to be

excellent tools in defining the intricate anatomy of the LA and the surrounding structures.<sup>3-5</sup> The addition of true 3D anatomical information to EAM by using fusion methods has been shown to improve the procedural outcome and safety.<sup>6-9</sup> 3DATG and its overlay on live fluoroscopy has been successfully used to image the LA with quality comparable to CT and guide AF ablation as a single tool.<sup>10,11</sup> Fusion of 3DATG with CARTO has been reported and resulted in successful pulmonary vein (PV) isolation with an acceptable distance error on integration of the 3DATG and CARTO images.<sup>12</sup> Fusion of 3DATG with NavX mapping has not been previously reported and can potentially reduce radiation exposure and procedural time. We present our first experience with catheter AF ablation guided by 3DATG fusion with NavX.

The primary objective of this study was to determine the feasibility of using 3DATG fusion with NavX in AF ablation. In addition, this study compares the procedural time, radiation exposure, and follow-up success of AF ablation by using 3DATG fusion with NavX vs using NavX only.

**Table 1** Clinical characteristics of the study population

	Fusion group	Control group	P
Sex: Man, n (%)	18 (75)	7 (58.3)	.31
Age (y), mean ± SD	61.0 ± 8.0	59.2 ± 9.5	.59
Body mass index (kg/m <sup>2</sup> ), mean ± SD	31.1 ± 6.1	33.6 ± 8.4	.30
Diabetes, n (%)	3 (12.5)	4 (25)	.19
Hypertension, n (%)	23 (95.8)	11 (91.7)	1.00
Creatinine (mg/dL), mean ± SD	0.96 ± 0.2	1.04 ± 0.3	.30
NYHA II, n (%)	20 (83.3)	10 (83.3)	1.00
NYHA III, n (%)	4 (16.7)	2 (16.7)	1.00
CAD, n (%)	10 (41.7)	4 (33.3)	.70
AF—nonparoxysmal, n (%)	22 (91.7)	12 (100)	.54
Previous ablation, n (%)	6 (25)	2 (16.7)	.69
AAD, n (%)	24 (100)	12 (100)	1.00
LA volume (mL), mean ± SD	79.1 ± 29.9	98.3 ± 50.9	.32
LVEF (%), mean ± SD	54.1 ± 9.6	49.8 ± 8.2	.17

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease; LA = left atrium; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

## Methods

Data were collected retrospectively for 24 consecutive patients undergoing 3DATG fusion with NavX from February 2011 to November 2011 (fusion group). Twelve consecutive patients who had NavX-only EAM guided AF ablation over the same time period served as the control group. Institutional Review Board waiver was obtained, given retrospective nature of the study. Patients were excluded if they had cardiac CT/NavX fusion or CARTO EAM guided AF ablation. Patients' demographic and clinical characteristics are shown in Table 1. Left ventricular ejection fraction and LA volume were measured from the most recent 2-dimensional echocardiogram. Fluoroscopy time and radiation dose were routinely recorded from the Philips Allura Xper FD 10 system throughout the procedure. The technique to perform 3DATG and overlay it on live fluoroscopy has been previously described. In brief, a C-arm X-ray system rotates around the patient to obtain a circumferential run of many exposure images of the LA distributed over a 240° (or similar) trajectory. The LA and PVs are opacified indirectly by automatically injecting 80-100 mL of contrast (Omnipaque, GE Healthcare, Princeton, NJ) through a pigtail catheter positioned at the right atrium/inferior vena cava junction and waiting for the contrast material to pass through the lungs and appear in the LA. These rotational angiographic images of the LA and PVs are then segmented and registered by using a specialized computer system (EP Navigator, Philips Healthcare, Best, The Netherlands). Esophagus is opacified by administering small amounts of oral contrast (Barium Sulfate Esophageal Cream 60% w/w; E-Z-Paste, E-Z-EM, Inc, Lake Success, NY) or visualized by the esophageal temperature probe (18F Esophageal Disposable Temperature Probe, GE Healthcare Finland, Helsinki, Finland). These esophagus

shadows are also segmented and included into the final reconstructed 3D images. The software then allows repeated registration of the segmented 3D volume on a live fluoroscopy screen by using fixed anatomical landmarks such as bronchial carina that can be easily recognized on both 3D reconstructed images and live fluoroscopy.<sup>13</sup>

Procedure start time was recorded when femoral vein access was obtained, and end time was recorded when catheters were removed from the LA. The number of fiducial points required for satisfactory image fusion was recorded. Procedural characteristics used to compare both study groups are shown in Table 2. The procedural approach to transseptal puncture and stepwise approach to AF ablation was similar to previously described and was the same in both study groups.<sup>14</sup> Typical catheter setup included a PV mapping catheter (Inquiry Optima, St Jude Medical and Lasso, Biosense Webster), a decapolar coronary sinus catheter (XPT, C.R. Bard, Lowell, MA or similar) and a 3.5-mm irrigated-tip ablation catheter (Celsius ThermoCool, Biosense Webster or Cool Path, St Jude Medical). Intravenous heparin was given after transseptal puncture to maintain an activated clotting time of 300-400 seconds throughout the period of LA access. Immediate success was defined as an achievement of successful electrical isolation of all PVs and conduction block across the ablation lines if they were applied according to the stepwise approach.<sup>15</sup> Clinical data at follow-up were evaluated for rhythm, use of antiarrhythmic medications, cardioversions, and repeat AF ablation. Chronic success was defined by the absence of symptomatic recurrences as judged during patient interviews at regular follow-ups and the absence of AF on electrocardiograms obtained at those visits and on routine ambulatory monitoring.

**Table 2** Procedural characteristics

	Fusion group	Control group	<i>P</i>
Fluoroscopy time (min), mean ± SD	50.5 ± 15.3	69.7 ± 21.5	< .001
Total radiation dose (mSv), mean ± SD	20.4 ± 4.4	34.0 ± 9.7	.04
Procedural time (h), mean ± SD	4.3 ± 0.8	5.1 ± 0.5	< 0.001

### 3DATG and NavX image fusion

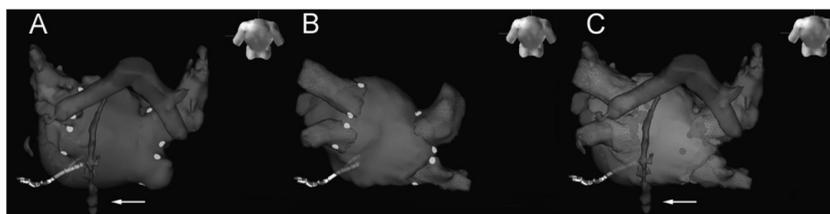
3DATG was segmented on an EP Navigator workstation (Philips Healthcare); this information was then transferred to the EnSite Velocity workstation (St Jude Medical) for image integration (Figure 1A). Limited EAM of the LA and PVs was obtained with Lasso or Optima and ablation catheters using common mapping techniques (Figure 1B). Fiducial points at easily recognizable anatomical locations (antral and carinal portions of the PVs and the LA appendage ridge) were selected on both EAM and transferred 3DATG shells (Figures 1A and 1B). Fusion of both 3D images was then accomplished by using a field scaling algorithm. The fused EAM-3DATG image (Figure 1C) was then used to guide catheter mapping and ablation. Ablation lesions were tracked on fused maps (Figure 1C). In the case of 3DATG truncation of a segment of the LA or PVs, NavX map data were used to complete the combined map (Figure 2).

### Statistical analysis

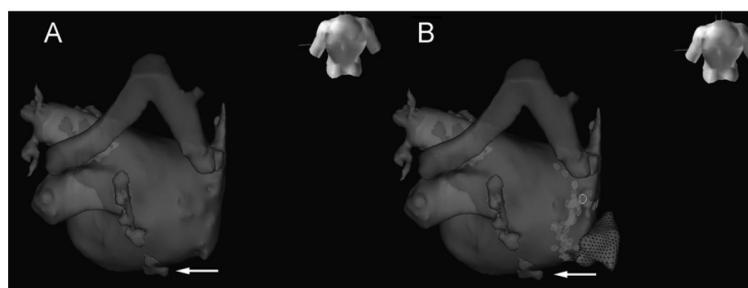
Results were entered in SPSS version 19.0 (SPSS, Inc, Chicago, IL). Control and fusion groups were compared by using the 2-tailed unpaired Student *t* test with unequal variance for continuous variables. The  $\chi^2$  and 2-tailed Fisher exact tests were used to compare categorical variables. Procedural and clinical outcomes were compared between both groups. A *P* value of  $< .05$  was considered statistically significant.

### Results

Demographic and clinical characteristics in both groups were comparable (Table 1). The majority of patients in both groups had nonparoxysmal AF and had de novo ablation procedures. 3DATG/NavX fusion was successful in all patients. Fusion of 3DATG and NavX was considered successful when the software allowed combining both images without any major visual discrepancies between the 2 on the fused shell. Truncated 3DATG images



**Figure 1** Fusion of 3-dimensional (3D) rotational angiogram with NavX. **A:** 3D rotational angiogram of the left atrium in the angulated posterior-anterior (PA) view. Also shown are shadows of the coronary sinus diagnostic catheter, bronchial carina (green color), and esophagus (white arrow). Fiducial points on easily recognizable anatomical landmarks (pulmonary veins and left atrial appendage ridge [not seen]) used for fusion of NavX and 3D rotational angiogram are shown by yellow dots in panels A and B. **B:** NavX map of the left atrium and 4 pulmonary veins in the angulated PA view. Also shown is a shadow of the coronary sinus diagnostic catheter. **C:** Fused NavX/3D rotational angiogram image in the angulated PA view (using field scaling algorithm). The surface of the fused anatomical shell is partially represented by 3D rotational angiographic data (blue color) and partially by NavX (gray color). Also shown is a shadow of the coronary sinus diagnostic catheter. This fused shell was used for catheter navigation, mapping, and ablation lesion tracking (shown by red dots).



**Figure 2** Complimentary nature of 3-dimensional (3D) rotational angiogram and NavX. **A:** 3D rotational angiogram of the left atrium in angulated posterior-anterior (PA) view with tracheal carina shown in green. Esophagus shadow by oral contrast administration during 3D rotational angiogram is shown in dark red color (white arrow). This image was partially truncated due to imprecise isocentering. Right lower pulmonary vein is almost completely truncated. **B:** Fused NavX/3D rotational angiogram image (angulated PA view) shows right lower pulmonary vein from NavX data "welded" to the combined shell (gray color with mesh). Ablation lesions around the right pulmonary veins are shown by red dots. Tracheal carina and esophagus as in panel A.

were inadvertently obtained in 2 patients owing to isocentering errors prior to image acquisition. The right lower PV was truncated in both cases and was successfully enhanced by NavX EAM (Figure 2). The number of fiducial points required to fuse 3DATG and NavX was  $12 \pm 2$ . The fusion process occurred in parallel with preparation for radio-frequency (RF) delivery without adding any significant delay to the procedural sequence. Procedural characteristics of fluoroscopy time, total radiation dose, and procedure time are shown in Table 2. All 3 assessed parameters were significantly lower in the Fusion group. The mean ablation times between the 2 groups were similar, that is,  $83.6 \pm 30$  minutes for the fusion Group vs  $81 \pm 20$  minutes for the control group.

One patient in the fusion group did not complete the procedure because of his or her inability to tolerate moderate sedation. There was 1 complication in each group. One patient in the fusion group developed pericardial tamponade toward the end of the AF ablation requiring urgent pericardiocentesis. This patient became restless and had exaggerated cardiac movements with deep inspiration while an Agilis NxT Steerable Introducer (St Jude Medical) was in the LA. Clinical suspicion for tamponade was confirmed by transthoracic echocardiogram. Pericardial effusion was drained uneventfully, and the patient recovered completely and remained in sinus rhythm at follow-up.

One patient in the control group developed an enlarged cardiac silhouette toward the end of PV isolation without any hemodynamic instability. A transthoracic echocardiogram showed a moderate-sized effusion, which was managed conservatively. The patient recovered uneventfully and was in sinus rhythm at follow-up. All other patients in the fusion and control groups were in sinus rhythm at the end of the procedure with electrical isolation of all PVs. At an average follow-up of  $10 \pm 3$  months for the fusion group and  $11.9 \pm 5.3$  months for the control group (Table 3), 14 (58.3%) patients in the fusion group and 6 (50%) patients in the control group were in sinus rhythm (off or on antiarrhythmic agents). Two patients from each group were lost to follow-up. Eight patients in the fusion group and 4 patients in the control group had repeat RF ablations for AF.

**Table 3** Clinical follow-up

	Fusion group	Control group	<i>P</i>
Follow-up (mo), mean $\pm$ SD	$10 \pm 3$	$11.9 \pm 5.3$	.26
AF recurrence, n (%)	10 (41.7)	6 (50)	.72
AAD, n (%)	7 (29.2)	4 (33.3)	1.00
DC cardioversion, n (%)	4 (16.7)	3 (25)	.66
Repeat AF ablation, n (%)	8 (33.3)	4 (33.3)	1.00

AAD = antiarrhythmic drug; AF = atrial fibrillation; DC = direct current.

## Discussion

This was the first study to demonstrate feasibility of an imaging approach involving fusion of 3DATG and NavX data. Combined EAM was associated with reduced procedural and fluoroscopy times and total radiation dose when compared with NavX-only mapping. Clinical outcome acutely and at follow-up was similar with both approaches.

The 2 groups under study were well matched in demographic and clinical characteristics at baseline. Operators employed similar procedural techniques, and the follow-up period was comparable. Other imaging modalities that can further reduce radiation exposure such as intracardiac echocardiography were not used in this study.<sup>16</sup>

Fusion of CT and MRI with EAM has been reported to be both feasible and highly accurate with minimal discrepancy of about 2 mm for CT in both animal and human models when images are properly registered.<sup>17</sup> Early experience confirmed a high accuracy of catheter navigation and good correlation between LA size determined by EAM and CT/MRI.<sup>18</sup> Martinek et al<sup>19</sup> reported in a series of 100 patients with drug-resistant AF significantly improved ablation success and safety (PV stenosis) in a Carto-Merge group vs a conventional EAM (Carto-XP) group. Caponi et al<sup>20</sup> found that Carto-Merge shortened X-ray exposure as compared to Carto-XP but there was almost no difference in clinical outcomes. Results from the Italian CartoMerge Registry<sup>6</sup> demonstrated significantly better procedural duration and clinical outcomes in the MERGE group vs the CARTO-only group. Brooks et al<sup>21</sup> described their initial experience with NavX image integration by using the NavX Fusion software and found that it is highly accurate and associated with a progressive reduction in fluoroscopy time relative to the procedural duration.

The use of 3DATG data for fusion with EAM provides the advantages of having the entire procedure done in a single hospital visit while also reducing the radiation exposure to the patient, as shown in this study. 3DATG can be imported into the CARTO system<sup>12</sup> or NavX and provide real-time anatomical information to supplement EAM. Imaging of the LA in the procedural setting of AF ablation provides real-time anatomical information that eliminates the variability associated with fluid volume and other physiologic changes. In one of the early trials using the fusion technique, Heist et al<sup>18</sup> showed that patients with larger LA volume may be prone to greater error during the integration of CARTO EAM with CT and MRI.

Our study demonstrated that NavX/3DATG fusion resulted in reduced radiation exposure compared to NavX alone. This decrease was likely due to the addition of anatomical information translating into more accurate catheter navigation and less reliance on fluoroscopy. An electro-anatomical map enhanced with true anatomical information from 3DATG becomes more realistic and is likely to facilitate a more effective ablation. In addition, the decrease in radiation exposure with fusion technique is beneficial for patients and the staff. Similar total RF time in both study groups suggests that decrease in fluoroscopy occurred during the initial acquisition of EAM and subsequent catheter navigation. This decrease in fluoroscopy time may have accounted for the reduction in total procedural time in the fusion group. The addition of true anatomical information from the angiogram and the resultant true electroanatomical fused map is likely to be more accurate based on operators experience with it and prior published results with 3DATG and EP Navigator.<sup>10,22</sup> The presence of true anatomical surfaces in difficult locations (ridges, unusual angulations, etc.) on fused maps is likely to assist the operator, facilitating improved catheter navigation and ablation accuracy. A NavX map not enhanced by 3D anatomical data may be based on computer assumptions that do not accurately reflect the true LA anatomy. This may result in additional fluoroscopy use when trying to map and navigate these imprecisely represented areas.

This study offers some intriguing possibilities for the use of 3DATG fusion with NavX in AF ablation. Rotational angiography is simple to perform, and it has, after digital processing, anatomical accuracy comparable to CT with the margin of discrepancy generally below 2 mm.<sup>10,23</sup> The segmentation process occurs in parallel with EAM so that the overall procedural time is not adversely affected. Fusion of images is a relatively simple procedure and can be done successfully in the control room, while the main operators are preparing to deliver RF ablation. The possible downside to this technique is an allergic reaction to the contrast medium, but the same applies to CT with intravenous contrast administration. Patients with claustrophobia may potentially find this process easier to tolerate than CT or MRI. The use of MRI is restricted in patients with implan-table cardiac devices, although this may gradually have less of an impact with the advent of MRI-safe technologies.

NavX and 3DATG are not mutually exclusive but rather complimentary imaging modalities. Concerns for the 2 incomplete 3DATG images were tackled in the current study by mapping the missing areas with EAM and “welding” it on the fused image (Figure 2). This was particularly true for the lower PVs that were more likely to be truncated. Knowledge of the complimentary nature of both methods may give additional confidence to the less experienced operator.

The fusion process itself was short, although we did not account for this specifically owing to the retrospective nature of the study. In fact, it did not add to the overall procedure time since it occurred while preparing for RF delivery. The number of fiducial points required to fuse the images was  $12 \pm 2$ —relatively small—and this further simplified the integration process. We also tried to collect a limited NavX map (mainly PVs, and LA appendage and its ridge) in an attempt to further reduce radiation exposure. These limited NavX maps rely on anatomical data from 3DATG and did not result in additional challenges during the integration process or subsequent catheter navigation.

Rotational angiography does not significantly

increase the procedural cost beyond the cost of a pigtail catheter and a small amount of contrast medium once the appropriate 3D reconstruction software that comes with the angiography system has been acquired. The per case cost of NavX is considerable but adds no additional cost to the described technique as an EAM system would be routinely used for AF ablation irrespective of other imaging modalities.

The extra radiation from performing 3DATG was reported to be about  $2.1 \pm 0.3$  mSv, which compares very favorably to a traditional 64-slice CT scanner.<sup>10</sup> However, the improved 320-slice CT scanners reportedly provide lower exposure. Therefore, the gap between 3DATG and CT radiation exposure is narrowing.<sup>24</sup> This study represents another step in the current trend to reduce radiation exposure with lengthy electrophysiological procedures. Recent reports have documented successful fluoroscopy-free AF ablation by using multiple nonfluoroscopic imaging modalities.<sup>25</sup> The latest development of the Medi-Guide technique presents yet another imaging approach with the potential for only initial limited fluoroscopy. One could envision incorporation of true anatomical data from 3DATG into these nonfluoroscopic protocols to enhance their accuracy while keeping low fluoroscopy exposure.

## Study limitations

This was a single center, retrospective analysis done with a fairly small sample size. The data on the potential decrease in radiation exposure need to be validated in a prospective study. Similar efficacy and complication rate in both study groups suggest noninferiority of the fusion approach. However, this will also require confirmation in a prospective study. In addition, this retrospective study did not address issues of registration and navigation accuracy.

## Conclusions

This study was the first to evaluate the use of 3DATG/NavX fusion technique for AF ablation and showed that this approach is feasible and safe in an appropriately equipped electrophysiology laboratory. 3DATG/NavX fusion was associated with significantly reduced procedural and fluoroscopy times, and radiation exposure when compared to a NavX-only strategy to guide RF catheter ablation for AF. 3DATG/NavX fusion may offer a competitive alternative to other image integration strategies by potentially reducing procedural time and radiation exposure. This would be better defined by larger prospective randomized trials.

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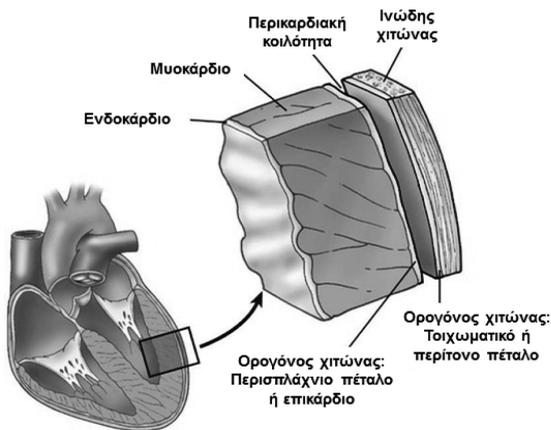
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# Χειρουργική Παθολογία του Περικαρδίου

Γεώργιος Λάζαρος, Πέτρος Νιχογιαννόπουλος

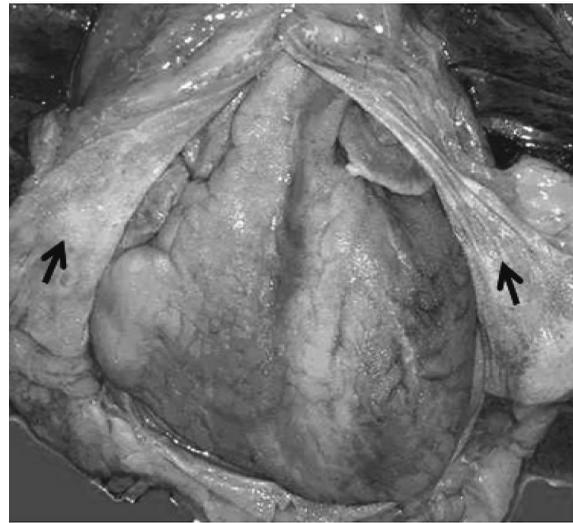
## ΑΝΑΤΟΜΙΑ ΤΟΥ ΠΕΡΙΚΑΡΔΙΟΥ

Το περικάρδιο είναι ένα όργανο με μορφή θύλακα ο οποίος περιβάλλει την καρδιά και την αρχή των μεγάλων αγγείων, αρτηριακών και φλεβικών, στη βάση της καρδιάς. Αποτελείται από 2 χιτώνες έναν εσωτερικό ορογόνο και ένα εξωτερικό ινώδη (Εικόνες 1 και 2).



Εικόνα 1. Σχηματική απεικόνιση φυσιολογικού περικαρδίου.

Ο ορογόνος χιτώνας του περικαρδίου αποτελείται από μία μονήρη στοιβάδα μεσοθηλιακών κυττάρων και περιλαμβάνει δύο πέταλα: i. ένα εσωτερικό που προσφύεται στενά στην επιφάνεια της καρδιάς και το επικαρδιακό λίπος και ονομάζεται περισπλάχνιο ή σπλαχνικό πέταλο ή επικάρδιο και ii. από το περίτονο πέταλο του περικαρδίου



Εικόνα 2. Ανατομικό παρασκεύασμα καρδιάς - περικαρδίου (βέλη)

ου το οποίο δημιουργείται από την αναδίπλωση του περισπλάχνιου πετάλου στη βάση της καρδιάς και καλύπτει εσωτερικά τον ινώδη χιτώνα. Το σύμπλεγμα περίτονου πετάλου και ινώδους χιτώνα είναι μη διαχωρίσιμο και ονομάζεται τοιχωματικό περικάρδιο (Εικόνα 1). Το πάχος του τοιχωματικού περικαρδίου φυσιολογικά κυμαίνεται από 0,8-2,5cm και αυξάνεται σε παθολογικές καταστάσεις όπως φλεγμονή και συμπιεστική περικαρδίτιδα.

Μεταξύ του περισπλάχνιου και περίτονου πετάλου του ορογόνου χιτώνα του περικαρδίου αφορίζεται η περικαρδιακή κοιλότητα η οποία περιέχει 15-50ml διαυγούς περικαρδιακού υγρού

που είναι υπερδιήθημα του πλάσματος, με χαμηλή περιεκτικότητα σε πρωτεΐνες και παρόμοια περιεκτικότητα σε ηλεκτρολύτες με εκείνη του πλάσματος.

### ΛΕΙΤΟΥΡΓΙΕΣ ΤΟΥ ΠΕΡΙΚΑΡΔΙΟΥ

Στο περικάρδιο έχουν αποδοθεί διάφορες λειτουργίες, ωστόσο η σημασία του στην καρδιακή λειτουργία παραμένει αμφίβολη, δεδομένου ότι είτε σε περιπτώσεις συγγενούς απουσίας του περικαρδίου, είτε μετά από θεραπευτική ολική περικαρδιακτομή, δεν παρατηρούνται δυσμενείς επιπτώσεις που να μεταφράζονται σε αναγνωρίσιμη νοσηρότητα ή αυξημένη θνητότητα.

Μεταξύ των διαφόρων λειτουργιών που έχουν αποδοθεί στο περικάρδιο φαίνεται λογικό να συμμετέχει στη διατήρηση της ανατομικής θέσης της καρδιάς μέσω των προσφύσεων του τοιχωματικού περικαρδίου, υποβοηθώντας την καρδιά να παίρνει λειτουργικά την καταλληλότερη θέση μέσα στο θώρακα, ελαττώνει την τριβή της καρδιάς μέσω του περικαρδιακού υγρού με τις γειτονικές δομές παρέχοντας προστασία από μικροτραυματισμούς, ενώ αξιοσημείωτη είναι και η συμβολή του στην αποφυγή υπέρμετρης διάτασης των καρδιακών κοιλοτήτων σε περιπτώσεις οξείας υπερφόρτισης όγκου, περιορίζοντας μεταξύ άλλων τη λειτουργική ανεπάρκεια των κολποκοιλιακών βαλβίδων και ασκώντας ρυθμιστικό ρόλο στην αλληλεξάρτηση των κοιλιών. Επιπρόσθετα, πιστεύεται ότι το περικάρδιο αποτελεί φυσικό φραγμό στη μετάδοση λοιμώξεων στην καρδιά από πνεύμονες, μεσοθώρακιο και άλλες γειτονικές δομές, καθώς και από αντίστοιχη επέκταση διασυνεχίας κακοήθων όγκων. Επίσης, συνεισφέρει σε συνεργασία με τους γειτνιάζοντες ιστούς στη διατήρηση αρνητικών τιμών ενδοθωρακικής πίεσης, γεγονός που εξασφαλίζει την πλήρωση των κόλπων κατά την καρδιακή συστολή.

### ΠΑΘΟΛΟΓΙΕΣ ΤΟΥ ΠΕΡΙΚΑΡΔΙΟΥ ΜΕ ΧΕΙΡΟΥΡΓΙΚΟ ΕΝΔΙΑΦΕΡΟΝ

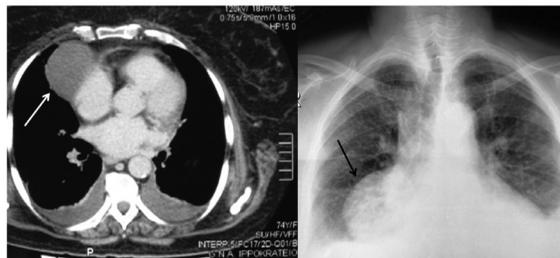
Τα περικαρδιακά σύνδρομα περιλαμβάνουν τις συγγενείς ανωμαλίες, κύστεις και όγκους του περικαρδίου, την οξεία και υποτροπιάζουσα περικαρδίτιδα, τον καρδιακό επιποματισμό, τη χρό-

νια συμπιεστική περικαρδίτιδα και τη χρόνια περικαρδιακή συλλογή υγρού. Ακολουθεί αναφορά στα παραπάνω σύνδρομα με έμφαση κατά κύριο σε εκείνα στα οποία υπάρχει (καρδιο)χειρουργικό ενδιαφέρον.

#### 1. Συγγενείς και επίκτητες ανωμαλίες του περικαρδίου

Οι συγγενείς ανωμαλίες του περικαρδίου είναι σχετικά σπάνιες και περιλαμβάνουν τις συγγενείς και επίκτητες κύστεις, τα εκκολπώματα και την τμηματική ή πλήρη έλλειψη του περικαρδίου.

Οι κύστεις εντοπίζονται κατά κανόνα στις καρδιοφρενικές γωνίες (Εικόνα 3) και η επίπτωση τους στο γενικό πληθυσμό είναι ~1:100.000.



Εικόνα 3. Αξονική τομογραφία (αριστερό πλαίσιο) και ακτινογραφία θώρακα ασθενούς με περικαρδιακή κύστη (βέλη).

Οι κύστεις δεν επικοινωνούν με την περικαρδιακή κοιλότητα σε αντίθεση με τα εκκολπώματα. Συνήθως δεν προκαλούν συμπτώματα και συνιστούν τυχαίο εύρημα, ωστόσο σε ορισμένες περιπτώσεις μεγάλων σε μέγεθος κύστεων, μπορεί να προκαλέσουν συμπτώματα όπως θωρακική δυσφορία, εκτακτοσυτολική αρρυθμία και δύσπνοια λόγω πιεστικών φαινομένων στο μυοκάρδιο. Η θεραπεία τους είναι η διαδερμική παρακέντηση και παροχέτευση με ενδεχόμενη έγχυση σκληρυντικών ουσιών (αιθανόλης). Σε αποτυχία της παρακέντησης ή σε υποτροπή σε συμπτωματικούς ασθενείς συνιστάται η χειρουργική αφαίρεση.

Επίσης, επί παρουσίας κύστεων στην περιοχή πάντα θα πρέπει να εξετάζεται και το ενδεχόμενο επίκτητων κύστεων, είτε εχινόκοκκων είτε φλεγμονώδους αιτιολογίας. Ειδικά για την εχινόκοκκο κύστη καρδιακή συμμετοχή περιγράφεται σε ποσοστό έως 2% των περιπτώσεων περίπου και

σε ενδημικές περιοχές θα πρέπει να συμπεριλαμβάνεται στη διαφοροδιάγνωση των κυστικών καρδιακών μορφωμάτων. Η αύξηση τους είναι συνήθως αργή και συμπτώματα (συνήθως μη ειδικά) εκδηλώνονται στο 10% περίπου των περιπτώσεων. Η ρήξη με επακόλουθες αλλεργικές εκδηλώσεις και η συμπίεση γειτονικών δομών αποτελούν δυνητικές συνέπειες της κύστης. Η χειρουργική θεραπεία είναι η θεραπεία εκλογής σε συνδυασμό με περιεγχειρητική χορήγηση αλμπενδαζόλης (η οποία αποτελεί και τη μοναδική προσέγγιση σε ανεγχείρητους ασθενείς λόγω συνοσηροτήτων ή λόγω πολλαπλών κύστεων).

Σχετικά με τα ελλείμματα του περικαρδίου φαίνεται ότι τα τμηματικά (μερικά) είναι τα πλέον επικίνδυνα, δεδομένου ότι έχει περιγραφεί εγκολεασμός του μυοκαρδίου που μπορεί να έχει σαν αποτέλεσμα την εμφάνιση αρρυθμιών ή/και αιφνίδιου θανάτου. Η πλήρης απουσία του περικαρδίου διαπιστώνεται συχνότερα από ότι στο παρελθόν σαν αποτέλεσμα της ολοένα αυξανόμενης διάδοσης των απεικονιστικών εξετάσεων της καρδιάς. Ο επιπολασμός της εκτιμάται σε 0.002-0.004% του πληθυσμού. Μπορεί να είναι μεμονωμένη ή να συνοδεύεται από άλλες καρδιακές και εξωκαρδιακές ανωμαλίες.

## 2. Όγκοι περικαρδίου

Οι πρωτοπαθείς όγκοι του περικαρδίου είτε καλοήθεις (λιπώματα και ινώματα) είτε κακοήθεις (μεσοθηλιώματα, αγγειοσαρκώματα, ινοσαρκώματα, όλα με κάκιστη πρόγνωση) είναι πολύ σπάνιοι. Συχνότερες είναι οι μεταστάσεις στο περικάρδιο κυρίως σε καρκίνο πνεύμονα, μαστού, οισοφάγου, μελάνωμα και αιματολογικές κακοήθειες.

Σε ασθενείς με περικαρδιακή συλλογή και υποκείμενη κακοήθεια, η συλλογή δεν οφείλεται σε μετάσταση στο περικάρδιο αλλά σε άλλα αίτια όπως λοιμώξεις στα πλαίσια της ανοσοκαταστολής, ακτινοβολία, ή σε φάρμακα που χρησιμοποιούνται για την θεραπεία του όγκου. Η επιβεβαίωση της μεταστατικής περικαρδίτιδας γίνεται με κυτταρολογική εξέταση του περικαρδιακού υγρού, ή με βιοψία του περικαρδίου. Η διαγνωστική συνεισφορά του προσδιορισμού των καρκινικών δεικτών στο περικαρδιακό υγρό είναι αντι-

κείμενο διχογνωμίας. Ο απεικονιστικός έλεγχος με αξονική ή μαγνητική τομογραφία παρέχει πληροφορίες σχετικά με την τοπική ή σε απόσταση επέκταση του όγκου.

Ο διαχωρισμός μεταξύ μεταστατικής ή μη περικαρδίτιδας είναι ιδιαίτερα σημαντικός γιατί η πρόγνωση στη μεταστατική περικαρδίτιδα είναι πολύ κακή. Συγκεκριμένα το 86% των ασθενών καταλήγει εντός 12 μηνών, με το 1/3 περίπου να καταλήγει εντός 1 μηνός. Σχετικά με τη θεραπεία σε περιπτώσεις επιποματισμού έχει ένδειξη η περικαρδιοκέντηση. Η υποψία νεοπλασματικής περικαρδίτιδας (μαζί με την υποψία πυώδους περικαρδίτιδας), αποτελεί ένδειξη για πραγματοποίηση διαγνωστικής περικαρδιοκέντησης. Σε περίπτωση που από τη μελέτη του περικαρδιακού υγρού και κυρίως από την κυτταρολογική εξέταση διαπιστωθεί μεταστατική περικαρδίτιδα, σε κάθε περίπτωση η στοχευμένη συστηματική θεραπεία του πρωτοπαθούς όγκου αποτελεί τον ακρογωνιαίο λίθο (χημειοθεραπεία ή/και ακτινοβολία σε ακτινοευαίσθητους όγκους όπως τα λεμφώματα και οι λευχαιμίες). Σε περίπτωση υποτροπής της περικαρδιακής συλλογής που είναι συχνή (40-70%), οι θεραπευτικές επιλογές περιλαμβάνουν την νέα παρακέντηση-παροχέτευση με έγχυση κυτταροστατικών (πχ cisplatin σε καρκίνο πνεύμονα thiotera σε καρκίνο μαστού), ή σκληρυντικών ουσιών (τετρακυκλίνη), την περικαρδιοτομή με μπαλόνι και τη χειρουργική δημιουργία χειρουργικού παραθύρου. Φαίνεται από προκαταρκτικές μελέτες ότι το χειρουργικό παράθυρο είναι ασφαλές και περισσότερο αποτελεσματικό συγκρινόμενο με τις υπόλοιπες μεθόδους. Σε περιπτώσεις που ο όγκος είναι εξαιρεσίμος (ή παρηγορητικά σε μη εξαιρεσίμους όγκους) μπορεί να επιχειρηθεί συνδυασμός χειρουργικής εξαίρεσης και συστηματική χημειοθεραπεία με πτωχά ωστόσο μακροπρόθεσμα ποσοστά επιβίωσης.

## 3. Καρδιακός επιποματισμός

Ο καρδιακός επιποματισμός αποτελεί μία δυνητικά απειλητική για τη ζωή κατάσταση και είναι ίσως η πιο επίφοβη επιπλοκή της οξείας περικαρδίτιδας. Οφείλεται σε αργή ή ταχεία συλλογή υγρού, αίματος, πηγμάτων ή αέρα στην περικαρδιακή κοιλότητα, σαν αποτέλεσμα φλεγμονής,

τραύματος, ή ρήξης μίας καρδιακής κοιλότητας. Με ειδική αναφορά στην οξεία περικαρδίτιδα, ο καρδιακός επιπωματισμός αναπτύσσεται λόγω συσσώρευσης υγρού στην περικαρδιακή κοιλότητα, λόγω της τοπικής φλεγμονής και χαρακτηρίζεται από αύξηση των ενδοκοιλοτικών πιέσεων, προοδευτικό περιορισμό της διαστολικής πληρώσεως των κοιλιών και ελάττωση του όγκου παλμού και της καρδιακής παροχής. Τα κυριότερα αίτια καρδιακού επιπωματισμού συνοψίζονται στον Πίνακα 1.

#### Πίνακας 1. Αίτια καρδιακού επιπωματισμού.

##### A. Κοινά αίτια

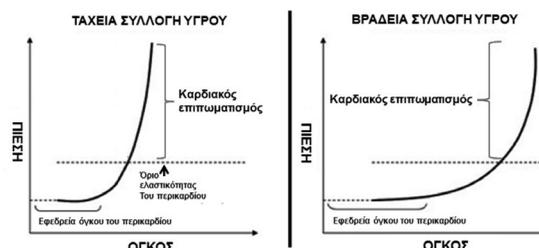
1. Οξεία ιδιοπαθής-ιογενής περικαρδίτιδα
2. Φυματιώδης περικαρδίτιδα
3. Νεοπλασματική περικαρδίτιδα
4. Περικαρδιακό τραύμα, ιατρογενές π.χ. σε εμφύτευση ηλεκτρονικών συσκευών ή επεμβάσεις στα στεφανιαία) ή μη

##### B. Σπανιότερα αίτια

1. Συστηματικά αυτοάνοσα νοσήματα (συστηματικός ερμηματώδης λύκος, σκληρόδερμα)
2. Ακτινοβολία μεσοθωρακίου
3. Μετεμφραγματική περικαρδίτιδα
4. Ουραιμία
5. Διαχωρισμός αορτής
6. Πυώδης περικαρδίτιδα
7. Πνευμοπερικάρδιο

Η εμφάνιση καρδιακού επιπωματισμού εξαρτάται από την ποσότητα και το ρυθμό αύξησης της ποσότητας του περικαρδιακού υγρού, καθώς και από τη διατασιμότητα (ενδοτικότητα) του περικαρδίου (Εικόνα 4). Ταχεία άθροιση μικρής ποσότητας υγρού (έως και 100-200ml) όπως σε περιπτώσεις αιμοπερικαρδίου, μπορεί να προκαλέσουν καρδιακό επιπωματισμό ενώ αντίθετα, αιμοδυναμικές επιπτώσεις μπορεί να μην εμφανιστούν ακόμη και σε ποσότητες 2 λίτρων με την προϋπόθεση ότι ο ρυθμός αύξησης του υγρού είναι πολύ αργός (πχ φυματιώδης περικαρδίτιδα και νεοπλασίες). Η ερμηνεία παρέχεται από την Εικόνα 4, στην οποία φαίνεται ότι υπάρχει ένα όριο ελαστικότητας άμεσα εξαρτώμενο από το ρυθμό αύξησης της περικαρδιακής συλλογής. Πέραν αυ-

τού του ορίου ακόμη και ασήμαντες αυξήσεις του όγκου του περικαρδιακού υγρού επιφέρουν σημαντική αύξηση της ενδοπερικαρδιακής κοιλότητας.



Εικόνα 4. Καμπύλη πίεσης όγκου εντός της περικαρδιακής κοιλότητας.

Τα κύρια κλινικά σημεία σε περιπτώσεις καρδιακού επιπωματισμού συνοψίζονται στην κλασική τριάδα του Beck, που περιλαμβάνει αύξηση της φλεβικής πίεσης (διάταση σφαγιτίδων φλεβών), ελάττωση της αρτηριακής πίεσης και βύθιους καρδιακούς τόνους. Συνοδά σημεία είναι η ταχυκαρδία και η αρτηριακή υπόταση. Το σημείο κλειδί ωστόσο στη διάγνωση και την ανάδειξη των αιμοδυναμικών συνεπειών του καρδιακού επιπωματισμού είναι ο παράδοξος σφυγμός που αντιστοιχεί στην εισπνευστική ελάττωση της συστολικής αρτηριακής πίεσεως >10 mmHg.

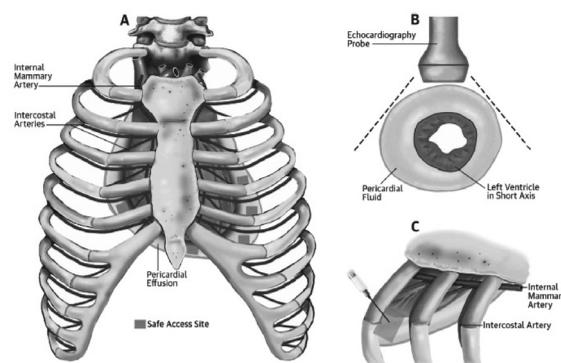
Επικουρικά στην κλινική εξέταση στη διάγνωση συνεισφέρουν το ηλεκτροκαρδιογράφημα (χαμηλά δυναμικά), η ακτινογραφία θώρακα (διεύρυνση της καρδιακής σιλουέτας χωρίς ενδείξεις συμφόρησης των πνευμονικών πεδίων, η οποία ωστόσο (μπορεί να απουσιάζει σε αιφνίδια συλλογή υγρού όπως πχ σε καρδιακό τραύμα) και τέλος σημαντικότερο όλων το ηχοκαρδιογράφημα το οποίο παρέχει πολύτιμες πληροφορίες για τις αιμοδυναμικές συνέπειες της συλλογής υγρού (περικαρδιακή συλλογή υγρού με σύμπτωση collapse των δεξιών καρδιακών κοιλοτήτων, αναπνευστικές διακυμάνσεις του επάρματος E στη διαμυτροειδική και διατριγλωχινική ροή και διάταση με μειωμένη διακύμανση της κάτω κοίλης φλέβας).

Όπως φαίνεται και στον Πίνακα 1 η περικαρδίτιδα (ιδιοπαθής-ιογενής, φυματιώδης ή νεοπλασματική) αποτελεί το συχνότερο αίτιο καρδιακού επιπωματισμού. Η συχνότερη μορφή οξείας περικαρδίτιδας στις ανεπτυγμένες χώρες είναι η ι-

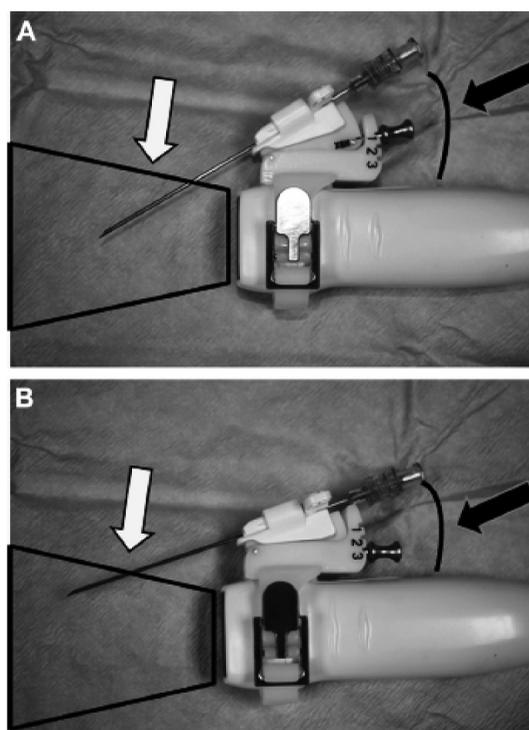
διοπαθής περικαρδίτιδα (πρακτικά ιογενείς με τους δύο όρους να θεωρούνται ταυτόσημοι) η οποία ευθύνεται για το 80-90% των περιπτώσεων. Στο υπόλοιπο 10-20% των περιπτώσεων οξείας περικαρδίτιδας ο έλεγχος αποκαλύπτει κάποιο δευτεροπαθές (ειδικό) αίτιο όπως κακοήθεια (~5%), τα συστηματικά αυτοάνοσα νοσήματα (5%), μετεμφραγματική περικαρδίτιδα και μεταβολικά αίτια όπως η ουραιμία, το μυξοίδημα, καθώς και άλλα σπανιότερα. Στις αναπτυγμένες χώρες, αναδυόμενη αιτία οξείας περικαρδίτιδας αποτελεί η ιατρογενής μετατραυματική μορφή ως απόρροια καρδιοχειρουργικής επέμβασης, αγγειοπλαστικής των στεφανιαίων αρτηριών ή επεμβάσεων εμφύτευσης βηματοδότη, απινιδιστή και επεμβάσεις κατάλυσης. Στις υπό ανάπτυξη χώρες μακράν το συχνότερο αίτιο περικαρδίτιδας αποτελεί η φυματιώδης περικαρδίτιδα (~70%). Είναι αξιοσημείωτο ότι ο καρδιακός επιπωματισμός είναι σπάνιος στις ιδιοπαθείς-ιογενείς μορφές (1,2%) και συχνός στις περιπτώσεις δευτεροπαθούς περικαρδίτιδας (έως 20%).

Θεραπευτικά η διαδερμική περικαρδιοκέντηση αποτελεί την προσέγγιση πρώτης γραμμής σε περιπτώσεις οξέος καρδιακού επιπωματισμού. Η φόρτιση όγκου με 250-500ml σε 5-10 λεπτά μπορεί να χρησιμοποιηθεί σαν προσωρινό μέτρο στην προσπάθεια σταθεροποίησης υποτασικών ασθενών μέχρι την περικαρδιοκέντηση. Συνιστάται όπως η επέμβαση πραγματοποιείται υπό ηχοκαρδιογραφική καθοδήγηση, ιδανικά σε πραγματικό χρόνο (real time). Με την ηχοκαρδιογραφική μελέτη καθορίζεται ποια είναι η καταλληλότερη θέση για την παρακέντηση η οποία αντιστοιχεί στο σημείο της πρόσθιας θωρακικής μοίρας που είναι πλησιέστερα στην μεγαλύτερη ποσότητα περικαρδιακού υγρού. Η συχνότερη προσπέλαση είναι η υποξιφοειδική ωστόσο κατά περίπτωση υπάρχουν διάφορες επιλογές όπως φαίνεται και στην Εικόνα 5.

Για τη διευκόλυνση της επέμβασης έχουν επνοηθεί ειδικοί βραχίονες με υποδοχή της βελόνας περικαρδιοκέντησης που προσαρμόζονται στον ηχοκαρδιογραφικό μορφομετατροπέα και καθοδηγούν σε πραγματικό χρόνο την περικαρδιοκέντηση (Εικόνα 6).



Εικόνα 5. Θέσεις ασφαλούς περικαρδιοκέντησης. Τα πράσινα τετράγωνα αντιστοιχούν στις δυναμικές θέσεις περικαρδιοκέντησης. Τροποποιημένος από Haddad El, et al. *J Am Coll Cardiol* 2015;66:1119-1128.



Εικόνα 6. Βραχίονες προσαρμοζόμενοι στον ηχομορφομετατροπέα δια καθοδήγηση περικαρδιοκέντησης. Τροποποιημένος από Maggolini S et al. *Am J Cardiol* 2016;117:1369-1374.

Με τις παραπάνω προϋποθέσεις τα ποσοστά μειζόνων επιπλοκών έχουν μειωθεί σε <2%. Εναλλακτικά η καθοδήγηση μπορεί να γίνει στο εργαστήριο καρδιακών καθετηριασμών με ακτινοσκόπηση κατά την οποία η καρδιακή σιλουέτα οριοθετείται εξωτερικά από ένα φωτεινό δακτύλιο (σημείο της άλω - halo sign). Και σε αυτή την περίπτωση τα ποσοστά επιπλοκών είναι πολύ χαμηλά.

Επισημαίνεται ότι ενώ μέχρι πρόσφατα το αιμοπερικάρδιο με επιπωματισμό στα πλαίσια διαχωριστικού ανευρύσματος αορτής αποτελούσε απόλυτη αντένδειξη στην περικαρδιοκέντηση, σύμφωνα με νεότερες αντιλήψεις οι οποίες αποτυπώνονται στις κατευθυντήριες οδηγίες της Ευρωπαϊκής Καρδιολογικής Εταιρίας (2015) σχετικές με τα περικαρδιακά σύνδρομα, αναμένοντας την καρδιοχειρουργική επέμβαση, συνιστάται η τοποθέτηση καθετήρα παροχέτευσης στο περικάρδιο με αφαιρέσεις τόσης ποσότητας υγρού ώστε να εξασφαλίζεται αιμοδυναμική σταθερότητα (με ΑΠ στόχο περί τα 100mmHg,) χωρίς παράλληλα να προκαλείται επέκταση του διαχωρισμού.

Η χειρουργική επέμβαση με δημιουργία περικαρδιακού παράθυρου αποτελεί εναλλακτική τεχνική παροχέτευσης της περικαρδιακής συλλογής. Με την τεχνική αυτή δημιουργείται μία ιατρογενής επικοινωνία μεταξύ της περικαρδιακής και της υπεζωκοτικής κοιλότητας. Η χειρουργική προσπέλαση επιφυλάσσεται σε περιπτώσεις που η περικαρδιακή συλλογή δεν είναι προσπελάσιμη με ασφάλεια διαδερμικά όπως π.χ. σε περιπτώσεις εντοπισμένων (εγκυστομένων) συλλογών. Επιτρέπει την πλήρη αφαίρεση του υγρού η οποία δεν είναι εφικτή σε αρκετές περιπτώσεις με τη περικαρδιοκέντηση λόγω τοπικών συμφύσεων και εγκύστωση του υγρού, ενώ σε περιπτώσεις με διαφοροδιαγνωστικά προβλήματα θα προσφέρει με τη δυνατότητα λήψης ιστού (βιοψίας περικαρδίου) πολύτιμες πληροφορίες. Μία άλλη ένδειξη χειρουργικής παροχέτευσης του περικαρδίου είναι η πυώδης περικαρδίτιδα στην οποία λόγω των ενδοπερικαρδιακών συμφύσεων και του αυξημένου ιξώδους της συλλογής δεν επιτυγχάνεται ικανοποιητική παροχέτευση της κοιλότητας αυξάνοντας σημαντικά τον κίνδυνο συμπίεσης περικαρδίτιδας. Η νεοπλασματική περικαρδίτιδα και κυρίως σε περιπτώσεις επινέμεσης της κακοήθειας στο περικάρδιο το περικαρδιακό παράθυρο μαζί με τη συστηματική χημειοθεραπεία αποτελεί τη συνιστώμενη προσέγγιση για την αποφυγή των υποτροπών (η περικαρδιοτομή με μπαλόνι αποτελεί εναλλακτική λύση σε αυτούς τους ασθενείς κυρίως σαν παρηγορητική θεραπεία σε βαρέως πάσχοντες με κακή πρόγνωση).

Σε ότι αφορά στη χειρουργική τεχνική για τη

δημιουργία παράθυρου περιγράφονται 2 κυρίως τεχνικές: η μία με υποξιφοειδική προσπέλαση και η άλλη με θωρακοτομή και προσπέλαση του περικαρδίου μέσω μίας τομής στο πέμπτο μεσοπλεύριο διάστημα. Χωρίς να υπάρχει επαρκής τεκμηρίωση για την ανωτερότητα της μίας έναντι της άλλης μεθόδου, φαίνεται ότι η πρώτη συνδυάζεται με λιγότερο μετεγχειρητικό πόνο και συντομότερο χρόνο αφαίρεσης της τοπικής παροχέτευσης, ενώ η δεύτερη φαίνεται να υπερτερεί ως προς την εμφάνιση υποτροπών και ανάγκη για νέα επέμβαση. Επισημαίνεται ότι τα τελευταία χρόνια κερδίζει συνεχώς έδαφος η θωρακοσκοπική χειρουργική (VATS: video assisted thoracic surgery), η οποία με ελάχιστα επεμβατική τεχνική παρέχει σε σημαντικό βαθμό τα πλεονεκτήματα του συμβατικού χειρουργικού παράθυρου.

Μία επιπλοκή η οποία έχει συνδυαστεί με αρχικά τουλάχιστον ανεπίπλεκτη παροχέτευση μεγάλων περικαρδιακών συλλογών με επικείμενο ή έκδηλο επιπωματισμό (με περικαρδιοκέντηση ή κυρίως χειρουργική) είναι το σύνδρομο αποσυμπίεσης της περικαρδιακής κοιλότητας (pericardial decompression syndrome). Η οντότητα αυτή περιγράφηκε για πρώτη φορά από τους Δ. Αγγουρά και Τ. Δόσιο επ' ευκαιρία μίας σχετικής περίπτωσης. Το σύνδρομο ακολουθεί παροχέτευση του περικαρδίου, εισβάλλει από λίγα λεπτά έως 48 ώρες μετά την παροχέτευση του υγρού και εκδηλώνεται ως πνευμονικό οίδημα ή καρδιογενές shock, με θνητότητα που ανέρχεται στο 30% (με κακή έκβαση να περιγράφεται κυρίως μετά από χειρουργική παροχέτευση η οποία συνεπάγεται άμεση και αιφνίδια αποσυμπίεση του περικαρδίου). Υπάρχουν διάφορες θεωρίες ως προς την παθογένεια του συνδρόμου. Η πλέον αληθοφανής είναι εκείνη στην οποία υποστηρίζεται ως υποκείμενος μηχανισμός η απότομη έκπτυξη των δεξιών καρδιακών κοιλοτήτων λόγω αυξημένης φλεβικής επιστροφής μετά την αποσυμπίεση του περικαρδίου η οποία γίνεται εις βάρος της αριστερής κοιλίας μέσω της διακοιλιακής αλληλεπίδρασης, με τελική συνέπεια την εκδήλωση κάμψης της αριστερής κοιλίας.

Τέλος ένα σημαντικός προβληματισμός που υπάρχει σε μεγάλες περικαρδιακές συλλογές με επικείμενο επιπωματισμό είναι ο χρονισμός της

παροχέτευσης του περικαρδιακού υγρού. Απάντηση σε αυτό το ερώτημα επιχειρεί να δώσει ένας πίνακας βαθμονόμησης κινδύνου που προτάθηκε από την ομάδα εργασίας περί των νόσων του περικαρδίου της Ευρωπαϊκής Καρδιολογικής Εταιρείας (Πίνακας 2). Ο πίνακας αυτός λαμβάνει υπόψη δεδομένα που αφορούν στην αιτιολογία, την κλινική εικόνα και τον απεικονιστικό έλεγχο προσδίδοντας ένα βαθμό σε κάθε επιμέρους συνιστώσα των τριών αυτών παραμέτρων. Εάν η συνολική βαθμολογία είναι  $\geq 6$  τότε απαιτείται άμεση παροχέτευση του υγρού λόγω του αυξημένου κινδύνου επικείμενης αιμοδυναμικής αστάθειας. Εάν αντίθετα το score είναι  $<6$  τότε η παροχέτευση μπορεί να καθυστερήσει 12-48 ώρες. Αυτή η πληροφορία είναι ιδιαίτερα σημαντική για λήψη αποφάσεων ειδικά σε κέντρα που δεν υπάρχει εμπειρία και υποδομές για τη παροχέτευση του περικαρδίου.

**Πίνακας 2.** Βαθμολογικό σύστημα επιλογής ασθενών υποψήφιων για άμεση περικαρδιοκέντηση.

<b>Βήμα 1: βαθμολόγηση αιτιολογίας</b>	
Κακοήθης νόσος	2
Φυματίωση	1
Πρόσφατη ακτινοβολία	1
Πρόσφατη ιογενής λοίμωξη	1
Υποτροπιάζουσα περικαρδιακή συλλογή, προηγηθείσα περικαρδιοκέντηση	1
Χρόνια τελικού σταδίου νεφρική νόσος	1
Ανοσοανεπάρκεια ή ανοσοκαταστολή	1
Υπο- ή υπερθυρεοειδισμός	-1
Συστηματική αυτοάνοση νόσος	-1
<b>Βήμα 2: Βαθμολόγηση κλινικών χαρακτηριστικών</b>	
Δύσπνοια-ταχύπνοια	1
Ορθόπνοια χωρίς υγρούς ήχους στην ακρόαση θώρακα	3
Αρτηριακή πίεση $<95$ mmHg	0,5
Επιδεινούμενη φλεβοκομβική ταχυκαρδία	1
Ολιγουρία	1
Παράδοξος σφυγμός $>10$ mmHg	2
Θωρακικό άλγος με χαρακτηριστικές περικαρδίτιδας	0,5

Περικαρδιακός ήχος τριβής	0,5
Ταχεία επιδείνωση των συμπτωμάτων	2
Βραδεία εξέλιξη της νόσου	-1

### **Βήμα 3: Βαθμολόγηση απεικονιστικών ευρημάτων**

Μεγαλοκαρδία στη ακτινογραφία θώρακα	1
Ηλεκτρική εναλλαγή στο ηλεκτροκαρδιογράφημα	0,5
Χαμηλά δυναμικά στο ηλεκτροκαρδιογράφημα	1
Κυκλοτερής περικαρδιακή συλλογή ( $>2$ cm στη διαστολή)	3
Μέτρια περικαρδιακή συλλογή (1-2cm στη διαστολή)	1
Μικρή περικαρδιακή συλλογή ( $<1$ cm στη διαστολή), μη τραυματικής αιτιολογίας	-1
Σύμπτωση δεξιού κόλπου $>1/3$ της διαστολικής περιόδου	1
Κάτω κοίλη φλέβα $>2,5$ cm με διακύμανση $<50\%$	1,5
Σύμπτωση δεξιάς κοιλίας (collapse)	1,5
Σύμπτωση αριστερού κόλπου	2
Αναπνευστικές μεταβολές στη διαμειτροειδική-διατριγλωχινική ροή	1
Αιωρούμενη καρδιά (swinging heart)	1

### **4. Υποτροπιάζουσα περικαρδίτιδα**

Η υποτροπιάζουσα περικαρδίτιδα αποτελεί την πιο συχνή επιπλοκή της οξείας περικαρδίτιδας. Πρώτη υποτροπή εμφανίζεται στο 15-30% των περιπτώσεων οξείας περικαρδίτιδας. Η πρώτη υποτροπή ακολουθείται από μία δεύτερη σε ποσοστό 25-50%, η τρίτη μετά από μια δεύτερη στο 20-40% (σε όλες τις περιπτώσεις το χαμηλότερο ποσοστό αφορά περιπτώσεις που χορηγήθηκε κολχικίνη ενώ το υψηλότερο σε εκείνες που δεν χορηγήθηκε). Πολλαπλές υποτροπές εμφανίζονται στο 6% περίπου των περιπτώσεων. Υποτροπή εμφανίζεται συνήθως 18-20 μήνες μετά το αρχικό επεισόδιο. Φαίνεται ότι όσο απομακρυνόμαστε χρονικά από το οξύ επεισόδιο, τόσο μειώνεται η πιθανότητα εμφάνισης υποτροπής.

Οι κλινική εικόνα των υποτροπών είναι κατά κανόνα παρόμοια με εκείνη του οξέος επεισοδίου, αν και οι κλινικές εκδηλώσεις είναι συνήθως η-

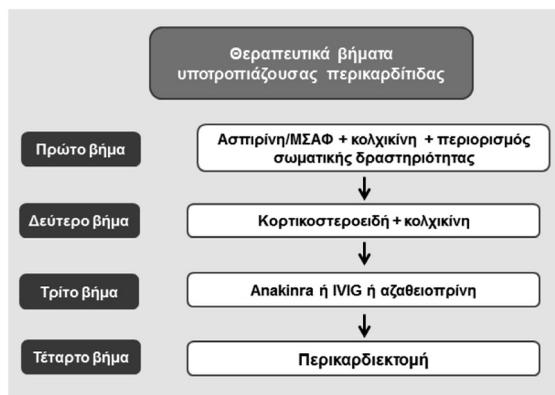
πιότερες αν και ο αριθμός των υποτροπών καθώς και τα μεσοδιαστήματα μεταξύ αυτών εμφανίζουν μεγάλες διακυμάνσεις μεταξύ των ασθενών. Επίσης η πιθανότητα επιπωματισμού είναι χαμηλότερη σε επόμενα επεισόδια σε σχέση με εκείνη του αρχικού επεισοδίου.

Θεραπευτικά στην υποτροπιάζουσα περικαρδίτιδα τα φάρμακα που χορηγούνται στην υποτροπιάζουσα περικαρδίτιδα είναι τα ίδια και με το ίδιο δοσολογικό σχήμα που εφαρμόζεται στο πρώτο επεισόδιο περικαρδίτιδας (Εμπειρικά και σύμφωνα με γνώμες ειδικών ωστόσο, η διάρκεια θεραπείας θα πρέπει να είναι μεγαλύτερη (πιθανότερα διπλάσια) σε σχέση με το πρώτο επεισόδιο.

Χειρουργικό ενδιαφέρον σε υποτροπιάζουσα περικαρδίτιδα έχουν εξαιρετικά επιλεγμένες περιπτώσεις στις οποίες έχουν αποτύχει όλα τα συντηρητικά μέτρα. Σε αυτές τις περιπτώσεις η ολική περικαρδιεκτομή θα πρέπει να εξετάζεται σαν τελευταία θεραπευτική προσέγγιση. Συγκεκριμένα η περικαρδιεκτομή αποτελεί θεραπευτική επιλογή σε ασθενείς με συχνές, έντονα συμπτωματικές και δυσχερώς η μη ελεγχόμενες φαρμακευτικά υποτροπές, και σε εκείνους με μείζονες επιπλοκές από τη φαρμακευτική αγωγή και κυρίως από τη μακροχρόνια χορήγηση κορτικοστεροειδών. Επίσης, υποψήφιοι είναι και οι σπάνιοι ασθενείς με υποτροπιάζοντα επεισόδια καρδιακού επιπωματισμού. Κατά την χειρουργική επέμβαση θα πρέπει να καταβάλλεται κάθε προσπάθεια να αφαιρεθεί το σύνολο του περικαρδίου, διαφορετικά τα συμπτώματα μπορεί να επιμείνουν. Με τις σύγχρονες χειρουργικές τεχνικές σε εξειδικευμένα κέντρα η περιεγχειριρτική θνητότητα είναι μηδενική ενώ το ποσοστό μείζονων επιπλοκών είναι 3%.

Στην Εικόνα 7 αναπαράγονται οι οδηγίες για την θεραπευτική αντιμετώπισης της υποτροπιάζουσας περικαρδίτιδας σύμφωνα με τις κατευθυντήριες οδηγίες της Ευρωπαϊκής καρδιολογικής Εταιρίας. Όπως φαίνεται η περικαρδιεκτομή αποτελεί την τελευταία επιλογή (4<sup>ο</sup> βήμα) μετά από αποτυχία των προηγούμενων τριών.

Σε σχέση με την πρόγνωση η υποτροπιάζουσα περικαρδίτιδα, σε αντίθεση με την αρνητική επίπτωση που επιφέρει στην ποιότητα ζωής των ασθενών, έχει καλή μακροχρόνια πρόγνωση. Βά-



Εικόνα 7. Αλγόριθμος αντιμετώπισης υποτροπιάζουσας περικαρδίτιδας βάσει των συστάσεων της Ευρωπαϊκής καρδιολογικής Εταιρίας. ΜΣΑΦ=Μη Στεροειδή Αντιφλεγμονώδη Φάρμακα. IVIG=Ενδοφλέβια χορηγούμενες ανθρώπινες ανοσοσφαιρίνες.

σει αποτελεσμάτων μετανalύσεων, καρδιακός επιπωματισμός καταγράφεται στο 3,5% των περιπτώσεων, ενώ σε καμία περίπτωση δεν παρατηρείται εμφάνιση δυσλειτουργίας της αριστερής κοιλίας σε μέση περίοδο παρακολούθησης 60 μηνών. Το ποσοστό συμπτωτικής περικαρδίτιδας είναι περιέργως ακόμη χαμηλότερο και από εκείνο της οξείας ιδιοπαθούς περικαρδίτιδας (0,3% έναντι ~1% αντίστοιχα).

### 5. Χρόνια συμπτωτική περικαρδίτιδα

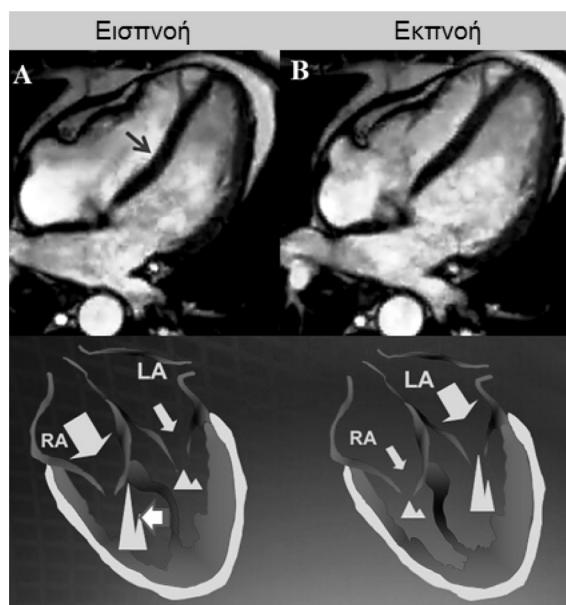
Η χρόνια συμπτωτική περικαρδίτιδα αν και δεν είναι τόσο συχνή επιπλοκή (σε περίοδο παρακολούθησης 60 μηνών τα ποσοστά εμφάνισης της στις ανεπτυγμένες χώρες είναι 0,48% για τις ιδιοπαθείς μορφές και 8,3% για τις δευτεροπαθείς μορφές), αποτελεί ιδιαίτερα προβληματική κλινική οντότητα και σε ότι αφορά στη διάγνωση, αλλά και στη θεραπευτική της αντιμετώπιση. Η χρόνια συμπτωτική περικαρδίτιδα είναι το αποτέλεσμα της εκφύλισης πάχυνσης και τελικά σύντηξης, ουλοποίησης και συχνά ασβέστωσης των περικαρδιακών πετάλων, με τελικό αποτέλεσμα την απώλεια της ελαστικότητας του περικαρδιακού σάκου.

Στις ανεπτυγμένες χώρες το συχνότερο αίτιο χρόνιας συμπτωτικής περικαρδίτιδας είναι η ιδιοπαθής μορφή σε ποσοστό 37% επί του συνόλου των περιπτώσεων και ακολουθεί η χρόνια συμπτωτική περικαρδίτιδα μετά από καρδιοχειρουργική επέμβαση. Σε αντίθεση με τις δυτικές κοινωνίες, η αιτιολογία στις υπό ανάπτυξη χώρες διαφέρει σημαντικά, με

τη φυματιώδη αιτιολογία να είναι το αίτιο στο 65% των περιπτώσεων, με δεύτερη σε συχνότητα την ιδιοπαθή μορφή.

Στη συμπιεστική περικαρδίτιδα, το ανελαστικό και ανένδοτο περικάρδιο αναστέλλει τη μετάδοση των αναπνευστικών μεταβολών των ενδοθωρακικών πιέσεων στις καρδιακές κοιλότητες. Συγκεκριμένα, κατά τη φάση της εισπνοής ενώ η μείωση της ενδοθωρακικής πίεσης προκαλεί μείωση της πίεσης στις πνευμονικές φλέβες (που είναι ενδοθωρακικά αγγεία), η πίεση στις αριστερές καρδιακές κοιλότητες παραμένει ανεπηρέαστη. Κατά συνέπεια η κλίση πίεσεως μεταξύ πνευμονικών φλεβών και του αριστερού κόλπου μειώνεται, κάτι που οδηγεί σε μειωμένη προφόρτιση αριστερής κοιλίας. Η μειωμένη διαστολική πλήρωση της αριστερής κοιλίας συνδυάζεται με ταυτόχρονη αύξηση της διαστολικής πλήρωσης της δεξιάς κοιλίας λόγω της αυξημένης φλεβικής επιστροφής (η ροή στην κάτω κοίλη φλέβα δεν επηρεάζεται από το καθεστώς ενδοθωρακικών πιέσεων, δεδομένου ότι εκτός από τα τελικά 1-2cm η κάτω κοίλη έχει εξωθωρακική πορεία). Η αύξηση του όγκου της δεξιάς κοιλίας δεν είναι διαχειρίσιμη από το ανελαστικό περικάρδιο με αποτέλεσμα τη μετατόπιση του μεσοκοιλιακού διαφράγματος προς τα αριστερά, κάτι που μειώνει ακόμη περισσότερο τη διαστολική πλήρωση της αριστερής κοιλίας (Εικόνα 8). Η παθολογική αυτή κίνηση του μεσοκοιλιακού διαφράγματος (αναπήδηση - bounce), είναι κεντρική εκδήλωση της συμπιεστικής περικαρδίτιδας και αποτελεί μεγιστοποίηση του φυσιολογικού φαινομένου της διακοιλιακής αλληλεξάρτησης (inter-ventricular interdependence).

Οι ασθενείς με συμπιεστική περικαρδίτιδα εμφανίζονται με δύο κατηγορίες συμπτωμάτων. Η πρώτη οφείλεται σε δεξιά καρδιακή ανεπάρκεια και εκδηλώνεται κλινικά με περιφερικά οίδημα ή οίδημα ανά σάρκα ανάλογα με το στάδιο της νόσου. Η συμπιεστική περικαρδίτιδα θα πρέπει να συμπεριλαμβάνεται στη διαφορική διάγνωση ασθενών η οποίοι παρουσιάζουν συμπτώματα δεξιάς καρδιακής ανεπάρκειας, ειδικά όταν στο ιστορικό τους υπάρχει μία από τις καταστάσεις που μπορεί να ευθύνονται για εμφάνιση συμπιεστικής περικαρδίτιδας. Η δεύτερη κατηγορία συ-

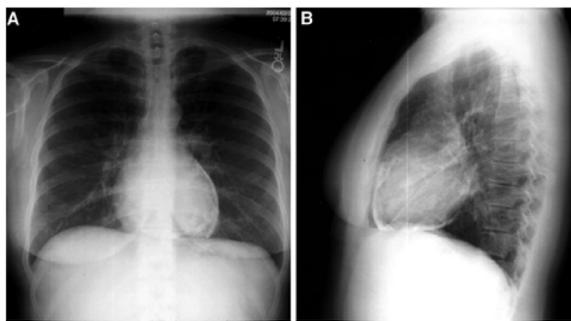


Εικόνα 8. Μαγνητική καρδιάς στην οποία φαίνεται η παθολογική εισπνευστική αναπήδηση (bounce) του μεσοκοιλιακού διαφράγματος σε ασθενή με συμπιεστική περικαρδίτιδα (βέλος). Στο κάτω πλαίσιο σχηματική απεικόνιση του φαινομένου. LA=αριστερός κόλπος, RA=δεξιός κόλπος. Τροποποιημένη από Wann S et al. *J Am Soc Echocardiogr* 2008;21:7-13.

μπτωμάτων συνδέεται με τη χαμηλή καρδιακή παροχή και εκδηλώνεται με εύκολη κόπωση και δύσπνοια προσπαθείας.

Διαγνωστικά η παρουσία ασβέστωσης στην ακτινογραφία θώρακα σε ασθενή με σημειολογία δεξιάς καρδιακής ανεπάρκειας είναι ισχυρά ενδεικτική συμπιεστικής περικαρδίτιδας. Η ασβέστωση του περικαρδίου είναι πιο εμφανής στην πλαγία λήψη (Εικόνα 9). Παρατηρείται στο 27% ασθενών με συμπιεστική περικαρδίτιδα, ωστόσο η απουσία της δεν αποκλείει την πάθηση. Παρομοίως, ασβέστωση του περικαρδίου μπορεί να παρατηρηθεί και χωρίς κλινική εικόνα συμπιεστικής περικαρδίτιδας. Στις τελευταίες περιπτώσεις όμως είναι πιο αδρή και συνήθως τμηματική.

Το ηχοκαρδιογράφημα παρέχει πολύτιμες πληροφορίες στη διάγνωση με κεντρικά ευρήματα την αναπήδηση (bounce) του μεσοκοιλιακού διαφράγματος, τη διάταση και μειωμένη αναπνευστική διακύμανση της κάτω κοίλης φλέβας, την επικράτηση του επάρματος E στην διαμυοειδική ροή (E>A) με μεγάλη διακύμανση αυτού (>30%) με τις αναπνευστικές κινήσεις, την εκ-



Εικόνα 9. Ασβέσωση του περικαρδίου σε ασθενή με συμπιεστική περικαρδίτιδα.

πνευστική μείωση του επάρματος D στις ηπατικές φλέβες με παλμικό Doppler, και το σημείο mitral annulus reversus στο μιτροειδικό δακτύλιο με τη μελέτη των ιστικών ταχυτήτων (μικρότερες ιστικές ταχύτητες στον πλάγιο μιτροειδικό δακτύλιο σε σχέση με εκείνες του μέσου). Επίσης η αξονική και μαγνητική τομογραφία καρδιάς, μπορεί να προσφέρουν πολύτιμα στοιχεία στην τεκμηρίωση της διάγνωσης της συμπιεστικής περικαρδίτιδας. Κατ' αρχήν και με τις δύο τεχνικές είναι δυνατή η ακριβής μέτρηση του πάχους του περικαρδίου. Το φυσιολογικό πάχος του περικαρδίου είναι  $<2\text{mm}$ . Πάχος μεγαλύτερο των  $4\text{mm}$ , με συμβατή κλινική εικόνα, υποδηλώνει συμπιεστική περικαρδίτιδα, ενώ πάχος  $>6\text{mm}$  έχει υψηλή ειδικότητα για τη διάγνωση της. Ωστόσο, επισημαίνεται ότι το φυσιολογικό πάχος περικαρδίου δεν αποκλείει τη διάγνωση της συμπιεστικής περικαρδίτιδας.

Ο καρδιακός καθετηριασμός αναδεικνύει τις αιμοδυναμικές διαταραχές που οφείλονται στη συμπιεστική περικαρδίτιδα και αποτελεί πολύτιμο «εργαλείο» στη διαφορική της διάγνωση από την περιοριστική μυοκαρδιοπάθεια. Με τις σύγχρονες ωστόσο απεικονιστικές τεχνικές σπάνια και μόνο σε αμφίβολες περιπτώσεις πλέον απαιτείται. Το χαρακτηριστικό εύρημα επί συμπιεστικής περικαρδίτιδας στον καρδιακό καθετηριασμό που αναδεικνύει τον παθολογικό τύπο πλήρωσης, είναι το σημείο deep and plateau ή σημείο της τετραγωνικής ρίζας στην σύγχρονη καταγραφή των πιέσεων της αριστερής και δεξιάς κοιλίας.

Θεραπευτικά, η μοναδική ριζική θεραπεία της χρόνιας συμπιεστικής περικαρδίτιδας είναι η ολική χειρουργική περικαρδικτομή. Ωστόσο, ακόμη και στα πλέον εξειδικευμένα κέντρα η χειρουργική

θνητότητα είναι υψηλή και κυμαίνεται από 4-12%. Επιπρόσθετα, πλήρης αποκατάσταση των αιμοδυναμικών διαταραχών μετεγχειρητικά παρατηρείται στο ~60% των ασθενών περίπου. Ασθενείς με μυοκαρδιακή ίνωση-ατροφία έχουν μεγαλύτερη περιεγχειρητική θνητότητα και δυσμενέστερη έκβαση. Η απουσία επικαρδιακού λίπους στην αξονική καρδιάς μαζί με την λέπτυνση των τοιχωμάτων ( $<1\text{cm}$  για το μεσοκοιλιακό διάφραγμα και το οπισθοπλάγιο τοίχωμα), καθώς και η μείωση της συστολικής πάχυνσης αποτελούν έμμεσες ενδείξεις μυοκαρδιακής ίνωσης. Επίσης, η μεγάλη διάρκεια των συμπτωμάτων πριν την χειρουργική επέμβαση αποτελούν δυσμενή προγνωστικά παράγοντα και συνδυάζονται με σύνδρομο χαμηλής παροχής μετεγχειρητικά σε ποσοστό έως και 28%. Και σε αυτή την περίπτωση ενοχοποιείται η ατροφία του μυοκαρδίου, το οποίο παροδικά ή μόνιμα δεν μπορεί να ανταποκριθεί μετεγχειρητικά στις νέες αιμοδυναμικές συνθήκες.

Η περικαρδικτομή πρέπει να είναι όσο το δυνατόν πληρέστερη και να αφορά αμφότερα τα πέταλα του περικαρδίου (σπλαχνικό και τοιχωματικό) με προσοχή να μην γίνει χειρουργική κάκωση των φρενικών νεύρων. Για να γίνει πλήρης αποφλοιώση του περικαρδίου (που περιλαμβάνει απελευθέρωση του δεξιού κόλπου, την άνω κοίλη και κυρίως την κάτω κοίλη και το παρακείμενο στο διάφραγμα τμήμα της δεξιάς κοιλίας) απαιτείται μέση στερνοτομή ενώ με την πρόσθιοπλάγια θωρακοτομή μπορεί να πραγματοποιηθεί μόνο μερική αποφλοιώση. Εξωσωματική κυκλοφορία απαιτείται σε συνύπαρξη άλλης καρδιακής παθολογίας που χρήζει αντιμετώπισης στον ίδιο χρόνο, ενώ θα πρέπει να είναι διαθέσιμη για την αντιμετώπιση αιμορραγικών επιπλοκών κατά τη διάρκεια της επέμβασης.

Από τους συνήθως προσδιοριζόμενους κλινικούς και εργαστηριακούς δείκτες σε ασθενείς που υποβλήθηκαν σε περικαρδικτομή, οι δείκτες που συνδυάστηκαν με πτωχή συνολική επιβίωση ήταν η επηρεασμένη νεφρική λειτουργία, η υψηλή συστολική πίεση στην πνευμονική αρτηρία, η επηρεασμένη συσπαστικότητα της αριστερής κοιλίας, το χαμηλό νάτριο ορού και η μεγαλύτερη ηλικία. Η ασβέσωση του περικαρδίου αντίθετα, δεν φαίνεται να είχε επίπτωση στην επιβίωση. Α-

σθενείς με ιστορικό ακτινοβολίας είχαν τη χειρότερη επιβίωση, ενώ την καλύτερη πρόγνωση την είχαν οι ασθενείς με ιδιοπαθή συμπίεστική περικαρδίτιδα. Δεν συνιστάται χειρουργική αντιμετώπιση σε ασθενείς σε λειτουργική κατηγορία IV κατά NYHA λόγω της πολύ υψηλής διεγχειρητικής θνητότητας και σε ασθενείς σε ασυμπτωματικούς ασθενείς σε πολύ πρώιμα στάδια της νόσου σε (λειτουργικό στάδιο I), χωρίς χρήση διουρητικών. Ωστόσο οι τελευταίοι θα πρέπει να παρακολουθούνται στενά για ενδεχόμενη εμφάνιση συμπτωμάτων.

Τέλος στο ευρύτερο κεφάλαιο της συμπίεστικής περικαρδίτιδας, η υγρή-συμπίεστική περικαρδίτιδα (effusive-constrictive pericarditis) είναι ένα ασύνηθες περικαρδιακό σύνδρομο, το οποίο μπορεί να διαλάβει σε ασθενείς οι οποίοι παρουσιάζονται αρχικά με καρδιακό επιπολισμό. Περιλαμβάνει ταυτόχρονη παρουσία περικαρδιακού υγρού υπό πίεση και καρδιακής συμπίεσης. Το χαρακτηριστικό γνώρισμα της πάθησης είναι ότι μετά την αφαίρεση του περικαρδιακού υγρού η πίεση του δεξιού κόλπου παραμένει αυξημένη. Η θεραπεία εκλογής και σε αυτή την περίπτωση είναι η ολική χειρουργική περικαρδιακτομή, που θα πρέπει να περιλαμβάνει και το σπλαχνικό περικάρδιο.

### 6. Χρόνια περικαρδιακή συλλογή υγρού

Χρόνια περικαρδιακή συλλογή ορίζεται η συλλογή που χρονολογείται τουλάχιστον από 3μήνου. Όπως προαναφέρθηκε η περικαρδιακή κοιλότητα περιέχει σε φυσιολογικές συνθήκες 15-50 ml περικαρδιακού υγρού το οποίο πιστεύεται ότι παράγεται από το περισπλάγιο πέταλο του ορογόνου χιτώνα. Σε διάφορες καταστάσεις όπως φλεγμονή, κακοήθειες, καρδιακή ανεπάρκεια κλπ., η ποσότητα του υγρού αυξάνει είτε λόγω αυξημένης παραγωγής είτε λόγω μειωμένης απορρόφησης, με συνέπεια να παρατηρείται άλλοτε άλλου βαθμού περικαρδιακή συλλογή υγρού.

Η ανίχνευση περικαρδιακής συλλογής υγρού είναι σχετικά σπάνια εύρημα στην καθημερινή κλινική πράξη είτε ως τυχαίο εύρημα, είτε ως εκδήλωση συστηματικής ή καρδιακής νόσου. Το φάσμα των περικαρδιακών συλλογών είναι ευρύ

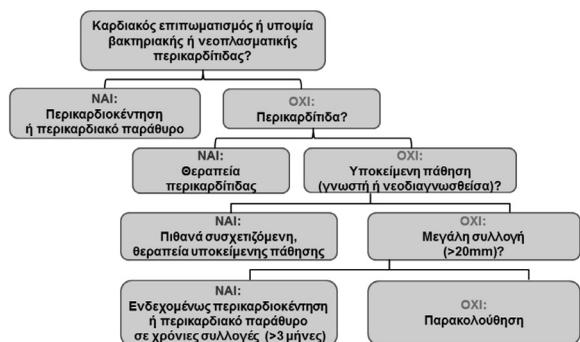
και περιλαμβάνει από μικρές περικαρδιακές συλλογές, έως μεγάλες συλλογές με ή χωρίς επιπολισμό. Τα επιδημιολογικά δεδομένα που αφορούν στην επίπτωση και τον επιπολισμό της περικαρδιακής συλλογής υγρού είναι πτωχά. Από στοιχεία που προέρχονται από τριτοβάθμια κέντρα αναφοράς για παθήσεις του περικαρδίου, η μέση ετήσια επίπτωση περικαρδιακών συλλογών ήταν 3% ενώ ο αντίστοιχος επιπολισμός 9%.

Αν και όλα τα πιθανά αίτια περικαρδιακής νόσου μπορεί να αποτελέσουν και αίτια περικαρδιακής συλλογής υγρού το συχνότερο αίτιο χρόνιων συλλογών είναι οι ιδιοπαθείς μορφές (ποσοστό 50%). Στην υποομάδα των ασθενών με μέτρια και μεγάλη ποσότητα υγρού, υποκείμενο (δευτεροπαθές) αίτιο εντοπίζεται στο ~50-60% των περιπτώσεων.

Το ηχοκαρδιογράφημα αποτελεί εξαιρετικά ευαίσθητη αλλά και ειδική μέθοδο για την ανίχνευση περικαρδιακής συλλογής υγρού, καθώς και πολύτιμο διαγνωστικό μέσο για τη διαχρονική παρακολούθηση αυτών των ασθενών. Με τη μέτρηση της διαμέτρου του περικαρδιακού υγρού στη διαστολή (χώρος ελεύθερος υπερήχων μεταξύ των δύο πετάλων του περικαρδίου) οι περικαρδιακές συλλογές χαρακτηρίζονται μικρές όταν η διάμετρος είναι <1cm, μέτριες όταν η διάμετρος είναι >1cm και <2cm και μεγάλες όταν η διάμετρος είναι >2cm.

Η αξονική και η μαγνητική τομογραφία έχουν εξαιρετική διαγνωστική ακρίβεια σε ότι αφορά στην ανίχνευση της περικαρδιακής συλλογής υγρού αλλά και στην ανάδειξη των αιτίων που την προκαλούν (παρουσία μαζών, λεμφαδένων κλπ), χωρίς εξάρτηση από την ποιότητα του ακουστικού παραθύρου. Η αξονική τομογραφία επίσης με τον προσδιορισμό των τιμών εξασθένησης (attenuation values), μπορεί να βοηθήσει στη διαφορική διάγνωση εξιδρωματικής συλλογής (20-60 μονάδες Hounsfield) και απλών διδρωματικών συλλογών (τιμές Hounsfield <10, όπως οι αντίστοιχες του νερού), ενώ στις αιμορραγικές συλλογές οι συνήθεις τιμές είναι >60.

Στην Εικόνα 10 συνοψίζεται ο θεραπευτικός αλγόριθμος που προτείνεται από την Ευρωπαϊκή Καρδιολογική Εταιρία για την αντιμετώπιση των χρόνιων περικαρδιακών συλλογών υγρού.



Εικόνα 10. Αλγόριθμος διαγνωστικής-θεραπευτικής προσέγγισης ασθενών με περικαρδιακή συλλογή υγρού.

Όπως προαναφέρθηκε σε περιπτώσεις καρδιακού επιπωματισμού η περικαρδιοκέντηση (ή εναλλακτική προσέγγιση όπως η χειρουργική διάνοιξη περικαρδιακού «παράθυρου») πρέπει να πραγματοποιηθεί άμεσα. Η χειρουργική διάνοιξη όπως ήδη ειπώθηκε προτιμάται σε περιπτώσεις που το υγρό για τεχνικούς λόγους δεν είναι προσπελάσιμο με περικαρδιοκέντηση, σε πυώδη περικαρδίτιδα για τοπικό καθαρισμό-λύση συμφύσεων, σε νεοπλασματική για πρόληψη υποτροπών και σε περιπτώσεις που απαιτείται βιοψία για διαφοροδιαγνωστικούς λόγους.

Σε ότι αφορά στην πρόγνωση, αυτή είναι πολύ καλή σε μικρές ιδιοπαθείς συλλογές. Επίσης σχετικά καλή είναι πρόγνωση και στις μέτριες και μεγάλες (ιδιοπαθείς) ασυμπτωματικές περικαρδιακές συλλογές υγρού με εμφάνιση επιπωματισμού σε μακροχρόνια περίοδο παρακολούθησης σε ποσοστό 8-30%. Στις τελευταίες περιπτώσεις συνιστάται ηχοκαρδιογραφική παρακολούθηση ανά 3 με 6 μήνες.

## ΕΠΙΛΕΓΜΕΝΕΣ ΜΟΡΦΕΣ ΠΕΡΙΚΑΡΔΙΤΙΔΑΣ ΜΕ (ΚΑΡΔΙΟ)ΧΕΙΡΟΥΡΓΙΚΗ ΕΜΠΛΟΚΗ

### 1. Σύνδρομο μετά περικαρδιοτομή

Το σύνδρομο μετά περικαρδιοτομή είναι μία προβληματική επιπλοκή μετά από καρδιοχειρουργική επέμβαση και συγκαταλέγεται στις δευτεροπαθείς μορφές περικαρδίτιδας, ειδικότερα στα αποκαλούμενα σύνδρομα μετά από περικαρδιακή βλάβη (Post pericardial injury syndromes ή post cardiac injury syndromes) Αποτελεί αρκετά συχνό αίτιο υποτροπιάζουσας περικαρδίτιδας.

Εκδηλώνεται από λίγες ημέρες έως αρκετές εβδομάδες μετά τη χειρουργική επέμβαση. Η επίπτωση του συνδρόμου υπολογίζεται σε 10-40% των ασθενών που υποβάλλονται σε καρδιοχειρουργική επέμβαση και η ευρεία διακύμανση του ποσοστού οφείλεται στα διαγνωστικά κριτήρια που έχουν υιοθετηθεί, από το είδος της καρδιοχειρουργικής επέμβασης, καθώς και από το καρδιοχειρουργικό κέντρο.

Παθογενετικά θεωρείται ότι η αρχική ιατρογενής κάκωση του περικαρδίου και του υπεζωκότα ευθύνεται για τις αιματηρές συλλογές που εμφανίζονται τις πρώτες μετεγχειρητικές ημέρες. Ωστόσο, από την κάκωση απελευθερώνονται και αντιγόνα που προέρχονται από τους δύο ορογόνους. Τα αντιγόνα δεσμεύονται από ειδικά κύτταρα (antigen presenting cells) και παρουσιάζονται στο ανοσοποιητικό σύστημα. Ακολουθεί διέγερση της χυμικής και κυτταρικής ανοσίας με επακόλουθο φλεγμονή των ιστών στόχων (περικαρδίου, υπεζωκότα ή και των δύο).

Η διάγνωση του συνδρόμου μετά περικαρδιοτομή είναι κλινική και βασίζεται στην ύπαρξη τουλάχιστον 2 από τα παρακάτω κριτήρια. Πυρετός μετά την πρώτη μετεγχειρητική εβδομάδα χωρίς ενδείξεις συστηματικής ή τοπικής λοίμωξης, πλευριτικού τύπου άλγος, περικαρδιακός ήχος τριβής, παρουσία πλευριτικής συλλογής, παρουσία περικαρδιακής συλλογής.

Οι πλευριτικές και περικαρδιακές συλλογές εντάσσονται σε ένα ευρύ κλινικό φάσμα που περιλαμβάνει από ασυμπτωματικές συλλογές, έως ευμεγέθεις συλλογές που προκαλούν είτε αναπνευστική δυσχέρεια (πλευριτικές συλλογές) είτε καρδιακό επιπωματισμό (περικαρδιακές). Οι συλλογές που εμφανίζονται άμεσα μετεγχειρητικά ή σε κάθε περιπτώσεις στις πρώτες μετεγχειρητικές ημέρες, εντάσσονται στο πλαίσιο των «μη ειδικών» μετεγχειρητικών συλλογών που είναι ουσιαστικά το αποτέλεσμα του χειρουργικού τραύματος.

Η συχνότητα περικαρδιακών συλλογών μετά από καρδιοχειρουργική επέμβαση υπολογίζεται μεταξύ 20-30%. Ευμεγέθεις κλινικά σημαντικές περικαρδιακές συλλογές, για τις οποίες απαιτείται ειδική αντιμετώπιση (φαρμακευτική ή επεμβατική με παροχέτευση του υγρού) και παρατεί-

νουν την παραμονή στο νοσοκομείο περιγράφονται στο ~1,5% των περιπτώσεων. Η πιθανότητα εμφάνισης περικαρδιακών συλλογών είναι χαμηλότερη σε επανεπεμβάσεις (redo - πιθανότατα λόγω συμφύσεων) και υψηλότερη σε ασθενείς στους οποίους διανοίγεται ο αριστερός υπεζωκοτικός χώρος κατά τη διαδικασία παρασκευής της έσω μαστικής αρτηρίας. Εμφανίζονται με μεγαλύτερη συχνότητα σε επεμβάσεις στις καρδιακές βαλβίδες, σε ανεύρυσμα αορτής, σε καρδιακή μεταμόσχευση, σε ασθενείς με νεφρική ανεπάρκεια, σε αυξημένο χρόνο εξωσωματικής κυκλοφορίας και σε επείγουσα καρδιοχειρουργική επέμβαση. Επιπωματισμός αναπτύσσεται σε ποσοστό 1-2% συχνά με αμβληγρά συμπτώματα. Στις περισσότερες περιπτώσεις εκδηλώνεται μετά την 7<sup>η</sup> μεταχειρητική ημέρα, συχνά όταν ο ασθενής έχει λάβει εξιτήριο από το νοσοκομείο.

Η συχνότητα πλευριτικών συλλογών μετά από καρδιοχειρουργική επέμβαση κυμαίνεται από 45-62%. Συνήθως είναι καλοήθης, μη ειδικές, ετερόπλευρες (κυρίως αριστερά) και περιγράφονται συχνότερα μετά από επέμβαση αορτοστεφανιαίας παράκαμψης με χρήση της έσω μαστικής αρτηρίας. Ωστόσο, περίπου 10-20% ασθενών έχει μεγαλύτερες συλλογές, ενώ το 10% των ασθενών που υποβάλλεται σε αορτοστεφανιαία παράκαμψη έχει συλλογές που καταλαμβάνουν >25% του ημιθωρακίου. Συνήθως υποστρέφουν μετά από χρονικό διάστημα 1 έτους.

Σε σχέση με τη θεραπεία πολλές από τις συλλογές που εμφανίζονται στα πλαίσια του συνδρόμου μετά περικαρδιοτομή είναι ασυμπτωματικές και υποστρέφουν χωρίς καμία παρέμβαση. Στον αντίποδα, σε μεγάλες συμπτωματικές περικαρδιακές ή πλευριτικές συλλογές, μπορεί να απαιτηθεί είτε φαρμακευτική παρέμβαση είτε παροχέτευση της συλλογής.

Σε ότι αφορά στην παροχέτευση του περικαρδιακού υγρού έχει απόλυτη ένδειξη σε καρδιακό επιπωματισμό που εμφανίζεται σε ποσοστό 1-2%. Πιθανά θα πρέπει επίσης να πραγματοποιείται σε παρουσία μεγάλης συλλογής (>20mm) όταν συνυπάρχει διαστολική σύμπτωση των δεξιών καρδιακών κοιλοτήτων. Οι συμπτωματικές πλευριτικές συλλογές θα πρέπει αντιμετωπίζονται με διαδερμική παροχέτευση. Οι συλλογές μακρο-

πρόθεσμα έχουν την τάση να εγκυστώνονται γεγονός που καθιστά δυσχερή την παροχέτευση τους.

Η φαρμακευτική αντιμετώπιση του συνδρόμου είναι εμπειρική. Παραδοσιακά έχουν χρησιμοποιηθεί η ασπιρίνη, τα μη στεροειδή αντιφλεγμονώδη και τα κορτικοστεροειδή τα οποία παρότι δεν υπάρχουν δεδομένα από τυχαιοποιημένες μελέτες φαίνεται ότι είναι περισσότερο αποτελεσματικά. Στις τυχαιοποιημένες μελέτες POPE και POPE-2 αντίστοιχα η δικλοφενάκη και η κολχικίνη δεν ήταν αποτελεσματικά στη μείωση της ποσότητας της συλλογής, ούτε την αώτερη εκδήλωση καρδιακού επιπωματισμού. Αντίθετα για την πρόληψη του συνδρόμου έχει χρησιμοποιηθεί με επιτυχία η κολχικίνη όπως φάνηκε από τις τυχαιοποιημένες μελέτες COPPS ΚΑΙ COPPS 2.

Η πρόγνωση του συνδρόμου μετά περικαρδιοτομή είναι καλή με δεδομένο ότι οι σοβαρές επιπλοκές είναι σπάνιες. Σε περίοδο παρακολούθησης περίπου 20 μηνών, η επίπτωση καρδιακού επιπωματισμού ήταν 2%, των υποτροπών 3,7% ενώ δεν αναφέρθηκαν περιπτώσεις συμπιεστικής περικαρδίτιδας. Δεν παύει ωστόσο η πάθηση να είναι προβληματική γιατί συνεπάγεται μεγαλύτερο χρόνο παραμονής στο καρδιοχειρουργικό τμήμα, μεγαλύτερη περίοδο αποθεραπείας και περισσότερες επανεισαγωγές.

## 2. Χυλοπερικάρδιο

Το χυλοπερικάρδιο αναφέρεται σε περικαρδικά συλλογή από χυλό που είναι το περιεχόμενο των λεμφαγγείων. Αποτελεί σπάνια οντότητα η οποία είναι είτε πρωτοπαθής είναι δευτεροπαθής συνεπεία τραύματος του μείζονος θωρακικού πόρου (ιατρογενούς -συνήθως στα πλαίσια επεμβάσεως διόρθωσης συγγενών καρδιοπαθειών). Συχνά συνοδεύεται από χυλοθώρακα και δυναμικά μπορεί να επιπλακεί με καρδιακό επιπωματισμό, οξεία περικαρδίτιδα και χρόνια συμπιεστική περικαρδίτιδα. Το περικαρδιακό υγρό σε περίπτωση χυλοθώρακα είναι γαλακτώδες με περιεκτικότητα σε τριγλυκερίδια >500mg/dL και λόγο χοληστερόλης/τριγλυκερίδια<1 (Εικόνα 11).

Σε μεγάλες συμπτωματικές συλλογές η θεραπεία συνίσταται σε παροχέτευση με ταυτόχρονη παρεντερική σίτιση με ή χωρίς θεραπεία με ο-



Εικόνα 11. Μεγάλη περικαρδιακή συλλογή με γαλακτώδες περικαρδιακό υγρό οφειλόμενο σε χυλοθώρακα.

κτρεοτίδη. Επί αποτυχίας έχει ένδειξη η απολίπωση του θωρακικού πόρου. Χρήσιμη στη διάγνωση είναι η αξονική τομογραφία στην οποία

το περιεχόμενο της περικαρδιακής κοιλότητας έχει αρνητικές τιμές εξασθένησης (Hounsfield units).

Το χυλοπερικάρδιο δεν πρέπει να συγχέεται με την περικαρδίτιδα από χοληστερόλη (cholesterol pericarditis) στην οποία το περικαρδιακό υγρό είναι διαυγές και περιέχει κρυστάλλους χοληστερόλης. Η συγκέντρωση χοληστερόλης στο περικαρδιακό υγρό είναι ίση ή μεγαλύτερη από εκείνη του ορού. Παρατηρείται σε περιπτώσεις φυματιώδους περικαρδίτιδας, ρευματοειδούς αρθρίτιδας και τραύματος. Η περικαρδιοκέντηση είναι σπάνια αποτελεσματική και η ιδανική θεραπεία περιλαμβάνει ολική περικαρδιοεκτομή και θεραπεία του υποκείμενου αιτίου.

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# Preoperative detection and management of immune heparin-induced thrombocytopenia in patients undergoing heart surgery with iloprost

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## ABSTRACT

**Objective:** The objective of this study was to evaluate our protocol for the identification and management of patients with immune heparin-induced thrombocytopenia undergoing cardiac surgery.

**Methods:** Among 1518 patients who underwent cardiac surgery between June 1998 and May 2001, 32 (2.1%) presented with platelet counts less than 150,000/mm<sup>3</sup> preoperatively or a history of prolonged (>3 days) intravenous exposure to heparin or both. These 32 patients were evaluated with an enzyme-linked immunosorbent assay for antibodies against heparin-platelet factor 4 complex. Platelets of patients with detected antibodies were tested with the prostacyclin analog iloprost for inhibition of heparin aggregation and determination of the inhibiting concentration and corresponding intravenous infusion rate of iloprost. Patients with antibodies received heparin after complete platelet inhibition with iloprost infusion. Hypotension was prevented or treated with intravenous noradrenaline. Ten randomly selected patients with similar preoperative characteristics, no previous extended exposure to heparin, and normal platelet counts served as controls.

**Results:** Ten of the 32 patients (group A, 31.3%) and none of the controls had antibodies against heparin-platelet factor 4 complex. Patients in group A underwent surgery with iloprost (6-24 ng · kg<sup>-1</sup> · min<sup>-1</sup>) and had their blood pressure maintained at greater than 95 mm Hg with norepinephrine infusion (1-4 μg · kg<sup>-1</sup> · min<sup>-1</sup>). Operative

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mortality was zero. There were no thrombotic complications or bleeding requiring exploration. One patient in group A bled 1310 mL/6 hours but did not need exploration. There was no difference in postoperative blood loss and morbidity between groups. Platelet counts were reduced by  $12.5\% \pm 8.7\%$  (group A) and  $38.1\% \pm 15.2\%$  (control) ( $P < .001$ ) 1 hour postoperatively and reached preoperative values by the fifth postoperative day.

**Conclusions:** Immune heparin-induced thrombocytopenia can be detected preoperatively among patients with a low platelet count or a history of prolonged heparin exposure or both. Cardiac surgery can be safely undertaken using iloprost-induced platelet inhibition during heparinization.

Heparin-induced thrombocytopenia and thrombosis (HITT), or heparin-induced thrombocytopenia type II, is an immunologic disorder that affects patients who receive prolonged (>3 days) heparin anticoagulation.<sup>1-3</sup> When heparin enters the blood, it forms a complex with platelet factor (PF)4. Patients with HITT have been sensitized against the heparin-PF4 complex, producing mainly immunoglobulin G antibodies against it.<sup>4</sup> On reexposure to heparin, these antibodies bind to the heparin-PF4 complex at the platelet surface receptor Fc, causing platelet activation, release of procoagulant active microparticles and more PF4, and, consequently, platelet aggregation. The newly released PF4 reacts with the circulating heparin and eventually with the endothelial surface-attached heparin-like molecules, promoting reaction with the specific antibodies.<sup>2,3</sup> This leads to activation of more platelets and to a vicious cycle that causes platelet aggregation, thromboembolic complications, and bleeding diathesis in association with thrombocytopenia.<sup>3,5</sup> Patients with HITT antibodies are at high risk ( $\approx 50\%$ ) for experiencing thromboembolic complications, bleeding, and sudden death on reexposure to heparin. Death, limb loss, myocardial infarction, coronary artery graft occlusion, mesenteric infarction, deep venous thrombosis, pulmonary embolism, stroke, intracardiac mural thrombosis, bilateral adrenal hemorrhagic infarcts, and bleeding have occurred intraoperatively or early postoperatively in patients with HITT receiving heparin.<sup>1,3,5-8</sup>

The management of patients with HITT antibodies who require cardiac surgery is challenging, because heparin anticoagulation is an integral part of cardiac operations performed with or without extracorporeal circulation. A standard approach to

these patients has not yet been established, although several therapeutic options have been proposed on the basis of using anticoagulants other than heparin.<sup>1,3</sup> However, experience with the Food and Drug Administration-approved alternative anticoagulants is limited, specific antidotes are not available, and special tests not readily available are required to monitor the effectiveness of the alternatives.<sup>3,5,6</sup>

In an effort to prevent serious perioperative thromboembolic and bleeding complications in our patients, we established a protocol for the identification and management of HITT-sensitive patients who need cardiac surgery with full heparinization. The purpose of this project was 2-fold: the preoperative recognition of patients with heparin-sensitive antiplatelet antibodies and the prevention of platelet activation by temporary platelet function inhibition during heparinization. Our management protocol was based on reports by Addonizio and associates,<sup>9,10</sup> Kappa and collaborators,<sup>11,12</sup> and Palatianos and colleagues (on the use of the prostacyclin analog iloprost [ZK 36374]).<sup>13</sup> Addonizio and associates<sup>9,10</sup> and Kappa and associates<sup>11,12</sup> reported platelet preservation with iloprost during cardiopulmonary bypass (CPB) and showed that temporary platelet inhibition with iloprost allowed safe heparin administration in patients with HITT undergoing cardiac or vascular operations.

## Methods

### Patients

From June 1998 to June 2001, 1518 patients underwent cardiac surgery in our department. Of

these patients, 32 (2.1%) were found to have thrombocytopenia (platelet counts  $< 150,000/\text{mm}^3$ ) or a positive history of prolonged ( $>3$  days) exposure to heparin or both. These 32 patients underwent the usual hemostatic assessment and had their bleeding times tested. They were also tested for heparin-induced platelet aggregation (HIPA) using porcine heparin (heparin sodium, Leo Pharmaceutical Products, Ballerup, Denmark) after 14 days from cessation of any aspirin intake. Patients with plasma aggregating normal donor platelets in the presence of heparin (positive HIPA assay) were evaluated with an enzymelinked immunosorbent (ELISA) assay (Diagnostica Stago, Taverny, France) for anti-heparin-PF4 antibodies (HITT antibodies).<sup>2,4,14,15</sup> Patients with HITT antibodies were subsequently tested with a HIPA assay using increasing micromolar concentrations of iloprost (Ilomedin, Berlex Laboratories, Edison, NJ) to determine the dose that completely inhibited platelet aggregation to heparin.<sup>9-12</sup> During surgery, patients with anti-heparin-PF4 antibodies were treated with iloprost to achieve complete inhibition of HIPA before heparinization (group A or treated group). Ten additional patients with normal platelet counts and without history of prolonged exposure to heparin or thrombosis were matched for age, gender, and procedure, and were included in the study as controls (group C). Our hospital's ethics committee approved the use of iloprost in our patients with HITT antibodies. Each patient signed an informed consent form.

#### **Anesthesia Protocol**

Anesthesia was induced with midazolam (0.05-0.075 mg/kg of body weight), etomidate (0.3 mg/kg), and fentanyl (10-15  $\mu\text{g}/\text{kg}$ ). Neuromuscular block was induced by intravenous pancuronium or rocuronium (0.15 mg/kg) and maintained by continuous infusion of cisatracurium (1.5-2.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Anesthesia was maintained using sevoflurane 0.5% to 2.0% in oxygen/air and additional boluses of fentanyl as needed or a continuous infusion of remifentanyl (0.2-1.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

Each patient had a 3-lumen central venous catheter, pulmonary artery catheter, and radial arterial catheter positioned before anesthesia induction.

During surgery, there was continuous monitoring of the central venous, pulmonary artery, and arterial pressures; urinary output; electrocardiogram; and nasopharyngeal and rectal temperatures. Tissue oxygenation was monitored with pulse oximetry, and arterial blood gases were frequently tested.

#### **Surgical Protocol and Postoperative Management**

After anesthesia induction, iloprost infusion was started at 3  $\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  intravenously and was increased progressively (doubled) every 5 minutes up to the dose corresponding to the concentration of iloprost, which in vitro inhibited platelet aggregation to heparin. A HIPA test was performed 5 minutes after reaching the target dose. Once complete inhibition of platelet aggregation to heparin was demonstrated, the patients were given porcine heparin for full heparinization (heparin sodium, 300 IU/kg intravenously). Norepinephrine was infused at 0.05  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  to prevent or treat hypotension (systolic blood pressure  $< 100$  mm Hg). For cases requiring CPB, the activated coagulation time (ACT) was maintained at more than 480 seconds throughout perfusion. Additional heparin was administered if needed. CPB was established with a roller pump (Stockert-Shiley Instruments, Munich, Germany), a hollow fiber membrane oxygenator (Quadrox, Jostra, Hirrlingen, Germany), and an arterial filter (HBF 40, Jostra) at 32 °C to 33 °C for cases undergoing coronary revascularization procedures and at 28 °C for valve surgery cases. Cardioprotection was achieved with induced cardioplegic arrest. Cold (8 °C) blood cardioplegic solution was infused retrograde through the coronary sinus and antegrade through the aortic root. Surface-heparinized extracorporeal circuits were not used in these patients. Off-pump procedures were performed using the Octopus 3 flexible stabilization system (Medtronic, Inc, Minneapolis, Minn) under systemic heparinization (heparin dose 150-200 IU/kg, ACT  $> 350$  seconds). On termination of CPB, or after construction of the bypass grafts for the off-pump coronary bypass cases, protamine sulfate (Leo Pharmaceutical Products) was administered to neutralize the heparin and return the

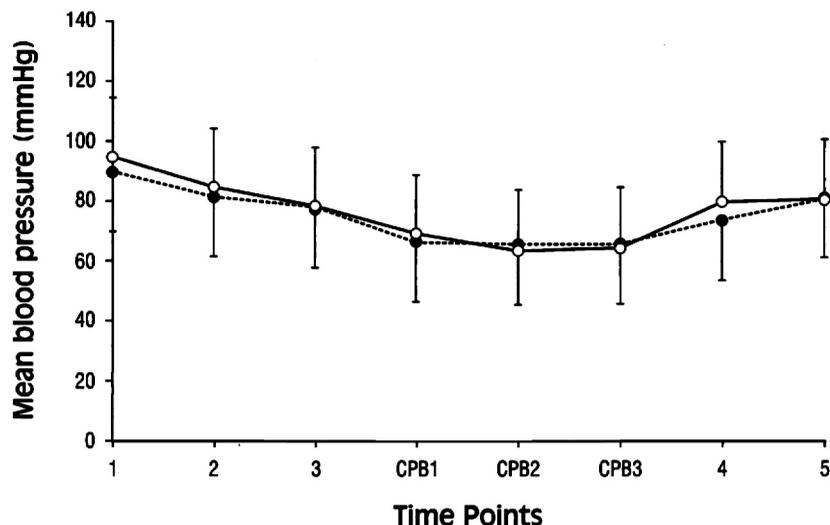


Figure 1. Mean blood pressure changes. Time points: 1, on arrival to the operating room; 2, iloprost infusion begins; 3, before CPB; CPB1, after start of perfusion; CPB2, middle of perfusion; CPB3, before end of perfusion; 4, after CPB; 5, first hour in ICU. Control group (solid line); iloprost-treated group (dashed line).

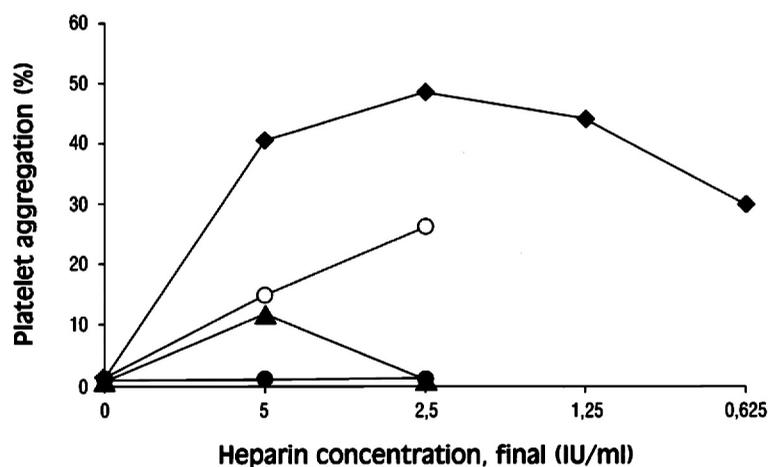


Figure 2. Effect of iloprost at various concentrations and corresponding infusion rates on HIPA in vitro. +, No iloprost; O, iloprost 60 µg/mL (3 ng · kg<sup>-1</sup> · min<sup>-1</sup>); E, 120 µg/mL (6 ng · kg<sup>-1</sup> · min<sup>-1</sup>); ◆ iloprost, 240 µg/mL (12 ng · kg<sup>-1</sup> · min<sup>-1</sup>).

ACT to normal values. The patients were transferred to the intensive care unit (ICU), ventilated, continuously monitored for arterial and pulmonary artery pressures and electrocardiogram, and administered iloprost infusion. After demonstration of the absence of circulating heparin with the Hepcon HMS/HMS Plus blood analyzer (Medtronic, Inc), the iloprost infusion was reduced to half and was further halved every 30 minutes until it was discontinued after the first hour in the ICU. Iloprost was used solely for platelet inhibition

according to the protocol dose. It was not modified to treat blood pressure changes. These conditions were treated as needed with the standard medications used in the immediate postoperative period. Blood losses from the chest tubes were recorded every hour.

Postoperative management was performed according to a standard protocol. If there was increased bleeding diathesis, red blood cells, platelets, and fresh frozen plasma were administered as needed to maintain the hematocrit above 26%

in hemodynamically stable patients or to correct prolonged coagulation parameters. No heparin was administered to the patients thereafter. The intravenous lines were flushed with heparin-free saline, and any need for anticoagulation was achieved with acenocoumarin (Sintrom, Novartis-Pharma, Basel, Switzerland). Platelet counts were obtained preoperatively, 1 hour after surgery, and on the first and fifth postoperative days, and were corrected for hemodilution according to hematocrit values.

### Statistical Methods

The analysis of the data collected for the study was performed using the following statistical methods, depending on the nature of the data analyzed:

Longitudinal data (ie, measurements on the same variable taken at consecutive time points for each patient) were evaluated by repeated-measures analysis of variance (RM-ANOVA). All other continuous variables measured at a single time point (eg, duration of ICU stay and amounts of blood loss), aggregates of the longitudinal data, and percent reduction of platelet counts from the preoperative values were evaluated by the *t* test and its nonparametric equivalent (Wilcoxon rank-sum test). Changes from baseline at each time point of measurement within each group (eg, no intergroup comparisons) were evaluated using the Student paired *t* test and the Wilcoxon signed-rank test. The association between length of perfusion and platelet count reduction was assessed with Spearman's correlation. In general, during the analysis, the parametric methods were used after testing for normality. If the test rejected the normality assumption, then the nonparametric method was used. The *P* values reported are accompanied by the type of test they are derived from. All calculations were performed using the SASJ statistical package (SAS Institute, Inc, Cary, NC).

### Results

Ten patients were found to have HIT antibodies (0.65% of our total patient population; 31.3% of

the patients presented with thrombocytopenia or history of prolonged heparin therapy). Their preoperative bleeding times were within normal range ( $6.4 \pm 1.94$  minutes). Patient characteristics and surgery data appear in Table 1. Iloprost was infused at 6 to 24  $\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , achieving complete platelet inhibition to heparin. In the control group, mean maximal blood pressure decreased by  $26.5 \pm 11.1$  mm Hg before CPB, whereas in the iloprost-treated group, systolic pressure decreased by  $37.0 \pm 10.3$  mm Hg before CPB ( $P = .03$ , Wilcoxon test). Blood pressure was easily controlled using norepinephrine infusion or phenylephrine boluses (Figure 1). Two patients with high blood pressure did not require norepinephrine; their blood pressure was readily controlled during iloprost infusion with phenylephrine boluses (100  $\mu\text{g}$ ). Platelet counts were significantly reduced 1 hour after surgery in both groups ( $P < .0001$ , RM-ANOVA). The control group displayed a greater decrease in platelet count from baseline at 1 hour and 1 day postoperatively than the treated group ( $P < .0001$  and  $.0487$ , respectively, RM-ANOVA) (Table 2). Iloprost caused a concentration-dependent inhibition of platelet aggregation preoperatively in vitro (Figure 2). Complete inhibition of platelets occurred with iloprost infusion at 6 to 24  $\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , corresponding to plasma concentrations of 120 to 480 pg/mL. After intravenous iloprost administration, the HIPA test became negative at the corresponding concentrations, as was identified in vitro in 9 patients. In the remaining patient, the iloprost infusion rate had to be doubled during surgery to obtain complete platelet inhibition.

There was no operative mortality. Hematocrit values decreased significantly in both groups over time ( $P < .0001$ , RM-ANOVA) (Table 2). There was no significant difference between groups overall or in the time progression of the hematocrit value or at any time point measured. In the treated group, 1 patient bled  $>1000$  mL (1310 mL) in the first 6 postoperative hours but did not require exploration; he had prolonged coagulation parameters without free circulating heparin (negative Hepcon test). The bleeding was controlled with fresh frozen plasma, platelet, and red blood cell transfu-

**TABLE 1. Patient characteristics and operative data**

	Treated group (n = 10)	Control group (n = 10)
Female gender	1	1
Age (y)	61.1 ± 7.2	62.7 ± 8.4
Operation performed		
CABG	7	7
MVR	3	1
CABG and MV repair	0	1
CABG and MVR	0	1
CPB time (min)	67.6 ± 53.0	97.1 ± 59.6
Heparin dose (IU)	16,950 ± 5,449	22,100 ± 9,868
Protamine dose (mg)	135.00 ± 51.9	160.00 ± 45.9
ACT (sec)		
Baseline	133 ± 15	130 ± 23
During CPB	523 ± 122	499 ± 116
After protamine	141 ± 20	132 ± 11

The ± values are SDs. ACT, Activated coagulation time; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MV, mitral valve; MVR, mitral valve replacement.

sions. There was no significant difference in mediastinal blood losses in the first 6 postoperative hours between the treated and control groups ( $317.5 \pm 355.9$  mL vs  $304.5 \pm 126.8$  mL, respectively,  $P = .3634$ , Wilcoxon test) and no difference in transfusion requirements ( $P = .67$ , Wilcoxon test). A patient in the treated group demonstrated low cardiac output that required the use of an intraaortic balloon pump for 24 hours. Mild transient jaundice appeared in 1 patient in each group. In the control group, 1 patient required prolonged (>48 hours) intubation, and another patient required reoperation with construction of a venous bypass graft because of malfunction of an internal thoracic artery bypass graft. The lengths of postoperative stay in the ICU and postoperative hospitalization were  $1.6 \pm 1.2$  days and  $6.5 \pm 1.9$  days, respectively, without significant difference between groups.

## Discussion

Thrombocytopenia in patients with prior prolonged exposure to heparin or with thrombotic or thromboembolic events under heparin therapy may indicate the presence of HITT.<sup>1-4</sup> However, this immune disorder may be concealed, and severe thromboembolic events may develop on heparin administration in some patients with normal platelet counts.<sup>4</sup> Unfortunately, in a large proportion of patients, the condition is recognized after the occurrence of a serious complication. In their 14-year series, Warkentin and Kelton<sup>1</sup> found that approximately half of HITT-sensitive patients were recognized only after a complicating thrombotic event. A high index of suspicion is mandatory for preoperative recognition of patients with HITT and prevention of devastating complication(s) on heparin administration. The condition may be diagnosed by HIPA and serotonin radioimmunoassay release tests or serologically by ELISA for detection of HITT-specific antibodies against the heparin-PF4 complex.<sup>3,4</sup>

Our protocol addresses the preoperative recognition of HITT-sensitive patients and their intraoperative management for prevention of activation of the HITT process. In this protocol, HITT is diagnosed preoperatively by screening all patients who present with low platelet counts ( $<150,000/\text{mm}^3$ ) or a history of prolonged heparin therapy or thrombosis regardless of platelet count. Currently, in our practice, all our patients scheduled for surgery undergo a preadmission complete blood count and platelet count within the frame of a preadmission evaluation. No patient with a low platelet count is scheduled for surgery without prior investigation of his or her thrombocytopenia. In our laboratory,

**TABLE 2. Changes in hematocrit and platelet counts**

Parameter	Treated group	Control group	P value (test)
Platelet count ( $\times 10^3/\text{mm}^3$ )			
Baseline	151.6 ± 63.012	212.7 ± 52.637	NS
First hour in ICU	135.7 ± 65.488	127.7 ± 27.949	.0001 (RM-ANOVA)
First postoperative day	114.8 ± 49.409	136.7 ± 40.472	.0487 (RM-ANOVA)
On discharge	165.2 ± 65.149	198.6 ± 96.464	NS
Hematocrit (%)			
Baseline	42.28 ± 1.99	41.01 ± 3.52	NS
First hour in ICU	31.07 ± 4.72	30.3 ± 4.58	NS
First postoperative day	32.08 ± 3.01	33.33 ± 3.66	NS
On discharge	32.69 ± 5.50	33.11 ± 3.85	NS

RM-ANOVA, Repeated-measures analysis of variance; ICU, intensive care unit; NS, not significant.

the special diagnostic workup can be completed within 5 to 6 hours. The determination of the iloprost concentration that inhibits HIPA is usually performed within 1 hour before heparinization for CPB. Therefore, with proper mobilization of the involved services, this protocol can be applied to cases requiring urgent surgery. Since we started using this protocol, we have not seen any of the unexpected postoperative hard-to-manage bleeding that we used to face sporadically. In our experience, 31.3% of patients with thrombocytopenia who presented for cardiac surgery tested positive for HITT antibodies. Patients testing positive for HIPA are further tested with ELISA for HITT antibodies. In patients with HITT antibodies, surgery is postponed for approximately 3 months if their condition allows it. If the antiplatelet antibodies disappear from the patient's plasma, surgery proceeds with standard CPB and heparin. Any further exposure postoperatively to either unfractionated or low molecular weight heparin is strictly avoided.<sup>3,5,16-18</sup> In case the patient's condition forbids delay of surgery, we use iloprost for temporary platelet inhibition (as described previously) to prevent HITT-related complications. Again, heparin is not used postoperatively in any form. This protocol allows the safe use of heparin during CPB in patients with HITT antibodies.

Iloprost, a stable analog of prostacyclin with a half-life of 30 minutes, is effective in completely inhibiting platelets by binding to specific platelet receptors, activating adenylyl cyclase, and increasing the intracellular cyclic adenosine monophosphate levels. In addition, iloprost acts on the arterial smooth muscle with a vasodilatory effect that may lead to hypotension.<sup>19</sup> At appropriate infusion rates, iloprost allows safe heparin administration in patients with HITT antibodies provided there is close monitoring

of hemodynamics and careful use of alpha agonists (norepinephrine and phenylephrine) to prevent or treat hypotension.<sup>9-13</sup> Our data support the hypothesis that heparin may be used with impunity in patients with HITT when their platelets are completely inhibited with iloprost and their hemodynamics are closely monitored. The main side effect of iloprost is hypotension secondary to vasodilation. However, in our experience, hypotension during iloprost infusion was readily controlled with norepinephrine infusion ( $1-4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) or phenylephrine boluses. In this report, we present our first 10 patients in whom HITT antibodies were detected preoperatively. Our overall hospital experience to date with patients who test positive for HITT is satisfactory. This protocol has been used successfully for the identification and management of these patients so they can undergo cardiac surgery without the thrombotic and hemorrhagic complications related to their sensitivity to heparin.

## Conclusion

HITT should be suspected in every patient with thrombocytopenia or a positive history of prolonged heparin therapy or thrombosis. In such patients, any heparin should be avoided until testing for immune anti-heparin-PF4 antibodies is completed. Immune HITT antibodies can be effectively diagnosed preoperatively, and patients can safely undergo cardiac surgery with temporary iloprost-induced platelet function inhibition during heparinization and cautious blood pressure control with alpha agonists.

We thank Yannis Bassiakos, PhD, for statistical analysis of the data.

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## Discussion

**Dr Michael A. Acker** (*Philadelphia, Pa*). Your method of prospective screening of patients at risk for HIT seems to have identified patients at risk for thrombotic complications and death. In your article you indicate that in elective cases the first thing one should do is probably wait 3 months, because often the antibody levels will decline and often disappear.

This becomes a bigger issue when you can't wait or when the antibody levels do not disappear. You successfully used iloprost in 10 patients identified with HIT, and you followed a similar successful series by Addonizio and colleagues and Kappa and colleagues from the University of Pennsylvania nearly 15 years ago. They found, as you did, that the vasodilatory side effects of iloprost can be reasonably handled in a safe fashion and that iloprost prevents platelet aggregation leading to bleeding and thrombotic complications. Unfortunately, iloprost is not available in the United States.

I have 3 questions, and there are 3 slides. You did not mention the serotonin release assay in your presentation, which is perhaps the oldest and still the most specific and sensitive test for HIT as far as indicating the development of thrombotic complications. You have not used this test. Why?

We found recently that many patients who test positive for heparin antibodies with the ELISA, test negative with the serotonin release assay. We have successfully proceeded with CPB using a 1-time heparin dose without adjuvant or alternative means of anticoagulation in this small group of patients. Do you believe that patients with a negative functional assay such as serotonin or platelet aggregation, yet a positive heparin antibody with the ELISA, define a different group of patients who can be treated safely in the traditional fashion?

Finally, given that iloprost is not available in the United States, and it is interesting to conjecture why not, what is your advice for the U.S. surgeon faced with a patient with HIT? Can you comment on the alternative anticoagulation strategies I have listed, such as alternative prostacyclin

analogs (eg, epoprostenol), direct thrombin inhibitors (there are several now), defibrinating agents (eg, ancrod and GPIIb or IIIa receptor inhibitors), or the heparinoids?

**Dr Palatianos.** There is no 100% sensitive assay to identify the patients who will have clinical HITT. We used the ELISA assay because it was available in our hospital. Indeed, there are some patients who test negative and may have clinical HITT, and there are patients who test positive for antibodies and will not have clinical HITT after heparinization for surgery. To improve diagnostic accuracy, we also test platelet aggregation to heparin. The serotonin release assay is a highly sensitive method for detection of HITT antibodies. However, it is technically demanding and not readily available in every hospital. When available, it should be used to identify patients prone to have HITT complications.

Patients who test positive for HITT antibodies with the ELISA test and test negative with the serotonin release assay should be restudied. If the ELISA assay remains positive, I think they should be treated as HITT prone.

Although iloprost is available in Europe, its use for prevention of HITT is not included among its accepted indications. We use it within the frame of the clinical study. There are recent reports promising that newer medications such as thrombin inhibitors or heparin substitutes may become available in the near future. However, a generalized experience with them is lacking.

I think it is important to identify these patients preoperatively. Carefully investigating the patients who come for surgery with low platelet counts or a history of prolonged heparin therapy may help in identifying patients with HITT antibodies. In general, we test the occasionally seen patient with thrombocytopenia with a bleeding time and perhaps with platelet aggregation studies. If these tests are normal, we should not stop there. Some of these patients may have HITT antibodies. With our protocol, we detected HITT antibodies in 31.3% of these patients. Once we identify the patients, if their condition allows us to wait, postponing surgery is the best thing to do until the antibodies clear, usually within 2 to 3

months. In case surgery cannot be postponed, the patients should be managed with a specific protocol addressing this serious and potentially dangerous problem.

**Dr Paschalis Tossios** (*Cologne, Germany*). We know that these patients are sometimes very sick and that they are very difficult to handle when the diagnosis is confirmed preoperatively. In my own experience, heparin-induced thrombocytopenia and associated complications occur more often postoperatively, and they might occur with venous and arterial thromboembolic complications, even with normal platelet counts. Do you have a protocol for when heparin-induced thrombocytopenia is diagnosed during the postoperative course?

**Dr Palatianos.** Basically, heparin, either unfractionated or low molecular weight, should not be given to these patients postoperatively, not even through a heparin flush to keep arterial or venous lines open. Of course, HIT antibodies may be present with a normal platelet count.

We have not observed any thrombosis in our patients. In case of thrombosis, any heparin preparation that the patient is receiving should be stopped, and some antithrombotic agent could be used. Of course, the site of thrombosis, clinical picture, timing, and general condition of the patient direct the treatment. For this condition, prevention is the best treatment. By making the platelets insensitive to the stimuli with iloprost, we prevent platelet activation and release reaction, aggregation, and thrombosis.

### Περίληψη στα Ελληνικά

#### Προεγχειρητική ανίχνευση και αντιμετώπιση θρομβοπενίας από ηπαρίνη με Ilprost σε ασθενείς που υποβάλλονται σε εγχειρήσεις ανοικτής καρδιάς

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**Εισαγωγή.** Παρουσία ευαισθητοποιημένων στην ηπαρίνη αιμοπεταλίων (heparin-induced thrombocytopenia and thrombosis, HITT) ενδέχεται να οδηγήσει σε συγκόλληση των αιμοπεταλίων, θρομβωτικές επιπλοκές, αιμορραγία και θάνατο κατά τις εγχειρήσεις ανοικτής καρδιάς, στις οποίες επαρκής συστηματικός ηπαρινισμός είναι απαραίτητος. Στόχος της παρούσης μελέτης ήταν η αξιολόγηση του πρωτοκόλλου μας για την αναγνώριση και αντιμετώπιση ασθενών με ανοσολογική θρομβοπενία από ηπαρίνη που υποβάλλονται σε εγχειρήσεις ανοικτής καρδιάς.

**Μέθοδος.** Μεταξύ 1518 ασθενών που υποβλήθηκαν σε εγχείρηση ανοικτής καρδιάς από τον Ιούνιο 1998 έως και τον Μάιο 2001, 32 (2,1%) είχαν προεγχειρητική θρομβοπενία (αριθμός αιμοπεταλίων  $<150.000/\text{mm}^3$ ) ή ιστορικό παρατεταμένης (άνω των 3 ημερών) ενδοφλέβιας χορήγησης ηπαρίνης. Οι ασθενείς εξετάστηκαν με ανοσολογικό προσδιορισμό για αντισώματα εναντίον του συμπλόκου ηπαρίνης-αιμοπεταλιακού παράγοντα 4. Τα αιμοπετάλια των ασθενών στους οποίους ανιχνεύθηκαν αντισώματα, εξετάστηκαν με το ανάλογο της προστακυκλίνης iloprost για αναστρέψιμη αναστολή συγκόλλησης από ηπαρίνη, και καθορισμό του ουδού συγκέντρωσης και της αντίστοιχης ενδοφλέβιας δόσης του iloprost. Ασθενείς με

αντισώματα ηπαρινίστηκαν μετά από πλήρη αναστολή των αιμοπεταλίων με έγχυση iloprost. Πρόληψη εμφάνισης ή αντιμετώπιση υπότασης επιτεύχθηκε με ενδοφλέβια νοραδρεναλίνη. Έτεροι 10 ασθενείς με παρόμοιες προεγχειρητικές παραμέτρους, φυσιολογικό αριθμό αιμοπεταλίων και χωρίς προηγούμενη έκθεση στην ηπαρίνη επιλέχθηκαν τυχαίως για να απαρτίσουν την ομάδα ελέγχου.

**Αποτελέσματα.** Αντισώματα εναντίον του συμπλόκου ηπαρίνη-αιμοπεταλιακός παράγοντας 4 ανιχνεύθηκαν σε 10 από τους 32 ασθενείς (31,3%, ομάδα A) και σε κανένα της ομάδας ελέγχου. Στους ασθενείς της ομάδας A χορηγήθηκε iloprost (6-24ng/kg/min) και η αρτηριακή τους πίεση διατηρήθηκε άνω των 95mmHg με έγχυση νοραδρεναλίνης (1-4μg/kg/min). Η χειρουργική θνητότητα ήταν μηδενική. Δεν εμφανίστηκαν θρομβωτικές επίπλοκες ή αιμορραγία που απαιτούσε χειρουργική διερεύνηση. Δεν υπήρξε διαφορά στη μετεγχειρητική απώλεια αίματος και τη νοσηρότητα μεταξύ των ομάδων. Ο αριθμός αιμοπεταλίων ελαττώθηκε κατά  $12,5\% \pm 8,7\%$  στην ομάδα A και κατά  $38,1 \pm 15,2\%$  στην ομάδα ελέγχου ( $p < 0,001$ ) την 1<sup>η</sup> μετεγχειρητική ώρα, και επανήλθε σε προεγχειρητικές τιμές την 5<sup>η</sup> μετεγχειρητική ημέρα.

**Συμπέρασμα.** Η ανοσολογικής αιτιολογίας θρομβοπενία από ηπαρίνη είναι ανιχνεύσιμη προεγχειρητικώς σε ασθενείς με χαμηλό αριθμό αιμοπεταλίων ή παρατεταμένη έκθεση στην ηπαρίνη. Συστηματικός ηπαρινισμός και εγχειρήσεις ανοικτής καρδιάς πραγματοποιήθηκαν με ασφάλεια χρησιμοποιώντας αναστρέψιμη αναστολή των αιμοπεταλίων με iloprost.



Περρέα Δέσποινα

# Προγνωστικός δείκτης εμφάνισης του οξέος εμφράγματος του μυοκαρδίου σε ασθενείς που υποβάλλονται σε καρδιοχειρουργική επέμβαση

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## Εισαγωγή

Η δυσλειτουργία των αγγειακών ενδοθηλιακών και των λείων μυϊκών κυττάρων αποτελεί κεντρική παθοφυσιολογική διαδικασία στην αθηροθρομβωτική νόσο. Η οξεία απόφραξη ενός ή περισσότερων στεφανιαίων αρτηριών προκαλεί το οξύ έμφραγμα του μυοκαρδίου (OEM), μια κατάσταση δυνητικά θανατηφόρα για την ζωή του ασθενούς και απαιτεί επείγουσα αντιμετώπιση<sup>1</sup>. Παρά την φαρμακολογική και τεχνολογική πρόοδο, σήμερα, το ποσοστό θνησιμότητας του OEM παραμένει υψηλό<sup>1</sup>. Επί πλέον, τα σύγχρονα επιστημονικά δεδομένα καταρρίπτουν την μακρόχρονη αντίληψη μίας αιτιολογικής σχέσης της βαρύτητας της στεφανιαίας νόσου με τον επιπολασμό του OEM. Πράγματι, γενετικές μελέτες δείχνουν ότι τα αλληλία κινδύνου για την στεφανιαία νόσο και το OEM δεν εμφανίζουν συγκριτικές ιδιότητες<sup>2,3</sup>. Λόγω της απρόβλεπτης κλινικής εμφάνισής του, το OEM αποτελεί στόχος των νέων διαγνωστικών στρατηγικών. Η διαστρωμάτωση του κινδύνου εμφάνισης του OEM έχει δοκιμαστεί με την χρήση μιας πολλών βιοχημικών, κλινικών και παρακλινικών παραμέτρων.

Η Σιρτουίνη 1 (Sirtuin 1-SIRT1), το δινουκλε-

οτίδιο της αδενινικής νικοτιναμίδης δεακετυλάσης (NAD), εμπλέκεται σε μεταβολικές οδούς και ασθένειες όπως ο διαβήτης, προστατεύοντας από την καρδιαγγειακή γήρανση και την αγγειακή δυσλειτουργία του τοιχώματος των αγγείων μέσω της προαγωγής ομοιοστατικών μηχανισμών έναντι του οξειδωτικού στρες<sup>4,5</sup>. Από την άλλη πλευρά, η μεταλλοπρωτεϊνάση της εξωκυττάριας ουσίας 2 (matrix metalloproteinase 2- MMP2) είναι μέλος της οικογένειας των μεταλλοπρωτεϊνών που εμπλέκονται, κυρίως, στην αναδιαμόρφωση των ιστών. Έχει συσχετιστεί με οξέα στεφανιαία σύνδρομα και κολπική μαρμαρυγή λόγω των προφλεγμονωδών τους δράσεων<sup>6</sup>.

Στόχος της παρούσας μελέτης είναι η διερεύνηση μιας πιθανής συσχέτισης της SIRT1 και του MMP2 με το οξύ έμφραγμα του μυοκαρδίου σε ασθενείς που υποβάλλονται σε χειρουργική επέμβαση ανοικτής καρδιάς.

## Υλικό και Μέθοδος

### 2.1. Επιλογή των ασθενών

Στην μελέτη μας συμπεριελήφθησαν 81 ασθενείς με προχωρημένη στεφανιαία νόσο που είχαν προγραμματιστεί για χειρουργείο αορτοστεφανιαί-

ας παράκαμψης και / ή χειρουργική επέμβαση μιτροειδούς βαλβίδας και / ή χειρουργική επέμβαση αορτικής βαλβίδας. Οι ασθενείς προήλθαν από το Ωνάσειο Καρδιοχειρουργικό Κέντρο και η επιτροπή βιοηθικής και δεοντολογίας αυτού ενέκρινε τη μελέτη μας, σύμφωνα με τις δεοντολογικές κατευθυντήριες γραμμές της Διακήρυξης του Ελσίνκι του 1975.

Οι ασθενείς ενημερώθηκαν λεπτομερώς για τη συμμετοχή τους στη μελέτη και παρείχαν γραπτή συναίνεση. Πραγματοποιήθηκε καταγραφή των δημογραφικών χαρακτηριστικών των ασθενών και της προεγχειρητική κλινικής τους κατάστασης, καθώς και συλλογή δειγμάτων αίματος, προεγχειρητικά.

Συμπεριελήφθησαν από το ιστορικό των ασθενών οι παραδοσιακοί παράγοντες κινδύνου που σχετίζονται με την στεφανιαία νόσο, όπως το κάπνισμα, ο διαβήτης, η παχυσαρκία, η υπέρταση, η υπερλιπιδαιμία. Με βάση τις μελετημένες επιδράσεις των SIRT1 και MMP2 στο κυτταροπλασματικό επίπεδο, υποθέσαμε μια σχέση των διαμεσολαβητών αυτών με τα κλινικά χαρακτηριστικά των ασθενών μας.

## 2.2. Μετρήσεις ELISA

Τα επίπεδα της SIRT1 στον ορό μετρήθηκαν με την μέθοδο ELISA χρησιμοποιώντας ένα εμπορικό αντιδραστήριο (ELISA, Wuhan USCN Business Co., Ltd). Η ελάχιστη ανιχνεύσιμη δόση της SIRT1 ήταν 0,28 ng / mL, με τυπικό εύρος ανίσχνευσης τα 0,78-50 ng / mL στον ανθρώπινο ορό. Τα επίπεδα του MMP2 στον ορό μετρήθηκαν, επίσης, με την μέθοδο ELISA (Quantikine HumanMMP2, R & D Systems και Minneapolis, MN). Η ελάχιστη ανιχνεύσιμη δόση του MMP2 κυμαινόταν από 0,03 έως 0,40 ng / mL. Η μέση συγκέντρωση ανίσχνευσης ήταν τα 0,16 ng / mL. Η τυπική περιοχή ανίσχνευσης ήταν τα 0-50 ng / mL.

## 2.3. Στατιστική ανάλυση

Οι συνεχείς μεταβλητές εκφράστηκαν ως  $\pm$  τυπική απόκλιση ή ως διάμεσος  $\pm$  εύρος τεταρτημορίου, ενώ οι κατηγορικές μεταβλητές σε απόλυτη τιμή ή ποσοστιαία τιμή (%). Η κατανομή όλων των συνεχών μεταβλητών δοκιμάστηκε για κανονικότητα με την παραμετρική δοκιμή Shapiro-Wilk και

γραφικά με τα σχεδιαγράμματα P-P. Ο λογαριθμικός μετασχηματισμός χρησιμοποιήθηκε σε μερικές περιπτώσεις επικαλυμμένων δεδομένων. Η συσχέτιση των μεταβλητών σε διατομεακό σχεδιασμό αξιολογήθηκε χρησιμοποιώντας την συσχέτιση του Pearson ή Spearman συντελεστή και με την προσέγγιση επιλογής μοντέλου Collet<sup>7</sup> που χρησιμοποιούνται για την κατασκευή πολυπαραγοντικών μοντέλων εξαρτώμενων μεταβλητών ενδιαφέροντος. Η συγγραμμικότητα ανεξάρτητων μεταβλητών αποφεύχθηκε με την εκτίμηση του μεταβλητού παράγοντα πληθωρισμού (VIF). Η σημαντικότητα των πρόσθετων μεταβλητών στην πολυπαραγοντική ανάλυση δοκιμάστηκε από το τεστ αναλογίας πιθανότητας των αντίστοιχων μοντέλων οπισθοδρόμησης. Σε μοντέλα λογικής παλινδρόμησης αξιολογήθηκε η προγνωστική αξία της SIRT1 και / ή του MMP2 με την εφαρμογή των καμπυλών ROC και συγκρίνοντας το εμβαδόν της αντίστοιχης περιοχής κάτω από τις καμπύλες (AUC). Η αύξηση της AUC θεωρήθηκε ως μέτρο της ικανότητας διάκρισης μεταξύ δύο μοντέλων πρόβλεψης λογικής παλινδρόμησης.

Η στατιστική ανάλυση πραγματοποιήθηκε από πακέτο STATA, έκδοση 11.1 (StataCorp, College Station, Texas, USA). Το σφάλμα τύπου I ήταν προκαθορισμένο στο 0,05.

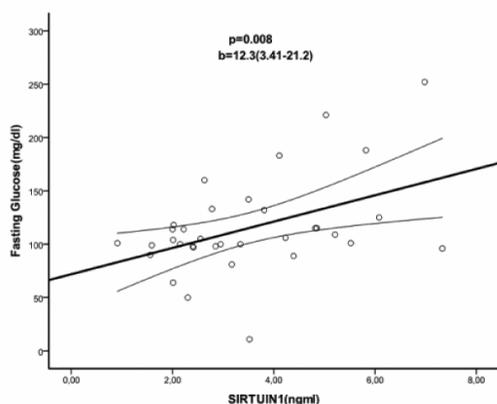
## Αποτελέσματα

Τα περιγραφικά χαρακτηριστικά του πληθυσμού μας συγκεντρώνονται στον Πίνακα 1. Παρουσιάζονται, επίσης, οι παράμετροι ενδιαφέροντος σύμφωνα με τα τεταρτημόρια αναφοράς SIRT1: Στον συνολικό πληθυσμό, τα μέσα επίπεδα της SIRT1 ήταν 2,96 (IQR: 2,14-4,53). Οι ασθενείς που διανέμονται στο κατώτερο τεταρτημόριο τείνουν να είναι υπέρτασοι και να παρουσιάζουν αυξημένο επιπολασμό του σακχαρώδη διαβήτη τύπου 2 ( $\Sigma\Delta 2$ ).

Όσον αφορά τις συσχετίσεις ανά ζεύγη, η SIRT1 συσχετίστηκε οριακά με το ιστορικό Υπέρτασης ( $r = 0,2$ ,  $p = 0,084$ ) και αντίστροφα με τα επίπεδα αναφοράς της ουρίας ( $r = 0,25$ ,  $p = 0,056$ ). Επίσης, μια σημαντική αντίστροφη συσχέτιση της SIRT1 με την παρουσία  $\Sigma\Delta 2$  αποτυπώθηκε ( $r = 0,36$ ,  $p = 0,001$ ).

Όταν πραγματοποιήθηκε επιπρόσθετη προσαρμογή για διάφορους συγχυτικούς παράγοντες, η SIRT1 συσχετίστηκε ανεξάρτητα με την παρουσία ΣΔ2. Μία μονάδα αύξηση των επιπέδων της SIRT1 συνδέθηκε με 49% αυξημένες πιθανότητες για ύπαρξη ΣΔ2, αφού ελήφθησαν υπόψη οι παραδοσιακοί παράγοντες κινδύνου. Οι εκκινήσεις αναπαραγωγής Bootstrap επιβεβαίωσαν την σύνδεση του SIRT1 με την επικράτηση του ΣΔ2 (OR = 1,45, 95% CIs 1,074-1,95,  $\rho = 0,015$ ). Έπειτα από ανάλυση ROC, τα επίπεδα της SIRT1 2.95 ng / mL αναγνώρισαν την παρουσία ΣΔ2 με ευαισθησία 82% και ειδικότητα 62%(περιοχή κάτω από την καμπύλη ROC: 0.7289, 95% CIs 0.623-0,827,  $\rho\beta$  0,001). Ταυτόχρονα, η ανάλυση γραμμικής παλινδρόμησης των επιπέδων γλυκόζης νηστείας με την SIRT1 σε στεφανιαίους ασθενείς, αποκάλυψε μια θετική συσχέτιση μεταξύ αυτών των δύο παραμέτρων (Γράφημα 1).

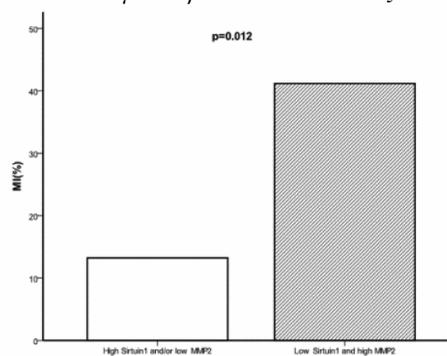
Γράφημα 1: Γραμμική παλινδρόμηση της γλυκόζης νηστείας στα επίπεδα SIRT1 σε ασθενείς με στεφανιαία νόσο (n = 45).



Στη συνέχεια, υπολογίστηκε ένας συνδυαστικός δείκτης χαμηλών τιμών SIRT1 και υψηλών τιμών MMP2 συνδυάζοντας το χαμηλότερο και το υψηλότερο τεταρτημόριο της βασικής κατανομής τους, αντίστοιχα. Ο συνδυαστικός δείκτης χρησιμοποιήθηκε σε περαιτέρω αναλύσεις ως διχοτομημένη μεταβλητή με τιμή 1 όταν τα επίπεδα SIRT1 κατανεμήθηκαν στο χαμηλότερο τεταρτημόριο και τα επίπεδα MMP2 στο υψηλότερο τεταρτημόριο, και με τιμή 0 σε όλες τις άλλες περιπτώσεις (Πίνακας 2). Ο συνδυαστικός δείκτης συσχετίστηκε με το ιστορικό OEM ( $r = 0,3$ ,  $\rho = 0,01$ ) (Γράφημα 2), καθώς συσχετίστηκε ο-

ριακά με την παρουσία ή το ιστορικό κολπικής μαρμαρυγής (AF) ( $r = 0,213$ ,  $\rho = 0,076$ ) (Γράφημα 3). Ο συνδυαστικός δείκτης συνδέθηκε επί-

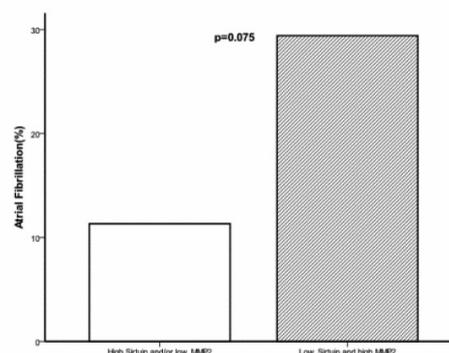
Γράφημα 2: Συσχέτιση του συνδυαστικού δείκτη SIRT1 και MMP2 με ιστορικό οξέος εμφράγματος του μυοκαρδίου του ασθενούς



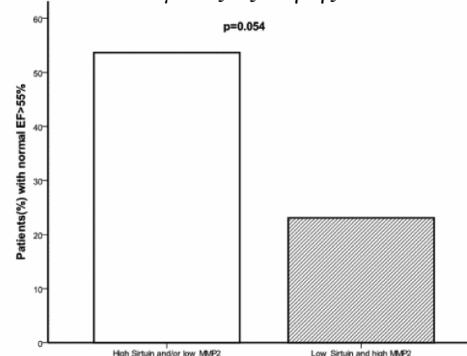
\*MI= myocardial infarction

σης ανεξάρτητα με το κλάσμα εξώθησης στον πληθυσμό μας, μετά από προσαρμογή για διάφορους συγχυτικούς παράγοντες(Γράφημα 4).

Γράφημα 3: Συσχέτιση του συνδυαστικού δείκτη SIRT1 και MMP2 με ιστορικό κολπικής μαρμαρυγής των ασθενών



Γράφημα 4: Ο συνδυαστικός δείκτης SIRT1 και MMP2 ως ανεξάρτητος προγνωστικός δείκτης του κλάσματος εξώθησης.



\*EF= Ejection fraction

**Πίνακας 1: Δημογραφικά στοιχεία και προεγχειρητικές κλινικές παράμετροι των ασθενών**

<b>Φύλο, n (%)</b>	Άνδρες	55 (68)	
	Γυναίκες	26 (32)	
<b>Ηλικία, χρόνια</b>	Μέση τιμή(εύρος)	67.2(33-84)	
<b>Δείκτης μάζας σώματος<sup>1</sup></b>	Μέση τιμή(εύρος)	28.5 (18-38)	
<b>Ομάδα αίματος, n (%)</b>	A	32(46)	
	B	12(17)	
	AB	1(1)	
	0	25(26)	
<b>Συννοσηρότητες</b>	Υπέρταση, n(%)	65(80)	
	Κάπνισμα, n(%)	44(54.3)	
	Πακετοέτη, μέση τιμή(εύρος)	56.4(7-150)	
	Υπερλιπιδαιμία, n(%)	56(69.1)	
	Στατίνες, n(%)	54(66.7)	
	Σακχαρώδης Διαβήτης, n(%)	23(28.3)	
	Περιφερική αρτηριακή νόσος, n(%)	23(28.3)	
	Κολπική μαρμαρυγή, n(%)	13(16)	
	Στεφανιαία νόσος, n(%)	54(66.7)	
	Αριθμός στεφανιαίων αγγείων που πάσχουν, n		
	1	14	
	2	7	
	3	16	
4	11		
5	1		
	Οξύ στεφανιαίο σύνδρομο, n (%)	17(20.9)	
	Χρόνια αποφρακτική πνευμονοπάθεια, n (%)	9(11.1)	
<b>Κατηγοριοποίηση κατά NYHA<sup>1</sup>, n(%)</b>	I	19(23.4)	
	II	12(14.8)	
	III	5(6.1)	
	IV	2(2.4)	
<b>Κατηγοριοποίηση κατά CCS<sup>2</sup> Class, n(%)</b>	I	13(16)	
	II	12(14.8)	
	III	5(6.1)	
	IV	4(4.9)	
<b>Βαλβιδική νόσος, n(%)</b>	Αορτική	Στένωση	30(37)
		Παλινδρόμηση	5(6.1)
	Mitral	Στένωση	19(23.4)
		Παλινδρόμηση	0(0)
		Συνδυασμός	2(2.4)
		Τριγλώχινα	Παλινδρόμηση
<b>Κλινικές και αιματολογικές παράμετροι, μέση τιμή(εύρος)</b>	Γλυκόζη(mg/dl)	105.3(11-252)	
	Κρεατινίνη(mg/dl)	1(0.6-1.9)	
	Ουρία(mg/dl)	33.3(11-143)	
	Κλάσμα εξώθησης (%)	52(30-70)	

<sup>1</sup>NYHA = New York Heart Association ; <sup>2</sup>CCS = Canadian Cardiovascular Society

**Πίνακας 2: Περιγραφικά χαρακτηριστικά του πληθυσμού της μελέτης όπως κατανέμονται στα αντίστοιχα τεταρτημόρια**

Παράμετροι ενδιαφέροντος	Τεταρτημόρια SIRT1/Τεταρτημόρια MMP-2		*p-value
	Υψηλότερο/Χαμηλότερο	Χαμηλότερο/Υψηλότερο	
Ηλία (χρόνια), μέση τιμή ± τυπική απόκλιση	66.4±11.1	69.2±6.5	0.319
Φύλο, n(%)	38(70.37%)	12(66.7%)	0.768
Δείκτης μάζας σώματος(kg/m <sup>2</sup> ), μέση τιμή ±τυπική απόκλιση	28.07±3.38	27.98±4.5	0.931
Υπέρταση, n(%)	42(79.3%)	14(82.4%)	0.780
Κάπνισμα, n(%)	35(66.04%)	8(47.1%)	0.162
Σακχαρώδης Διαβήτης τύπου 2, n (%)	14(26.42%)	6(35.29%)	0.481
Δυσλιπιδαιμία, n(%)	38(71.7%)	13(76.5%)	0.700
MMP-9(ng/ml), διάμεσος (ενδοτεταρτημοριακό εύρος)	67.4 (50.72-107.2)	82.8(53.16-104.5)	0.589
<b>Τύπος χειρουργείου, n (%)</b>			
Αορτοστεφανιαία παράκαμψη	25(46.3)	8(44.4)	
Μιτροειδής βαλβίδα	5(9.26)	3(16.67)	
Αορτική βαλβίδα	19(35.2)	5(27.78)	
Συνδυαστικό	5(9.26)	2(11.11)	0.814
Κλάσμα εξώθησης αριστερής κοιλίας(%) διάμεσος (ενδοτεταρτημοριακό εύρος)	55(50-60)	50(45-50)	0.059
Κλάσμα εξώθησης>55%. n(%)	22(53.7)	3(23.1)	0.054
Στεφανιαία νόσος, n(%)	37(68.52%)	13(76.47%)	0.531
Περιφερική αρτηριακή νόσος, n(%)	15(28.3%)	5(29.47%)	0.930
Ημέρες νοσηλείας, n(%)	7(7-8)	7(6-8)	0.983
Κολπική μαρμαρυγή, n(%)	6(11.32%)	5(29.4%)	0.075
OEM, n(%)	7(13.21)	7(41.18)	0.012

\* Οι τιμές P προέρχονται από τεστ τετράγωνου chi για τις ονομαστικές μεταβλητές και το Kruskal Wallis ή ανεξάρτητο δείγμα δοκιμής T για συνεχείς μεταβλητές.

Ασθενείς με υψηλά επίπεδα MMP2 και χαμηλά επίπεδα SIRT1 είχαν 80% μειωμένες πιθανότητες να παρουσιάσουν ένα φυσιολογικό κλάσμα εξώθησης(>55%), λαμβάνοντας υπόψη ανθρωπομετρικά χαρακτηριστικά και άλλες συννοσηρότητες. Μετά από επαναλήψεις bootstrap, τα διορθωμένα διαστήματα εμπιστοσύνης για το συνδυαστικό δείκτη ήταν 0,053-1,06 και η μετα-

βλητή προέβλεψε οριακά(p = 0,059) ένα χαμηλό κλάσμα εξώθησης.

Επιπλέον, ο συνδυαστικός δείκτης για SIRT1 και MMP2 συσχετίστηκε θετικά με την παρουσία κολπικής μαρμαρυγής στους ασθενείς μας. Ειδικότερα, οι ασθενείς που διανεμήθηκαν στο χαμηλότερο εύρος των επιπέδων της SIRT1 και το υψηλότερο εύρος των επιπέδων του MMP2

είχαν σχεδόν 4 φορές (OR = 4,19, 95% CIs 0.934-18.8,  $p = 0.061$ ) αυξημένες πιθανότητες να παρουσιάσουν κολπική μαρμαρυγή - λαμβάνοντας υπόψη τις διαφορές στην ηλικία, το φύλο, την παρουσία στεφανιαίας νόσου, τον ΣΔ2 και το ιστορικό υπέρτασης).

Αξιοσημείωτο είναι ότι ο συνδυαστικός δείκτης SIRT1-MMP2 συσχετίστηκε με το ιστορικό OEM στον πληθυσμό μας, ανεξάρτητα από τους παραδοσιακούς παράγοντες κινδύνου. Συγκεκριμένα, ασθενείς με συνδυασμό χαμηλών τιμών SIRT1 και υψηλών τιμών MMP2 είχαν δέκα φορές αυξημένες πιθανότητες να εμφανίσουν OEM μετά την προσαρμογή για παραδοσιακούς παράγοντες κινδύνου. Ο συνδυαστικός δείκτης προέβλεψε ανεξάρτητα τον επιπολασμό του OEM (95% CIs 1,44-25,9,  $p = 0,014$ ) με ρυθμίσεις επανειλημματοληψίας.

Όσον αφορά την βελτίωση των διακρίσεων, ο συνδυαστικός δείκτης αύξησε το εμβαδόν(AUC) της σχετικής καμπύλης ROC (0.902, 95% CIs 0.822-0.981) γιτην πρόβλεψη του OEM, όταν προστέθηκαν στο μοντέλο παραδοσιακοί παράγοντες κινδύνου(0.829, 95% CI 0.721-0.937) αλλά η διαφορά στις αντίστοιχες AUC δεν ήταν σημαντικές ( $p = 0,137$ ).

## Συζήτηση

Στην παρούσα μελέτη, εξαγάγαμε δεδομένα από 81 ασθενείς που είχαν προγραμματιστεί για αορτοστεφανιαία παράκαμψη ή για χειρουργείο βαλβίδας. Τα χαμηλά επίπεδα SIRT1 συσχετίστηκαν με τον σακχαρώδη διαβήτη τύπου 2, ενώ παρατηρήθηκε μία ασθενής συσχέτιση με την υπέρταση και επίπεδα της ουρίας. Όταν υπολογίστηκε ένας συνδυαστικός δείκτης χαμηλών επιπέδων SIRT1 και υψηλών επιπέδων MMP2, παρατηρήθηκε μία σημαντική συσχέτιση με ιστορικό εμφράγματος του μυοκαρδίου καθώς και με χαμηλό κλάσμα εξώθησης της αριστερής κοιλίας.

### *SIRT1 και Σακχαρώδης Διαβήτης τύπου 2*

Η SIRT1 είναι μία δεακετυλάση του NAD και βρίσκεται στον πυρήνα και στο κυτταρόπλασμα διαφόρων κυττάρων και έχει μελετηθεί εκτενώς

στην παθοφυσιολογία της αντίστασης στην ινσουλίνη και του σακχαρώδη διαβήτη<sup>8</sup>. Είναι καλά τεκμηριωμένο πως η SIRT1 συμμετέχει στη ρύθμιση του μεταβολισμού της γλυκόζης και των λιπιδίων μέσω της επίδρασής της στη σηματοδότηση της ινσουλίνης<sup>8</sup>. Τα αποτελέσματα της μελέτης μας, είναι σε συμφωνία με την υπάρχουσα βιβλιογραφία, προτείνοντας ότι οι ασθενείς με τα χαμηλότερα επίπεδα SIRT1 παρουσίασαν αυξημένη επίπτωση σακχαρώδη διαβήτη. Προς επίρρωση των αποτελεσμάτων της μελέτης μας, πραγματοποιήθηκε στατιστικός συνυπολογισμός συγχυτικών παραγόντων για ηλικία, βάρος κ.ά. Η υπάρχουσα βιβλιογραφία υποστηρίζει μία πολυπρισματική σχέση μεταξύ SIRT1 και διαβήτη, η οποία κατά βάση προέρχεται από τις αντιοξειδωτικές ιδιότητες της SIRT1. Ο ρόλος της SIRT1 στην αντίσταση στην ινσουλίνη αντικατροπίζεται πρωταρχικά στον ηπατικό και λιπώδη ιστό<sup>8</sup>. Αναφορικά με την αντίσταση στην ινσουλίνη, περιγράφεται ότι η SIRT1 βελτιώνει την ηπατική στεάτωση και το στρες του ενδοπλασματικού δικτύου, οδηγώντας σε ευαισθητοποίηση των ηπατοκυττάρων στην ινσουλίνη. Έχει προταθεί πως τα ρυθμιστικά μόρια των εμπλεκόμενων μηχανισμών είναι ο αυξητικός παράγοντας των ινοβλαστών 21 (FGF21)<sup>9</sup>, ο θηλαστικός παράγοντας του σύμπλοκου της ραπαμυκίνης (mTORC1)<sup>10</sup>, η συνθάση των λιπαρών οξέων (FAS) [11-2], η φωσφοενολοπυροσταφυλική καρμποξυκινάση (PEPCK)<sup>10</sup>, ο ενεργοποιημένος υποδοχέας πολλαπλασιασμού των υπεροξεισωματιών-γ (PPAR-γ)<sup>13</sup> και η καρμποξυλάση του ακετυλσυνένζυμου A<sup>12</sup>. Από πλευράς ευαισθησίας στην ινσουλίνη του λιπώδους ιστού, έχει προταθεί ότι η SIRT1 προωθεί το remodeling του λευκού σε φαιό λιπώδη ιστό, προωθώντας παράλληλα την έκφραση της αδιπονεκτίνης και αναστέλλοντας τη συσσώρευση μακροφάγων<sup>14</sup>. Ταυτόχρονα, η SIRT1 ενισχύει την έκκριση ινσουλίνης από τα β-κύτταρα του παγκρέατος<sup>15</sup>. Συγκεκριμένα, η υπάρχουσα βιβλιογραφία υποστηρίζει ότι η SIRT1 συμβάλλει στη διατήρηση της μάζας των β-κυττάρων, εμποδίζοντας τους μηχανισμούς απόπτωσης και ενισχύοντας την έκκριση της ινσουλίνης μέσω της καταστολής της πρωτεΐνης UCP2<sup>16</sup>. Παρά την αρνητική συσχέτιση SIRT1 και σακχαρώδη διαβήτη, παρατηρήθηκε μια θετική συσχέτισή της με τα επί-

πεδα σακχάρου στο αίμα. Αν και φαινομενικά αντιφατική, η εν λόγω παρατήρηση προκύπτει λόγω των ομοιοστατικών μηχανισμών του οργανισμού. Όπως προαναφέρθηκε, η SIRT1 ενισχύει την έκκριση ινσουλίνης<sup>17</sup>, με αποτέλεσμα να μπορούμε να υποθέσουμε ότι τα υψηλά επίπεδα γλυκόζης λειτουργούν σαν εκλυτικός παράγοντας για την αυξημένη έκφραση της SIRT1.

#### *SIRT1 και υπέρταση*

Οι αντιοξειδωτικές ιδιότητες της SIRT1 δεν περιορίζονται στο μεταβολισμό της ινσουλίνης. Διαδραματίζει σημαντικό ρόλο στην ομοιόσταση του οξειδωτικού στρες σε επίπεδο αγγείων. Συγκεκριμένα, ενεργοποιεί την ενδοθηλιακή συνθάση του μονοξειδίου του αζώτου (eNOS) και μειώνει την δραστηριότητα του NFκB<sup>18</sup>. Η απώλεια έκφρασης της σιρτουίνης σε ανθρώπινα λεία μυϊκά κύτταρα συνδέεται με μειωμένη δυνατότητα για επιδιόρθωση της αγγειακής βλάβης και φυσιολογικής απόκρισης στο στρες<sup>19, 20</sup>. Η SIRT1 φαίνεται να καταστέλλει την παθογένεση της αθηροσκλήρωσης<sup>21</sup> καταπέζοντας την υπερτροφία των λείων μυϊκών κυττάρων και προστατεύοντας ενάντια στην βλάβη του DNA, της εκφύλισης του ενδοθηλίου και της υπέρτασης. Συνεπώς, η οριακή συσχέτιση μεταξύ χαμηλών επιπέδων SIRT1 και υπέρτασης μπορεί να τεκμηριωθεί στο ανώτερο πλαίσιο.

#### *MMP2*

Το MMP2 είναι μία πρωτεΐνη που συμμετέχει στη διάσπαση της εξωκυττάριας ουσίας αποδομώντας το κολλαγόνο τύπου 4, το βασικό συστατικό της βασικής μεμβράνης. Κατ' επέκταση, το MMP2 λαμβάνει μέρος σε φυσιολογικές και παθολογικές διαδικασίες που αφορούν, εκτός των άλλων, και την ιστική αναδόμηση<sup>22</sup>. Ο ρόλος του MMP2 στην κολπική μαρμαρυγή έχει περιγραφεί εκτενώς<sup>23-27</sup> και αποδίδεται κυρίως στο remodeling των κόλπων. Δεδομένου ότι αυτή η συσχέτιση είναι γνωστή, δεν πραγματοποιήθηκε περαιτέρω ανάλυση αυτής.

#### ***Ο δείκτης SIRT1 και MMP2***

##### *Σύλληψη της ιδέας*

Το οξύ έμφραγμα του μυοκαρδίου είναι το κοινό σημείο της εκφύλισης των αγγείων και οδηγεί

κατά βάση σε δυσλειτουργία του μυοκαρδίου. Υπό αυτό το πρίσμα, γεννήθηκε η ιδέα για ένα συνδυαστικό δείκτη –αιτίας και αποτελέσματος. Για αποφυγή υποτίμησης της προγνωστικής αξίας του δείκτη επιλέχθηκαν μόρια τα οποία δεν είχαν γνωστά κοινά μεταβολικά μονοπάτια. Η SIRT1 επιλέχθηκε σαν δείκτης για την κατάσταση των αγγείων ενώ το MMP2 σαν δείκτης καρδιακής λειτουργίας.

Αν και τόσο η SIRT1 όσο και το MMP2 έχουν μελετηθεί ξεχωριστά στην καρδιαγγειακή νόσο, ο συνδυασμός των δύο στα πλαίσια προγνωστικού δείκτη δεν έχει αναφερθεί. Επιπροσθέτως, οι πιο πολλές μελέτες που αφορούσαν την SIRT1, έχουν πραγματοποιηθεί σε επίπεδο ιστού. **Αυτή είναι η πρώτη μελέτη που επιχειρεί συσχέτιση των επιπέδων SIRT1 στο περιφεριακό αίμα με κλινικές παραμέτρους.**

#### *Ο δείκτης σαν προγνωστικός παράγοντας*

Ο συνδυαστικός δείκτης παρουσίασε μία σημαντική συσχέτιση με το έμφραγμα του μυοκαρδίου και το κλάσμα εξώθησης. Στην πρώτη περίπτωση, μία οριστική σύνδεση των επιπέδων SIRT1 στο περιφερικό αίμα και του OEM δεν έχει καθιερωθεί. Η μόνη γνωστή πληροφορία είναι ότι συγκεκριμένοι πολυμορφισμοί στο γονίδιο της SIRT1 οδηγούν σε αυξημένο κίνδυνο εμφράγματος<sup>28, 29</sup>. Αν και τα ακριβή μεταβολικά μονοπάτια δεν έχουν προσδιορισθεί, μπορεί να θεωρηθεί ότι οι προαναφερόμενες παρατηρήσεις οφείλονται στην αντιφλεγμονώδη δράση της SIRT1. Το MMP2 κινείται σε αντίστοιχα μήκη κύματος, διαδραματίζοντας επιβαρυντικό ρόλο στην εμφάνιση μετεμφραγματικών επιπλοκών. Οι Squire και συν. παρουσίασαν συσχέτιση υψηλού κλάσματος εξώθησης και χαμηλών επιπέδων MMP2 μετά από OEM<sup>30</sup>. Το MMP2 σχετίζεται ακόμη με φλεγμονώδεις βλάβες μετά από έμφραγμα και επαναιμάτωση<sup>6</sup>. Οι εν λόγω αρνητικές δράσεις του MMP2 έχουν αποδειχθεί ως ένα βαθμό σε πειραματικά μοντέλα εμφράγματος, όπου παρατηρήθηκαν αυξημένα ποσοστά επιβίωσης ύστερα από αναστολή του MMP2<sup>31</sup>.

Όσον αφορά το κλάσμα εξώθησης, η υπάρχουσα βιβλιογραφία για τη SIRT1 είναι πενιχρή, ενώ η συσχέτιση κλάσματος εξώθησης και MMP2 μπο-

ρεί να βασιστεί στα πλαίσια του remodeling της αριστερής κοιλίας.

#### *Ιδιαίτερα χαρακτηριστικά του δείκτη*

Πέρα από την καινοτομία του, ο νέος αυτός δείκτης έχει συγκεκριμένα πλεονεκτήματα. Η προγνωστική του αξία δεν περιορίζεται από την χρονική του συσχέτιση με το έμφραγμα. Επιπλέον, είναι ανεξάρτητη της στεφανιαίας νόσου. Αυτό το γεγονός υποδηλώνει μια ισχυρή συσχέτιση και τονίζει πως και η αγγειακή βλάβη καθώς και οι επακόλουθες αλλαγές στη λειτουργικότητα του μυοκαρδίου συμμετέχουν προγνωστικά στα πλαίσια του εμφράγματος.

#### *Περιορισμοί*

Η συγκεκριμένη μελέτη έχει ορισμένους περιορισμούς που πρέπει να ληφθούν υπόψη. Ένας σημαντικός περιορισμός είναι η απουσία ομάδας

ελέγχου. Ωστόσο αυτό εν μέρει ξεπεράστηκε με την διαβάθμιση των ασθενών ανάλογα με το ιστορικό στεφανιαίας νόσου. Ένας άλλος περιορισμός της μελέτης μας είναι η αναδρομική φύση της. Μικρότερης σημασίας περιορισμοί είναι ο σχετικά μικρός αριθμός ασθενών και έλλειψη follow-up.

### **Συμπεράσματα**

Πέρα των περιορισμών της, η μελέτη μας προσφέρει μία νέα γνώση εισαγάγοντας έναν συνδυαστικό δείκτη χαμηλών επιπέδων SIRT1 και υψηλών επιπέδων MMP2. Αυτός ο δείκτης μπορεί να χρησιμοποιηθεί σαν προγνωστικός δείκτης για έμφραγμα του μυοκαρδίου ανεξαρτήτως της παρουσίας στεφανιαίας νόσου.

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# Μη Τεχνικές Δεξιότητες στην Επείγουσα Χειρουργική Αντιμετώπιση Μαζικών Συμβαμάτων

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Η επείγουσα χειρουργική αντιμετώπιση οξέων περιστατικών, πολυτραυματιών και άλλων έκτακτων συμβάντων «στον κατάλληλο χρόνο, στο κατάλληλο τόπο και από το κατάλληλο προσωπικό», αποτελεί βασική αρχή ανάπτυξης των περισσότερων συστημάτων υγείας διεθνώς.

Στην περίπτωση της επείγουσας ιατρικής διαχείρισης μαζικών συμβάντων από φυσικές ή ανθρωπογενείς καταστροφές παρουσιάζονται ιδιαίτερες που συχνά παρεμποδίζουν την παραπάνω αρχή. Αφενός συνήθως υπάρχει μεγάλος αριθμός τραυματιών σε σημείο που δημιουργείται μία δυσαναλογία μεταξύ των τραυματιών και των μέσων διάσωσης καθώς και του διαθέσιμου υγειονομικού προσωπικού και αφετέρου τις περισσότερες φορές οι δομές υγείας αναφοράς είναι κατεστραμμένες ή δεν είναι κατάλληλα οργανωμένες. Ειδικότερες δυσκολίες που αντιμετωπίζονται είναι οι ελλείψεις ή/και ανακριβείς πληροφορίες από και προς το πεδίο του συμβάντος, η πίεση του χρόνου, οι αντίξοες και αυξημένης επικινδυνότητας συνθήκες παροχής ιατρικών υ-

πηρεσιών, η προβληματική επικοινωνία, η συνεργασία και ο συντονισμός μεταξύ χειρουργών και υγειονομικών και λοιπών επαγγελματιών που προέρχονται από διαφορετικά υπόβαθρα και υπηρεσίες.

Γεννάται λοιπόν η ανάγκη οργανωσιακών, εκπαιδευτικών και δομικών αλλαγών στα συστήματα επείγουσας ιατρικής διαχείρισης ώστε να μπορούν να δοθούν έμπρακτα απαντήσεις σε κεντρικά ερωτήματα όπως

- Πώς μπορεί να διασφαλιστεί ότι το χειρουργικό προσωπικό θα είναι σε θέση να ανταπεξέλθει στο ιδιαίτερα απαιτητικό και πολύπλοκο τομέα της παροχής ιατρικής φροντίδας στο πεδίο
- Ποιοι είναι οι εκπαιδευτικοί παράμετροι εκείνοι που μπορούν να συνδράμουν στην αρτιότερη και ασφαλέστερη διενέργεια ιατρικών και ειδικότερα χειρουργικών πράξεων καθώς και την ομαλή έκβαση των ασθενών

Στην κλασσική θεώρηση, η άσκηση της χειρουργικής καθορίζεται από τις τεχνικές δεξιότη-

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τες αυτών που την ασκούν, γεγονός που δικαιολογεί και την σχετική προτεραιότητα στην εκπαίδευσή τους.

Ολοένα και περισσότερο αναγνωρίζεται στην διεθνή βιβλιογραφία και διαφαίνεται σε εκπαιδευτικά μοντέλα που τα τελευταία χρόνια έχουν αρχίσει να αναπτύσσονται σε χώρες όπως η ΗΠΑ, η Μεγάλη Βρετανία, η Αυστραλία αλλά και από διεθνείς οργανισμούς όπως ο Παγκόσμιος Οργανισμός Υγείας, η ανάγκη διερεύνησης του βαθμού επιρροής σειράς γνωστικών, κοινωνικών και διαπροσωπικών δεξιοτήτων και στάσεων των γενικών χειρουργών στον τρόπο διαχείρισης των συμβάντων αυτών.

Σύμφωνα με τις βασικές διαπιστώσεις και συστάσεις για την εκπαίδευση και την κατάρτιση σε θέματα ασφάλειας των ασθενών σε ολόκληρη την Ευρώπη - έτσι όπως αυτές έχουν αναπτυχθεί την τελευταία πενταετία - θα πρέπει να δοθεί έμφαση στην ανάγκη υποστήριξης και εστίασης σε «μη τεχνικές δεξιότητες» παράλληλα με την απαραίτητη θεωρητική και πρακτική κατάρτιση των γενικών χειρουργών.

Ο όρος «μη τεχνικές δεξιότητες» περιλαμβάνει το σύνολο των γνωστικών, κοινωνικών και διαπροσωπικών δεξιοτήτων και στάσεων ζωής, που συμπληρώνουν τις τεχνικές δεξιότητες και συμβάλλουν στην αποτελεσματικότητα και ασφάλεια των χειρουργικών πράξεων. Αφορούν την

επικοινωνία, τη συνεργασία, την ικανότητα σχεδιασμού, την αντιμετώπιση διενέξεων, την ιεράρχηση προτεραιοτήτων, τη διαχείριση των διαθέσιμων πόρων (ανθρώπινων και υλικών), και την ικανότητα λήψης αποφάσεων (βλ. Πίνακα 1).

Μπορούν να διαιρεθούν σε δυο υποομάδες: γνωστικές ή διανοητικές (πχ λήψη αποφάσεων, σχεδιασμός, επίγνωση της κατάστασης) και κοινωνικές ή διαπροσωπικές ικανότητες (πχ συνεργασία, επικοινωνία, ηγετικά προσόντα, δυνατότητα διαχείρισης stress και κόπωσης). Πρόκειται για ένα σύνολο κοινωνικών και επαγγελματικών δεξιοτήτων που είναι απαραίτητα ώστε να μπορεί κάποιος να ανταπεξέλθει στις δύσκολες συνθήκες εργασίας και συνεργασίας που προκύπτουν από ένα καταστροφικό γεγονός.

Παρόλο που υπάρχει ολοένα και μεγαλύτερο εκπαιδευτικό ενδιαφέρον σχετικά με τη διαχείριση καταστροφών, η ανασκόπηση της διεθνούς βιβλιογραφίας αναδεικνύει επαναλαμβανόμενα μοτίβα ελλιπούς ανταπόκρισης και διαχείρισης. Σταδιακά λοιπόν ο αποτελεσματικός και αποδοτικός σχεδιασμός μοντέλων επείγουσας ιατρικής διαχείρισης μαζικών συμβάντων με κεντρικό γνώμονα την ασφάλεια των ασθενών και την παροχή ποιοτικής περίθαλψης καλείται να εντάξει στην εστιασμένη εκπαίδευση και τις μη τεχνικές δεξιότητες. Σκοπός είναι η ενδυνάμωση των γενικών χειρουργών ούτως ώστε να αποκτούν επί-

**Πίνακας 1:** Ταξινόμηση των μη τεχνικών δεξιοτήτων με βάση τις κατευθυντήριες NOTTS (Non-Technical Skills for Surgeons (NOTSS) του Βασιλικού Κολλεγίου Χειρουργών του Εδιμβούργου, Μεγάλη Βρετανία

Κατηγορία	Επιμέρους Στοιχεία
<b>Επίγνωση του περιβάλλοντος/κατάστασης</b>	<ul style="list-style-type: none"> <li>• Συλλογή πληροφοριών</li> <li>• Κατανόηση πληροφοριών</li> <li>• Ετοιμότητα</li> </ul>
<b>Διαδικασία λήψης αποφάσεων</b>	<ul style="list-style-type: none"> <li>• Διερεύνηση επιλογών</li> <li>• Αξιολόγηση επιλογών και αποφάσεις</li> <li>• Επικοινωνία των επιλογών και αποφάσεων</li> <li>• Υλοποίηση και αξιολόγηση αποφάσεων</li> </ul>
<b>Επικοινωνία και Συνεργασία</b>	<ul style="list-style-type: none"> <li>• Ανταλλαγή πληροφοριών</li> <li>• Δημιουργία συνθηκών αμοιβαίας επικοινωνίας και κοινής κατανόησης</li> </ul>
<b>Ηγεσία</b>	<ul style="list-style-type: none"> <li>• Συντονισμός της ομάδας</li> <li>• Στοχοθεσία και διατήρηση προτύπων</li> <li>• Υποστήριξη μελών της ομάδας</li> <li>• Αντοχή στην πίεση</li> </ul>

Στην αντικειμενική εξέταση διαπιστώνεται συχνά (>90 %) ευαίσθητη ηπατομεγαλία, που οφείλεται σε διάταση των νευρικών απολήξεων της κάψας του Glisson, και σπληνομεγαλία (20%).<sup>14</sup> Το ήπαρ είναι μεγάλο, σκληρό και μπορεί να σφύζει. Έτσι, σε ανεπάρκεια της τριγλώχινας μπορεί να γίνονται αντιληπτές συστολικές σφύξεις του ήπατος (“σφύζων ήπαρ”), ενώ σε στένωση της τριγλώχινας προσυστολικές σφύξεις.<sup>15,16</sup> Επίσης, οι ασθενείς παρουσιάζουν διάταση των φλεβών του τραχήλου και ηπατοσφαγιτιδική παλινδρόμηση.<sup>17,18</sup> Σε ασθενείς με περικαρδίτιδα μπορεί να διαπιστωθούν σημεία καρδιακού επιποματισμού (παράδοξος σφυγμός, σημείο Kussmaul).

Οι ασθενείς δεν έχουν στίγματα χρόνιας ηπατικής νόσου (αγγειοματώδεις σπίλους κλπ) ή πυλαιοσυστηματικές αναστομώσεις (πχ κισσούς οισοφάγου). Συνυπάρχουν, συχνά, περιφερικά οιδήματα, πλευρίτιδα (συνήθως δεξιά) και ασκίτης (25% των ασθενών,<sup>3</sup> συχνότερα σε χρόνιες καταστάσεις παρά σε οξεία δεξιά καρδιακή ανεπάρκεια ή συμπίεστική περικαρδίτιδα). Ο ασκίτης μπορεί να είναι δυσανάλογα μεγάλος σε σχέση με τα περιφερικά οιδήματα και την βαρύτητα των υπολοίπων συμπτωμάτων της καρδιακής ανεπάρκειας ή της περικαρδίτιδας. Το λεύκωμα του ασκίτικού υγρού είναι μεγαλύτερο από το συνήθως παρατηρούμενο στην κίρρωση του ήπατος (>2,5 g/dl), με κλίση λευκοματίνης ασκίτικού υγρού και αίματος >1,1 g/dl και προσομοιάζει με το παρατηρούμενο σε σύνδρομο απόφραξης των ηπατικών φλεβών (Budd-Chiari).<sup>19,20</sup> Επίσης, το ασκίτικό υγρό περιέχει περισσότερα ερυθρά αιμοσφαίρια απ’ότι παρατηρείται σε άλλης αιτιολογίας κίρρωση του ήπατος. Σπανιότερα, μπορεί να διαπιστωθεί χυλώδης ασκίτης (τριγλυκερίδια >150mg/dl, ή τριγλυκερίδια υγρού>τριγλυκερίδια αίματος) που αποδίδεται σε αυξημένη πίεση στα λεμφικά αγγεία του μεσεντερίου που είναι δυνατόν να ραγούν.<sup>21,22,23</sup>

Εργαστηριακά, διαπιστώνονται αύξηση της χολερυθρίνης στο 25-80% (άμεση < έμμεση), των τρανσαμινασών (alanine aminotransferase-ALT, aspartate aminotransferase-AST), της γαλακτικής αφυδρογονάσης (Lactate Dehydrogenase, LDH) και της γ-γλουτάμυλ-τρανσπεπτιδάσης (Gamma-glutamyl transferase, γ-GT) στο 30-60%, παρά-

ταση του χρόνου προθρομβίνης (Χρ. Quick) στο 80-90%, υπολευκωματιναιμία στο 30-50% και ελαφρά υπεργαμμασφαιριναιμία στο 50% των ασθενών.<sup>24</sup> Η αλκαλική φωσφατάση (alkaline phosphatase, ALP) είναι φυσιολογική ή λίγο αυξημένη. Οι βιοχημικές αυτές διαταραχές υποχωρούν με τη βελτίωση της καρδιακής λειτουργίας.

Η χολερυθρίνη στο 1/3 των ασθενών υπερβαίνει τα 2mg/dl, αλλά παραμένει συνήθως σε επίπεδα <3mg/dl. Η συμφόρηση του ηπατικού παρεγχύματος προκαλεί αύξηση της πίεσης στα ηπατικά κολποειδή, η οποία συνεπάγεται καταστροφή του ενδοθηλίου τους, αύξηση της πίεσης άμεσα στα ηπατικά κύτταρα και ακολούθως στα χοληφόρα τριχοειδή με αποτέλεσμα την αύξηση της χολερυθρίνης. Ο ίκτερος βαθιάνει όσο τα επεισόδια της καρδιακής ανεπάρκειας επιτείνονται.<sup>5</sup> Η διαφορική διάγνωση του ικτέρου σε ασθενή με καρδιακή ανεπάρκεια περιλαμβάνει την συμφόρηση του ήπατος, την πνευμονική εμβολή (αυξημένη παραγωγή έμμεσης χολερυθρίνης από αποδόμηση των ερυθρών αιμοσφαιρίων), τη χοληδοχολιθίαση, τη σηψαιμία, την αιμόλυση και τη φαρμακευτική ηπατοτοξικότητα. Οι τρανσαμινάσες είναι λίγο (2-3 φορές η ανώτερη φυσιολογική τιμή - 2-3XΦΤ) αυξημένες αλλά μπορεί να αυξηθούν πολύ σε παροξύνσεις της νόσου (σε συνδυασμό με μείωση της καρδιακής παροχής –ισχαιμική ηπατίτιδα).<sup>5</sup>

Στο υπερηχογράφημα κοιλίας παρατηρείται συχνά διάταση της κάτω κοίλης φλέβας και των ηπατικών φλεβών.<sup>25</sup> Οι περισσότεροι ασθενείς παρουσιάζουν παθολογικά ευρήματα στο υπερηχογράφημα καρδιάς, που οφείλονται σε διατακτική μυοκαρδιοπάθεια, στεφανιαία νόσο, υπερτροφική μυοκαρδιοπάθεια, οξεία μυοκαρδίτιδα κ.ά. Οι αποτιτανώσεις στο περικάρδιο στην απλή ακτινογραφία ή στην αξονική τομογραφία βοηθούν στη διάγνωση της συμφυτικής περικαρδίτιδας. Η βιοψία ήπατος συχνά δεν είναι εφικτή λόγω του ασκίτη και των διαταραχών της πήξεως. Η ιστολογική εικόνα (με διάταση των κολποειδών και αιμορραγικές νεκρώσεις) μπορεί να ομοιάζει με την παρατηρούμενη στο σύνδρομο Budd-Chiari.<sup>26,27</sup> Όταν υπάρχει αμφιβολία για τη διάγνωση, διενεργείται δεξιός καρδιακός καθετηριασμός με προσδιορισμό των πιέσεων της πνευμονικής κυκλοφορίας.

γνωση του περιβάλλοντός τους σε καταστάσεις δυναμικές και ταχέως εξελισσόμενες, να μπορούν να αλληλοεπιδρούν και να λαμβάνουν γρήγορες αποφάσεις ιδιαίτερα σε επείγουσες καταστάσεις και υπό την επήρεια έντονου στρες.

Παράλληλα λοιπόν με τις τεχνικές δεξιότητες απαραίτητες για την αντιμετώπιση καταστροφών, όπως το να εκτιμάει ο χειρουργός τη σοβαρότητα ενός τραυματισμού, να κάνει διαλογή, να παρέχει πρώτες βοήθειες, να συντονίζει και να κα-

τευθύνει την έρευνα και διάσωση θυμάτων, να αντιμετωπίζει συμβάντα μαζικών απωλειών σε προ νοσοκομειακό επίπεδο κρίνεται απαραίτητη η καλλιέργεια και ενδυνάμωση σε ότι αφορά τις μη τεχνικές δεξιότητες, όπως η επικοινωνία, η συνεργασία, η ομαδική εργασία, η επίγνωση της κατάστασης, η ηγεσία, η κριτική σκέψη και η λήψη αποφάσεων κάτω από δύσκολες συνθήκες (βλ Πίνακα 2).

**Πίνακας 2:** Αναμενόμενα αποτελέσματα από την εκπαίδευση ως προς τις μη τεχνικές δεξιότητες με βάση τις κατευθυντήριες NOTTS (Non-Technical Skills for Surgeons (NOTSS) του Βασιλικού Κολλεγίου Χειρουργών του Εδιμβούργου, Μεγάλη Βρετανία

Κατηγορία	Αναμενόμενα αποτελέσματα
<b>Επίγνωση του περιβάλλοντος/κατάστασης</b>	Η ανάπτυξη και η διατήρηση μιας δυναμικής και εξελισσόμενης επίγνωσης της κατάστασης στο χειρουργείο με βάση την συγκέντρωση και αξιολόγηση δεδομένων από το περιβάλλον (ασθενής, ομάδα, χρόνοι, τεχνολογικός εξοπλισμός). Η κατανόηση αφορά την επίγνωση του τι ακριβώς συμβαίνει την συγκεκριμένη στιγμή αναφοράς αλλά και το ποια εν δυνάμει μπορεί να είναι η εξέλιξη στην συνέχεια.
<b>Διαδικασία λήψης αποφάσεων</b>	Δεξιότητες για τη διάγνωση και την επιλογή της αποδοτικότερης και αποτελεσματικότερης ιατρικής/χειρουργικής απόφασης.
<b>Επικοινωνία και Συνεργασία</b>	Δεξιότητες και επικοινωνιακή ικανότητα για ορθή καθοδήγηση της χειρουργικής ομάδας και λοιπών εμπλεκόμενων ειδικοτήτων ώστε να έχουν όλοι μια όσο το δυνατό πιο ολοκληρωμένη εικόνα της κατάστασης που εξελίσσεται και να μπορούν να πράξουν ανάλογα.
<b>Ηγεσία</b>	Καθοδήγηση της ομάδας στο χειρουργείο, υψηλού επιπέδου πρότυπα κλινικού έργου και φροντίδας του ασθενούς και ενσυναίσθηση σχετικά με τις ανάγκες των μελών της χειρουργικής ομάδας και λοιπών εμπλεκόμενων ειδικοτήτων.

Ο συνδυασμός αυτός τεχνικών ικανοτήτων και μη τεχνικών δεξιοτήτων θεωρείται ότι εν δυνάμει μπορεί να αποδώσει κατά τον σχεδιασμό και προετοιμασία για την αντιμετώπιση φυσικών και ανθρωπογενών καταστροφών. Στο πλαίσιο αυτό οι ανάγκες του πληθυσμού εξαιτίας της αύξησης του αριθμού αλλά και της ένταξης των συμβάντων με μαζικές απώλειες ζωής σε συνδυασμό με τις οικονομικές και οργανωτικές προκλήσεις που

αντιμετωπίζονται στο υγειονομικό χώρο την τρέχουσα περίοδο καθιστούν αναγκαίες την στοχευμένη και κατά περίπτωση σχετική ενεργοποίηση της ακαδημαϊκής κοινότητας.

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**Puskas John D.**

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# The impact of body mass index on morbidity and short- and long-term mortality in cardiac valvular surgery

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## ABSTRACT

**Objective:** Limited data exist on patients with cardiac cachexia or morbid obesity presenting for valvular heart surgery. The objective of this study was to investigate the relationship between body mass index and morbidity and mortality after valvular surgery.

**Methods:** A retrospective review of 4247 patients undergoing valvular surgery from 1996 to 2008 at Emory University

Healthcare Hospitals was performed. Patients were divided into 3 groups: body mass index 24 or less (group 1, n = 1527), body mass index 25 to 35 (group 2, n = 2284), and body mass index 36 or more (group 3, n = 436). Data were analyzed using multivariable regression analysis, adjusted for 10 preoperative covariates. A smooth kernel regression curve was generated using body mass index and in-hospital mortality as variables. Long-term survival comparisons were made using adjusted Cox proportional hazards regression models and Kaplan-Meier product-limit estimates. Kaplan-Meier curves were generated that provide survival estimates for long-term mortality using the Social Security Death Index.

**Results:** Patients in group 3 were significantly younger (group 1, 61.7 ± 16.1 years;

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group 2,  $61.9 \pm 13.6$ ; group 3,  $57.5 \pm 13.0$ ;  $P < .001$ ) and more likely to be female (group 1, 778/1527 [51.0%]; group 2, 912/2284 [39.9%]; group 3, 240/436 [55.0%];  $P < .001$ ). Mean ejection fractions were similar among groups ( $P = .51$ ). Patients in group 2 had significantly shorter postoperative length of stay (group 1,  $9.6 \pm 10.3$  days; group 2,  $8.7 \pm 8.2$  days; group 3,  $10.8 \pm 11.0$  days;  $P < .001$ ). In-hospital mortality for the entire cohort was 5.8% (245/4247), and by group was 111 of 1527 (7.3%) in group 1, 110 of 2284 (4.8%) in group 2, and 24 of 436 (5.5%) in group 3 ( $P = .006$ ). Actual survival at 1, 3, 5, and 10 years was significantly lower in group 1 ( $P < .001$ ). A lower body mass index was a significant independent predictor for both in-hospital and long-term mortality.

**Conclusions:** Patients with body mass index 24 or less are at significantly increased risk of in-hospital and long-term mortality after cardiac valvular surgery. This high-risk patient population warrants careful risk stratification and options for less-invasive valve therapies. (J Thorac Cardiovasc Surg 2011;142:1052-61)

It has been well defined that obesity has a major influence on the development of cardiovascular disease, leading to worsening physical function and quality of life.<sup>1,2</sup> The alterations to the vascular endothelium as a consequence of obesity include promotion of atherosclerosis, alteration in cardiac ventricular load and efficiency, promotion of adverse inflammatory milieu, and predisposition to proteinuria and renal dysfunction.<sup>3</sup> In light of the changes to the vascular endothelium and the prevalence of obesity-related coronary artery disease in the United States, the majority of the literature regarding outcomes of obese patients has concentrated on those undergoing coronary artery bypass grafting (CABG) or mixed cardiac surgical populations.<sup>4-13</sup>

Correspondingly, patients presenting with malnutrition represent another high-risk group presenting with cardiovascular disease. In contrast with obesity, malnutrition is an often overlooked preoperative comorbid condition in patients undergoing cardiac surgery.<sup>14</sup> Although some have noted that malnutrition increases short-term morbidity and mortality after cardiac operations,<sup>15-17</sup> others have shown more favorable in-hospital outcomes.<sup>5</sup> Studies evaluating malnutrition have concentrated on patients undergoing CABG.

The current study investigated the relationship between body mass index (BMI) and morbidity and mortality in 4247 patients undergoing cardiac valvular surgery. Specifically, we evaluated unadjusted in-hospital morbidity and mortality and long-term

all-cause survival within different quartiles of BMI values.

#### Abbreviations and Acronyms

AVR	= aortic valve replacement
BMI	= body mass index
CABG	= coronary artery bypass grafting
CI	= confidence interval
NYHA	= New York Heart Association
STS	= Society of Thoracic Surgeons

#### MATERIALS AND METHODS

This study sought to characterize the relationship between BMI and clinical outcomes after valve surgery. For descriptive purposes, patients were classified into 3 groups according to their BMI classification by O'Brien and colleagues:<sup>18</sup> (1) 24 or less, (2) 25 to 35, and (3) 36 or more. Patients were identified by querying the institutional Society of Thoracic Surgeons (STS) Adult Cardiac Database for consecutive patients who underwent valve surgery at Emory Healthcare Hospitals between January 1, 1996, and June 30, 2008. Patients with concomitant CABG were included, and patients undergoing emergency operation or operation under salvage conditions were excluded.

During this period, 4649 consecutive patients underwent valve surgery. Of these, 4247 patients (91.4%) had the available data to calculate BMI. Thus, 402 patients were excluded because their BMI control was missing. Extracted records in-

cluded demographic data, preexisting comorbidities, and clinical outcomes. The study was approved by the Emory University Institutional Review Board in compliance with Health Insurance Portability and Accountability Act regulations and the Declaration of Helsinki. The institutional review board waived individual patient consent secondary to the retrospective nature of the study.

### ***Interventions, Surgeons, and Surgical Technique***

Each patient underwent a single surgical session performed at the discretion of any of 19 faculty surgeons. Cardiac catheterization was performed in all patients aged more than 40 years or in younger patients with risk factors for coronary artery disease. Standard cardiopulmonary bypass techniques for valve operations were used in all patients. Surgical approach, valve prosthesis or repair techniques, and conduct of cardiopulmonary bypass and myocardial protection were left to the discretion of the attending cardiac surgeon. Typically, conventional cardiopulmonary bypass was performed using roller head pumps, membrane oxygenators, cardiotomy suction, arterial filters, cold antegrade and retrograde blood cardioplegia, and moderate systemic hypothermia (32°C–34°C). The operative field was routinely flooded with carbon dioxide, and de-airing maneuvers were performed in all cases before releasing the crossclamp.

### ***Long-Term Follow-up***

The Social Security Death Index is a publicly available national database of death records extracted from the US Social Security Administration's Death Master File Extract. Patients with a Social Security Number who have died since 1963 and whose death has been reported to the Social Security Administration will be listed in the Social Security Death Index. For each patient who died before the cutoff date of June 30, 2008, a mortality date was provided, allowing Kaplan–Meier long-term survival curves. Cause of death is not available; thus, this study describes all-cause long-term mortality.

### ***Variables of Interest***

Before analysis, 22 preoperative risk factors for the outcomes of interest were identified and har-

vested from the STS database (Table 1). Standard STS definitions for each risk factor and outcome were used. Race was dichotomized as Caucasian or non-Caucasian. Chronic lung disease was ordinarily measured in some later years and dichotomously measured in earlier years; in this study it was dichotomized. New York Heart Association (NYHA) heart failure classification was dichotomized as class III/IV or I/II. The primary outcomes examined in this study were in-hospital mortality and long-term survival; secondary end points included permanent stroke (cerebrovascular accident), myocardial infarction, the composite end point for any of these major adverse cardiac, and cerebrovascular events and operative reintervention.

The institutional medical records STS database was populated by trained personnel devoted exclusively to data management; thus, missing data were scarce. Data were 100% complete for each major postoperative hospital outcome. Data were missing for the following preoperative characteristics: NYHA classification III/IV ( $n = 1376$ , 32.4%), ejection fraction ( $n=771$ , 18.2%), last creatinine level ( $n=735$ , 17.3%), and Caucasian race ( $n = 336$ , 7.9%).

### ***Data Management and Statistical Analysis***

All data for consecutive patients were entered into a computerized surgical database, using the fields and definitions of the STS National Adult Cardiac Database.

Checks for data quality were used at the institutional level and before final entry into the STS national adult cardiac database.

A multiple imputation algorithm was used to impute missing values so that the whole sample could be analyzed. This was not done in an effort to re-create the truth; rather, the goal of the imputation was to avoid selection bias that can occur by deleting cases with missing variables of interest.

To initially evaluate the relationship between BMI and in-hospital mortality, kernel estimation smoothing was used. To this end, a plot was created where the x-axis was BMI and the y-axis was observed in-hospital mortality. Because observed mortality is dichotomous, the points on the plot at

each BMI value are calculated by taking an average of the observed mortality (so-called uniform kernel smoothing) for a “neighborhood” around the BMI value. The neighborhood is the collection of points within a small range around the BMI value; thus, the point on the plot is the average mortality rate for that small region of BMI values. The width of the neighborhood was set at 15%, meaning that each point plotted represents a moving average of 30% of the data.

To statistically evaluate the effects of BMI on in-hospital mortality, a multivariable logistic regression model was constructed. The model contains 10 additional preoperative covariates to adjust for potential selection bias: age, sex, dialysis, renal failure, heart failure, ejection fraction, presence of concomitant CABG, infectious endocarditis, previous stroke, and chronic lung disease. According to the smoothed curve, it was determined that BMI has a parabolic relationship with mortality; thus, BMI and BMI<sup>2</sup> were entered as a quadratic chunk into the regression model and evaluated as a chunk. Adjusted odds ratios associated with BMI and other covariates, along with 95% confidence intervals (CIs), were computed.

Long-term survival comparisons were made using adjusted Cox proportional hazards regression models and Kaplan–Meier product-limit estimates (unadjusted). Kaplan–Meier curves were generated that provide survival estimates at post-operative points in time. Differences between BMI classifications were determined by log-rank tests. These estimates include operative deaths.

Adjusted long-term survival comparisons were made by using proportional hazards regression to model the instantaneous hazard of death as a function of BMI and BMI<sup>2</sup>, adjusted for age, sex, dialysis, renal failure, heart failure, ejection fraction, presence of concomitant coronary artery bypass, infectious endocarditis, previous stroke, and chronic lung disease. The proportional hazards assumption was verified via a correlation analysis of the Schoenfeld residuals and ranked follow-up time. Hazard ratios were generated for each model term, along with 95% CI.

Data were managed and analyzed using SAS Version 9.1 (SAS Institute Inc, Cary, NC). Unadjusted comparisons were performed with chi-square tests and 2-sample t tests for categorical and continuous predictors, respectively. All statistical tests

**TABLE 1. Preoperative characteristics**

Characteristic	BMI ≤ 24 (n = 1527)	BMI 25–35 (n = 2284)	BMI ≥ 36 (n = 436)	P value
Age (mean ± SD)	61.7 ± 16.1	61.9 ± 13.6	57.5 ± 13.0	<.001
Female gender	778 (50.9%)	912 (39.9%)	240 (55.0%)	<.001
Caucasian*	1111 (78.3%)	1661 (79.2%)	281 (71.3%)	.003
Status				.046
Elective	1293 (84.7%)	1966 (86.1%)	356 (81.7%)	
Urgent	234 (15.3%)	317 (13.9%)	80 (18.3%)	
Ejection fraction (mean % ± SD)*	53.0 ± 13.5	52.6 ± 13.4	53.3 ± 12.8	.51
Hypertension	855 (56.0%)	1540 (67.0%)	349 (80.1%)	<.001
NYHA class 3 and 4*	475 (46.5%)	715 (46.9%)	169 (52.3%)	.16
Diabetes	186 (12.2%)	501 (21.9%)	164 (37.6%)	<.001
COPD*	273 (17.9%)	335 (14.7%)	101 (23.2%)	<.001
Previous myocardial infarction	236 (15.5%)	372 (16.3%)	78 (17.9%)	.46
Previous CVA	152 (10.0%)	183 (8.0%)	34 (7.8%)	.09
Previous valve surgery	108 (33.6%)	108 (26.5%)	10 (13.2%)	<.001
Cerebrovascular disease	229 (15.0%)	322 (14.1%)	63 (14.5%)	.74
Peripheral vascular disease	100 (6.6%)	147 (6.4%)	22 (5.1%)	.50
Mean preoperative serum creatinine*	1.46 ± 1.68	1.38 ± 1.50	1.38 ± 1.45	.30
Chronic renal insufficiency	178 (11.7%)	204 (8.9%)	48 (11.0%)	.019
Preoperative dialysis	82 (5.4%)	80 (3.5%)	20 (4.6%)	.019
Infectious endocarditis	167 (10.9%)	168 (7.4%)	31 (7.1%)	<.001
Dyslipidemia	298 (19.5%)	619 (27.1%)	159 (36.5%)	<.001
Current smoker	424 (27.8%)	664 (29.1%)	145 (33.3%)	.08
Preoperative IABP	8 (0.5%)	10 (0.4%)	2 (0.5%)	.93
Immunosuppressive therapy	85 (5.6%)	107 (4.7%)	29 (6.7%)	.17
STS Predicted risk of mortality*	4.9 ± 5.2	3.8 ± 4.0	3.5 ± 3.7	<.001

BMI, Body mass index; SD, standard deviation; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; IABP, intra-aortic balloon pump. \*Contains some missing data.

were 2-sided using an  $\alpha = 0.05$  level of significance. No adjustments for multiple tests were made.

## RESULTS

### *Preoperative and Operative Characteristics*

A total of 4247 patients underwent valve surgery at a single academic institution and comprise the study group. The patients were divided into 3 groups: group 1 (BMI  $\leq 24$ ,  $n = 1527$ ), group 2 (BMI, 25–35;  $n = 2284$ ), and group 3 (BMI  $\geq 36$ ,  $n = 436$ ). Preoperative characteristics are shown in Table 1. Notably, patients in group 3 were younger, more likely to be female, and more likely to have hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and dyslipidemia. Patients in group 1 were more likely to have had previous valve surgery, preoperative dialysis, and infectious endocarditis. In all groups, approximately one half of patients were in NYHA class III or IV, and the ejection fraction was 53%. The STS predicted risk of mortality was significantly higher in those patients with BMI 24 or less.

Table 2 describes operative procedures according to BMI group. Both aortic crossclamp and cardiopulmonary bypass times were significantly longer in group 3. The most common valve surgery was aortic valve replacement (AVR) in all groups. Bioprosthetic valve implantation was similar among groups at approximately 50%. CABG and placement of an intraoperative intraaortic balloon pump were more common in group 3.

### *In-Hospital Morbidity and Mortality*

Unadjusted in-hospital outcomes are described in Table 3. Overall, in-hospital mortality occurred in 245 patients (5.8%). Mediastinitis, new renal failure, prolonged ventilation, and total initial intensive care unit length of stay were more common in group 3. However, in-hospital mortality was significantly greater in group 1. The observed to STS predicted risk of mortality expected ratio was 1.48 in group 1, 1.17 in group 2, and 1.25 in group 3. After adjusting for 10 covariates using a multivariable logistic regression analysis (Table 4), BMI trended as an independent predictor for in-hospital mortality (odds ratio, 0.89; 95% CI, 0.78–1.01;

$P = .07$ ). However, the following variables emerged as statistically significant predictors of in-hospital mortality: renal insufficiency, advanced age, female gender, endocarditis, and previous stroke.

To evaluate the relationship between BMI and in-hospital mortality, kernel estimation smoothing was used and is represented in Figures 1 to 5. An initial analysis of all patients (Figure 1) reveals the lowest in-hospital mortality in those patients with a normal BMI. Furthermore, this bimodal curve reveals the highest mortality in those with the lowest BMI and increasing mortality in those with a BMI greater than 32. Further analysis revealed a similar curve for those undergoing isolated AVR (Figure 2). In those undergoing isolated mitral valve procedures (Figure 3), multiple valve procedures (Figure 4), or concomitant CABG (Figure 5), there was a significant increased mortality in those with a lower BMI.

### *Long-term Mortality*

The median follow-up for all patients was 4.4 years. Survival estimates for each group are shown in Table 5 and in the Kaplan–Meier curve in Figure 6. When all patients were grouped according to BMI status, 10-year survival was significantly reduced among patients with a BMI of 24 or less compared with those with higher BMI status (group 1: 53.5% vs group 2: 63.4% vs group 3: 62.2%;  $P < .001$ ). After multivariable adjustment, BMI was associated with reduced long-term survival (hazard ratio, 0.91; 95% CI, 0.86–0.97;  $P = .002$ ). Other significant independent predictors of long-term mortality are listed in Table 6 and include renal failure, older age, female sex, heart failure, endocarditis, stroke, and chronic lung disease.

## DISCUSSION

Although data on malnourished surgical patients have existed for some time, the role of low BMI as a risk factor for morbidity and mortality has been largely ignored, likely because of the burgeoning epidemic of obesity in the United States. This study serves to add to the growing body of literature detailing increased morbidity and mortality in patients

**TABLE 2. Operative characteristics for each body mass index group**

Operative data	BMI ≤ 24 (n = 1527)	BMI 25–35 (n = 2284)	BMI ≥ 36 (n = 436)	P value
BMI	22.1 ± 2.14 Median: 22.5	28.9 ± 2.7 Median: 28.4	39.6 ± 4.4 Median: 38.3	<.001
Aortic crossclamp time (min) (mean ± SD)	85.0 ± 32.7 Median: 80.0	90.4 ± 32.5 Median: 85	96.8 ± 37.7 Median: 89	<.001
CPB time (min) (mean ± SD)	123.3 ± 46.5 Median: 114	127.5 ± 42.6 Median: 120	135.0 ± 51.0 Median: 123	<.001
Isolated primary AVR	614 (40.2%)	1144 (50.1%)	246 (56.4%)	<.001
AVR valve size implanted	22.7 ± 2.4 Median: 23	Mean: 23.3 ± 2.5 Median: 23	Mean: 23.4 ± 2.4 Median: 23	<.001
Isolated primary MV procedure	449 (29.4%)	573 (25.1%)	82 (18.8%)	<.001
Double valve procedure	205 (13.4%)	205 (9.0%)	41 (9.4%)	<.001
Other valve procedures	242 (15.9%)	212 (9.3%)	46 (10.6%)	<.001
Concomitant CABG	443 (29.0%)	818 (35.8%)	142 (32.6%)	<.001
Bioprosthetic valve	791 (51.8%)	1131 (49.5%)	216 (49.5%)	.36
Intraoperative IABP insertion	60 (3.9%)	126 (5.5%)	33 (7.6%)	.005

BMI, Body mass index; SD, standard deviation; CPB, cardiopulmonary bypass; AVR, aortic valve replacement; MV, mitral valve; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump.

with low BMI after cardiac surgery. No study to date has examined the relationship between BMI and outcomes in patients undergoing strictly car-

diac valvular procedures. Similar to prior studies on this topic, the current study showed that obese patients (BMI>35) had a higher incidence of cer-

**TABLE 3. Unadjusted short-term postoperative outcomes for each age group**

Outcomes	BMI ≤ 24 (n = 1527)	BMI 25–35 (n = 2284)	BMI ≥ 36 (n = 436)	P value
Myocardial infarction	7 (0.5%)	15 (0.7%)	2 (0.5%)	.69
Cerebral vascular accident	48 (3.1%)	50 (2.2%)	14 (3.2%)	.14
Mediastinitis	7 (0.5%)	18 (0.8%)	13 (3.0%)	<.001
Septicemia	59 (3.9%)	60 (2.6%)	19 (4.4%)	.042
Heart block requiring pacemaker	51 (3.3%)	80 (3.5%)	14 (3.2%)	.94
Multisystem failure	35 (2.3%)	34 (1.5%)	12 (2.8%)	.08
New renal failure	105 (6.9%)	129 (5.7%)	41 (9.4%)	.01
New dialysis	34 (2.2%)	53 (2.3%)	12 (2.8%)	.81
Reexploration bleeding	113 (7.4%)	117 (5.1%)	17 (3.9%)	.003
Need for intraoperative PRBC transfusion	398 (26.1%)	542 (23.7%)	95 (21.8%)	.11
Mean PRBC unit transfused	0.83 ± 1.75	0.74 ± 1.67	0.75 ± 1.82	.26
Postoperative pneumonia	105 (6.9%)	131 (5.7%)	31 (7.1%)	.28
Postoperative ventilator (h) (mean ± SD)	41 ± 118 Median: 11	37 ± 110 Median: 8	58 ± 152 Median: 12.9	.004
Prolonged ventilation	190 (12.4%)	289 (12.7%)	93 (21.3%)	<.001
Postoperative IABP insertion	14 (0.9%)	16 (0.7%)	3 (0.7)	.74
New-onset atrial fibrillation	359 (23.5%)	568 (24.9%)	103 (23.6%)	.60
Gastrointestinal complication	78 (5.2%)	92 (4.0%)	20 (4.6%)	.25
Total initial ICU LOS (h) (mean ± SD)	107 ± 177 Median: 47.0	99 ± 174 Median: 45.2	129 ± 206 Median: 51	.035
Postoperative LOS (d) (mean ± SD)	9.6 ± 10.3 Median: 6	8.7 ± 8.2 Median: 6	10.8 ± 11.0 Median: 7	<.001
In-hospital mortality	111 (7.3%)	110 (4.8%)	24 (5.5%)	.006
STS PROM*	4.9 ± 5.2	3.8 ± 4.0	3.5 ± 3.7	<.001
O/E mortality	7.3/4.9 = 1.5 (n = 907)	4.5/3.8 = 1.17 (n = 1467)	4.4/3.5 = 1.25 (n = 295)	

BMI, Body mass index; SD, standard deviation; PRBC, packed red blood cell; IABP, intra-aortic balloon pump; ICU, intensive care unit; LOS, length of stay; STS, Society of Thoracic Surgeons; PROM, predicted risk of mortality; O/E, observed to expected. \*Data missing.

tain morbidities and resource use after valvular surgery. 19,20 They experienced longer cardiopulmonary bypass times, longer aortic crossclamp times, and a higher rate of intraoperative balloon counterpulsation. Accordingly, they also experi-

enced a greater degree of postoperative renal failure, mediastinitis, and prolonged ventilation. Although these patients had prolonged intensive care unit and hospital stay leading to increased resource use, they did not have greater in-hospital mortality

**TABLE 4. Estimates of preoperative predictors of in-hospital survival from multivariable logistic regression analysis**

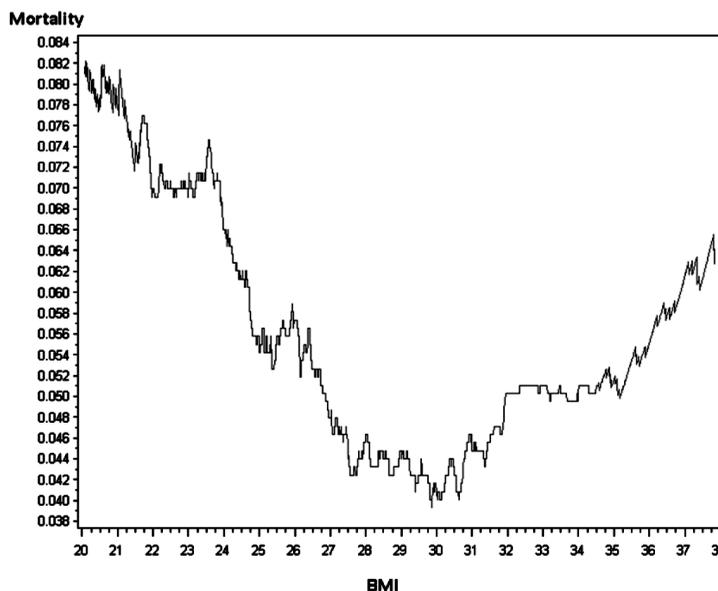
Preoperative variables	Odds ratio (95% CI)	P value
Age	1.04 (1.03–1.06)	<.00001
Chronic lung disease	1.13 (0.81–1.58)	.48
CVA	1.45 (0.98–2.13)	.06
EF	0.99 (0.98–1.00)	.19
Infectious endocarditis	1.78 (1.11–2.85)	.02
Female gender	1.79 (1.35–2.36)	.00004
Heart failure	1.23 (0.92–1.65)	.16
Renal failure	2.44 (1.61–3.70)	.00002
Renal failure requiring dialysis	2.36 (1.35–4.10)	.002
CAD requiring CABG	1.32 (0.99–1.76)	.06
BMI	0.89 (0.78–1.01)	.07

CVA, Cerebrovascular accident; EF, ejection fraction; CAD, coronary artery disease; CABG, coronary artery bypass grafting; BMI, body mass index.

(5.5%) when compared with patients with normal BMI (4.8%) and patients with the lowest BMI (7.3%). These data are consistent with other researchers who have noted an “obesity paradox” in a mixed cardiac surgical population showing decreased in-hospital and long-term mortality when compared with normalweight patients.<sup>12</sup> It is plausible that obese patients likely self-select, and those who undergo surgery have greater functional reserve than patients with low BMI. These similar trends for the obese patients reveal a 10-year survival similar to that of patients with normal BMI and significantly higher survival than that of patients with the lowest BMI. Data exist supporting the fact that overweight patients have lower mortality after cardiovascular events associated with

coronary artery disease and lower mortality from heart failure.<sup>3,21</sup>

Outcomes delineating the effects of malnutrition for patients undergoing cardiac surgery have been sparingly evaluated. Engelman and colleagues<sup>15</sup> evaluated a mixed cardiac surgical population of patients undergoing both CABG and valvular surgery. In a study that included more than 5000 patients (68% undergoing CABG), these researchers found that BMI less than 20 was independently associated with increased mortality, incidence of stroke, renal failure, and reexploration for hemorrhage after cardiopulmonary bypass. Although no plausible explanations were offered for the observed results in this study, the authors concluded that low BMI should be included in risk stratification models for cardiac surgery. In a population of more than 4000 patients undergoing isolated CABG in the United Kingdom, Reeves and colleagues<sup>9</sup> found an increased incidence of in-hospital mortality, renal failure, and prolonged ventilation in patients with BMI less than 20. Potapov and colleagues<sup>17</sup> published results of approximately 23,000 patients who underwent isolated CABG or CABG with valve surgery. The large number of patients in this study allowed researchers to separate patients into 20 separate BMI groups. The results from this study confirmed prior data in that patients with low BMI were at increased risk for



**FIGURE 1.** Smooth kernel estimation of in-hospital mortality for the BMI range of all patients. BMI, Body mass index.

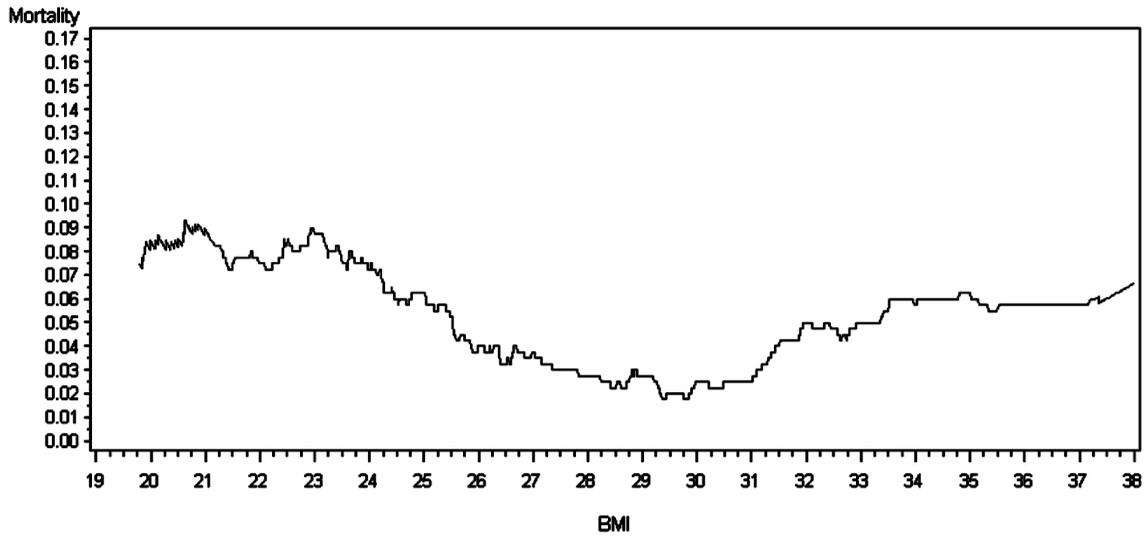


FIGURE 2. Smooth kernel estimation of in-hospital mortality for the BMI range of patients undergoing isolated AVR. *BMI*, Body mass index.

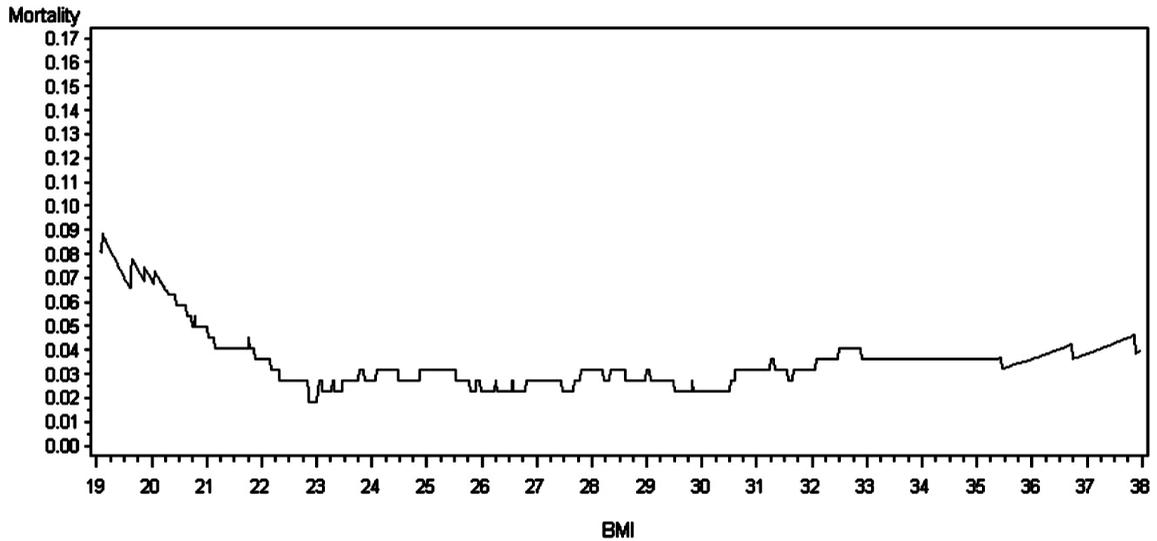


FIGURE 3. Smooth kernel estimation of in-hospital mortality for the BMI range of patients undergoing isolated mitral valve procedures. *BMI*, Body mass index.

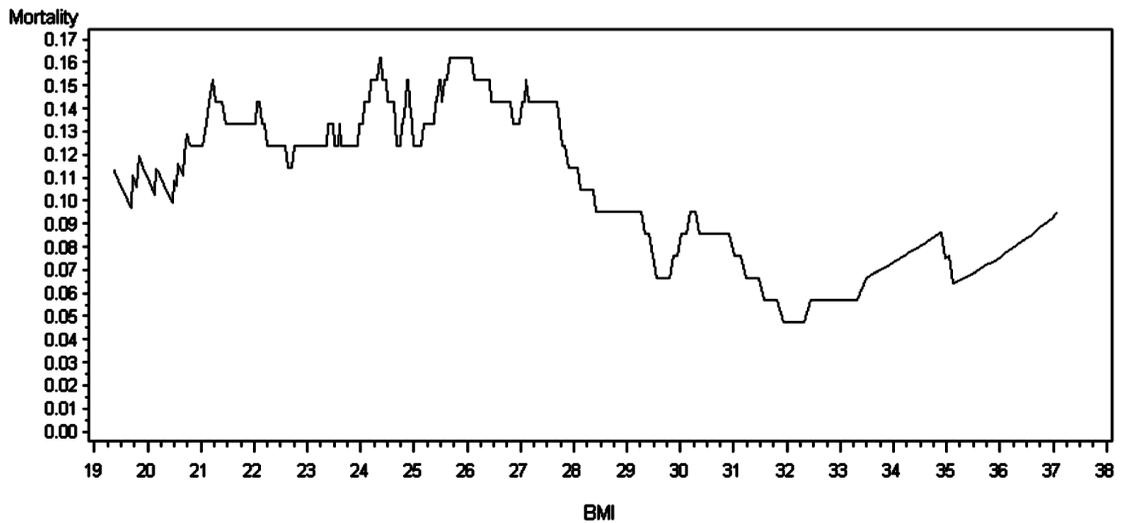


FIGURE 4. Smooth kernel estimation of in-hospital mortality for the BMI range of patients undergoing multiple valve procedures. *BMI*, Body mass index.

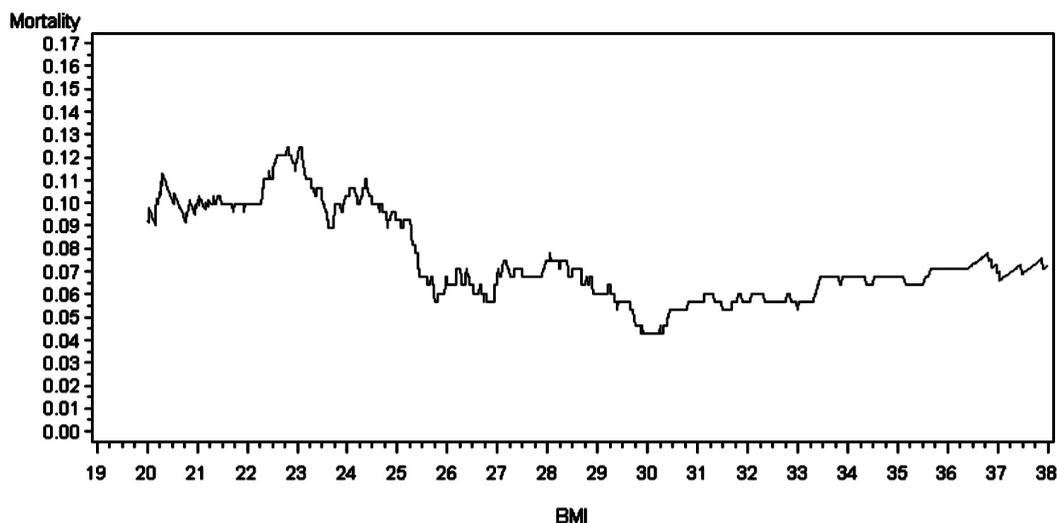


FIGURE 5. Smooth kernel estimation of in-hospital mortality for the BMI range of patients undergoing valve procedures with concomitant CABG. *BMI*, Body mass index.

TABLE 5. Survival estimates for each age group

Age group	1-y survival	3-y survival	5-y survival	10-y survival	<i>P</i> value
BMI $\leq$ 24 (n = 1527)	84.9%	77.7%	70.9%	53.5%	<.001
BMI 25–35 (n = 2284)	89.2%	84.5%	78.3%	63.4%	
BMI $\geq$ 36 (n = 436)	88.1%	80.2%	73.3%	62.2%	

*BMI*, Body mass index.

30-day mortality, renal failure, reintubation, and reexploration for hemorrhage.

In the current series, patients with low BMI had the highest in-hospital mortality when compared with patients with normal and high BMI as indicated by the observed to expected ratios and smooth kernel curves (Figure 1). The bimodal curves associated with in-hospital mortality were similar for those undergoing isolated AVR (Figure 2) and all patients undergoing valve surgery (Figure 1). However, the bimodal nature of the curves was not apparent in those undergoing mitral valve procedures, multiple valve surgeries, or concomitant CABG (Figures 3–5), with an increased in-hospital mortality highest among patients with a low BMI and morbidly obese patients. Although epidemiologic data suggest U- or J-shaped curves in relation to BMI and mortality,<sup>2,22</sup> the pathophysiologic perturbations of these curves in patients undergoing valvular surgery deserve further investigation.

It is plausible that patients who are underweight, when compared with patients with higher BMI, may not have the necessary metabolic reserve to overcome the further increased catabolic stress resulting from a stressful operation.<sup>3</sup> In addition, a

low BMI has been associated with increased hemodilution during cardiopulmonary bypass and a greater postoperative coagulopathy, whereas obesity has been associated with a protective effect on postoperative hemorrhage.<sup>4</sup> Ranucci and colleagues<sup>23</sup> have detailed an increased risk of postoperative hemorrhage requiring reexploration in patients with a low BMI. Although we did note an increased reexploration rate in group 1 in the current study, there was no difference in red cell transfusion among groups. The correlation of hypoalbuminemia as a surrogate for overall nutrition and poor outcomes after cardiac surgery remains divided.<sup>15,24,25</sup>

In addition to in-hospital morbidity and mortality, the current study evaluated all-cause long-term mortality in the low, normal, and high BMI groups. We have demonstrated a significant decrease in long-term survival associated with low BMI compared with the other BMI groups. Although patients in the low BMI group had more comorbidities and a greater preoperative predicted risk of mortality, they had greater long-term mortality that was unpredicted by a standard preoperative risk assessment tool. Prior studies have

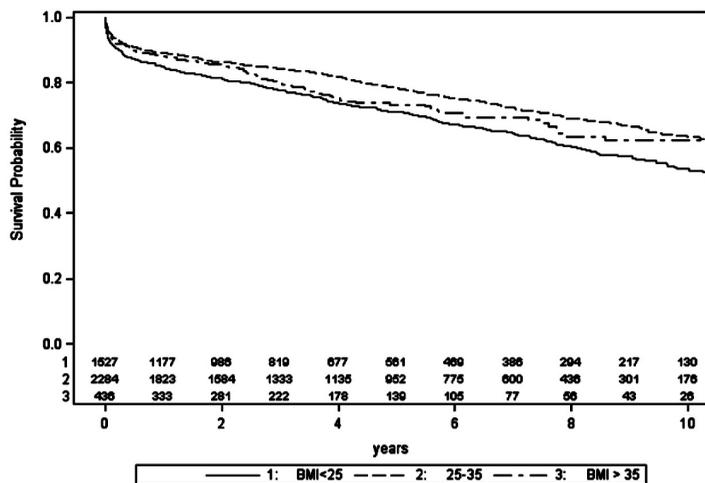


FIGURE 6. Kaplan-Meier survival estimates for patients with BMI 24 or less, 25 to 35, and 36 or more.  $P < .001$ . BMI, Body mass index.

shown BMI and outcomes to be independent of nutritional status,<sup>15</sup> and malnutrition alone does not seem to explain the results observed in this study. One explanation that relates to BMI is that of frailty and functional status. Frailty, as proposed by Fried and associates,<sup>26</sup> includes such functional measures as unintentional weight loss of more than 10 pounds, low physical activity, and grip strength. Performance status is currently unaccounted for by the 3 major metrics used to predict mortality from cardiac surgery (STS, Parsonnet, euroSCORE). The inclusion of performance status or frailty scores in addition to BMI may improve the accuracy of these mortality predictions. Also, as newer technologies become available that obviate the need for cardiopulmonary bypass (eg, percutaneous and transapical valve technologies), patients with low BMI may benefit from avoidance of bypass and

the attendant inflammatory response. Finally, in those patients for whom valve surgery is elective, a nutritional and physical enhancement program under the direction of trained professionals may serve to reduce morbidity and mortality.

#### Limitations

This study is limited by its observational nature and the inherent limitations of a retrospective database study. Although we controlled for confounding variables using logistic regression analysis, it is likely that all factors influencing selection bias were not accounted for in this analysis. Furthermore, the heterogeneity of the study population may make it difficult to draw broad conclusions on the basis of these data. The current database did not have certain preoperative laboratory values (eg, albumin or prealbumin) that may provide a more definitive objective assessment of malnutrition. Finally, important operative variables were not available, such as echocardiographic parameters, patient prosthesis mismatch, or small prostheses, which have been shown to affect long-term survival in certain subgroups.

#### CONCLUSIONS

Patients with low BMI experienced greater in-hospital and long-term mortality when compared with other BMI groups in this single-center study. Out-

TABLE 6. Significant preoperative predictors of long-term survival from multivariable survival analysis

Preoperative variables	Hazard ratio (95% CI)	P value
Age	1.04 (1.03–1.04)	<.00001
Chronic lung disease	1.50 (1.30–1.72)	<.00001
CVA	1.56 (1.32–1.85)	<.00001
EF	0.99 (0.99–1.00)	.04
Infectious endocarditis	1.58 (1.28–1.95)	.00002
Female gender	1.27 (1.12–1.43)	.0002
Heart failure	1.393 (1.22–1.58)	<.00001
Renal failure	2.17 (1.80–2.61)	<.00001
Renal failure requiring dialysis	2.69 (2.07–3.50)	<.00001
CAD requiring CABG	1.29 (1.13–1.47)	.0001
BMI	0.91 (0.86–0.97)	.002

CVA, Cerebrovascular accident; EF, ejection fraction; CAD, coronary artery disease; CABG, coronary artery bypass grafting; BMI, body mass index.

comes were independent of valve procedure and concurrent CABG. These patients warrant careful risk stratification and may require more intensive preoperative testing. When possible, preoperative conditioning and nutrition enhancement may improve short- and long-term outcomes. Further studies dissecting the causal relationship of low BMI

and poor outcomes in patients undergoing cardiac valve surgery are warranted. The authors from Emory University thank staff members Kim Baio for project oversight, Jean Walker and Susan Joyce for data abstraction, and Deborah Canup for database management.

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**Rammos Spyridon**

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# Normative angiographic data relating to the dimensions of the aorta and pulmonary trunk in children and adolescents

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**Abstract Background:** Definition of normative data of the great arteries from neonatal to adult ages may aid in assessment of the growth of cardiovascular structures, thus guiding the timing and type of intervention in patients with congenital cardiac disease. **Methods:** We calculated the cross-sectional areas of the arterial roots at the basal attachment of the valvar leaflets, the sinuses, and standardized distal sites using cineangiograms of 59 normal children and adolescents with mean age of 5.4 plus or minus 4.7 years and a range from 0.1 to 16 years, the children having a mean weight of 21.2 plus or minus 15.7 kilograms, with a range from 2.2 to 68 kilograms, and mean height of 108 plus or minus 35 centimetres, with a range from 43 to 184 centimetres. Values at each site were calculated averaging end-diastolic and end-systolic measurements, and indexed to body surface area. Results are expressed as the mean plus or minus the standard deviation. **Results:** The diameter of the aortic root at the basal attachment of the leaflets was 249 plus or minus 26, the midpoint of the sinuses 379 plus or minus 59, the sinutubular junction 290 plus or minus 58, the isthmus 158 plus or minus 36, the postisthmic region 152 plus or minus 33, and the descending aorta at the level of diaphragm 130 plus or minus 18 millimetres squared per metre squared. The pulmonary root measured at the basal attachment of the leaflets was 253 plus or minus 28, the midpoint of the sinuses 352 plus or minus 58, the sinutubular junction 293 plus or minus 58, the right pulmonary artery 176 plus or minus 25, the left pulmonary artery 153 plus or minus 20, and sum of right and left pulmonary arteries 330 plus or minus 37 millimetres squared per metre squared. All indexes were consistent over a wide range for body surface areas. **Conclusions:** Definition of normative data of the great vessels may aid in the evaluation of congenital or acquired abnormalities, serving as guidelines for intervention during medical or surgical management and follow-up.

**Keywords:** Arteries; valves; normative values

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Angiocardiology is a well-established method for evaluating congenital cardiac malformations, providing quantitative data that aids in assessing the severity of cardiovascular abnormalities. Reliable measurements of the aorta and pulmonary trunk in several lesions have contributed significantly to decision making for medical management, follow-up<sup>1</sup> and surgical intervention,<sup>2</sup> sometimes impacting on surgical mortality, as in the Fontan operation.<sup>3</sup> Normal angiographic diameters at selected sites for the aorta,<sup>1,4,5</sup> the pulmonary trunk<sup>6-8</sup> and its branches,<sup>9</sup> as well as normal great vessel echocardiographic measurements of the arterial trunks,<sup>10,11</sup> have previously been reported. All the investigations cited above, however, do not report vessel crosssectional areas, but focus on diameters, which they mostly correlate with age or body surface area. As far as we are aware, cross-sectional areas indexed to body surface area have only been reported for the right pulmonary artery<sup>12</sup> and the sum of the cross-sectional areas of the right and left pulmonary artery, the latter termed the pulmonary arterial index, and showing consistency over a wide range of body surface areas.<sup>13</sup> With this in mind, we have calculated similar cross-sectional areas for various sites within the arterial roots and trunks.

## Patients and methods

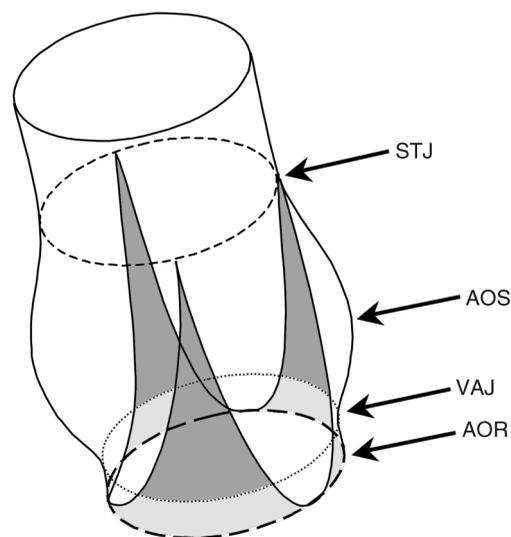
### Patients

Our population consisted of 59 patients, 36 male and 23 female, with essentially normal hearts, who underwent cardiac catheterisation for evaluation of suspected cardiac disease in the era prior to echocardiography. Their mean age was 5.4 plus or minus 4.7 years, with a median of 4.3 years, and a range from 0.1 to 16 years. Their mean weight was 21.2 plus or minus 15.7 kilograms, with a median of 17 kilograms, and a range from 2.2 to 68 kilograms. The mean height was 108 plus or minus 35 centimetres, with a median of 108 centimetres, and a range from 43 to 184 centimetres. Their mean body surface area was 0.78 plus or minus 0.42 square metres, with a median of 0.72 square metres, and a range from 0.15 to 1.89 square metres. None of the patients had disturbances of conduction or arrhythmias, 24 had

no detectable cardiac anomaly, while 35 had only mild anatomic abnormalities of no haemodynamic significance. Of the patients with mild anatomic abnormalities, 16 had pulmonary stenosis, with a systolic pressure gradient less than 15 millimetres of mercury, 4 had bicuspid aortic valves with systolic pressure gradients less than 15 millimetres of mercury, 2 had subvalvar aortic stenosis with systolic pressure gradients less than 15 millimetres of mercury, 5 had aberrant right subclavian arteries, 3 small patent arterial ducts, 2 small muscular ventricular septal defects, and 3 had Kawasaki syndrome without coronary arterial aneurysms. The patients with aortic valvar or subaortic abnormalities were excluded from the measurements made of the aortic root.

### Angiography

All the patients underwent cardiac catheterisation in a fasting state after written informed consent was obtained from their parent or guardian. Bi-plane angiography was performed after collection of data relating to saturations and pressure data. Right ventriculograms and pulmonary angiograms were profiled in posteroanterior projection with or without 30 degrees cranial angulation, and in lateral projection.



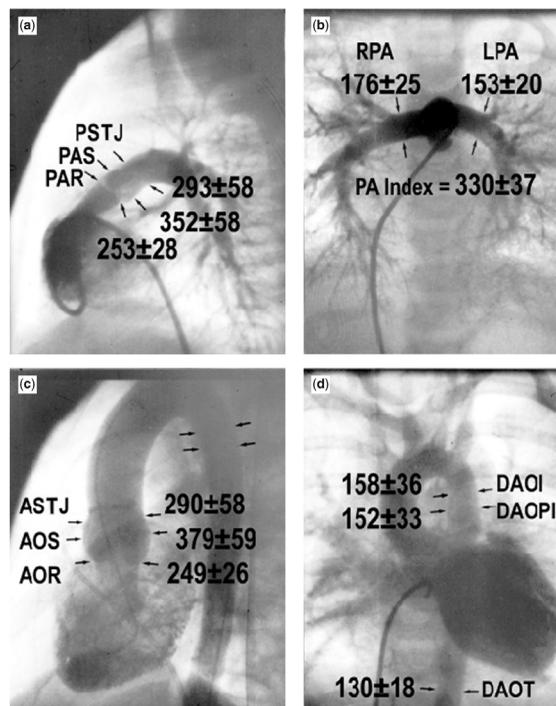
**Figure 1.** Diagrammatic representation showing the structures throughout the length of the aortic root. AOR: aortic ring; AOS: aortic sinus; STJ: sinotubular junction; VAJ: ventriculo-arterial junction. (Adapted from Anderson RH. *Clinical anatomy of the aortic root. Heart* 2000; 84: 670-673.)

Left ventriculograms were profiled in postero-anterior and long axial oblique projections, the latter in 60 degrees left anterior oblique with 30 degrees cranial angulation. Calibration was done using the internal diameter of the angiographic catheter in 22 patients, and a grid of known dimensions filmed in the same projection in 37 patients. Measurements were performed on a Tagarno viewing screen (Tagarno, Denmark) projected in a single plane, assuming a tubular shape of the structure under examination, and taking care to choose good quality frames during sinus beats.

Measurements of the arterial roots were designed to take account of their length and complexity (Fig. 1) as previously described.<sup>14</sup> The ventriculo-arterial junction represents the site where the ventricular structures change to the fibroelastic aortic wall, while the sinutubular junction marks the transition from the sinuses to the ascending aorta at the level of distal attachments of the valvar commissures. The measurement chosen for the "ring" was at the level of the basal attachments of the leaflets. The same definition was applied for defining the site of the "ring" in the pulmonary root.

We measured the pulmonary ring, the area of the pulmonary arterial sinuses at their widest points, the pulmonary sinutubular junction (Fig. 2a), the right and left pulmonary arteries just before the origin of the first branch (Fig. 2b), the aortic ring, the aortic sinuses at their widest point, the aortic sinutubular junction (Fig. 2c), the descending aorta at the isthmic region, the post-isthmic region, and at the level of the diaphragm (Fig. 2d). Measurements were repeated at both end-diastole and end-systole, or at the largest and smallest diameter during each cardiac cycle, and the mean was calculated. The cross-sectional areas, and indexation to body surface area, of the various cardiovascular structures were calculated as follows:

- Cross-sectional area (millimetres<sup>2</sup>) (diameter/2)<sup>2</sup>
- Index (millimetres<sup>2</sup>/metres<sup>2</sup>) cross-sectional area/body surface area
- Pulmonary arterial index (millimetres<sup>2</sup>/metres<sup>2</sup>) right pulmonary artery cross-sectional



**Figure 2.** Sites of measurement (arrows) and mean values plus or minus standard deviations for the indexes in the pulmonary trunk (a), the right and left pulmonary arteries (b), the ascending aorta (c), and descending aorta (d). AOR: aortic ring; AOS: aortic sinus; ASTJ: aortic sinutubular junction; DAOI: descending aorta at the isthmic region; DAOP: descending aorta at the post-isthmic region; DAOT: descending thoracic aorta at the level of the diaphragm; LPA: left pulmonary artery; RPA: right pulmonary artery; PA Index: pulmonary arterial index; PAR: pulmonary arterial ring; PAS: pulmonary arterial sinus; PSTJ: pulmonary sinutubular junction.

area left pulmonary artery cross-sectional area)/body surface area<sup>13</sup>

#### Statistical analysis

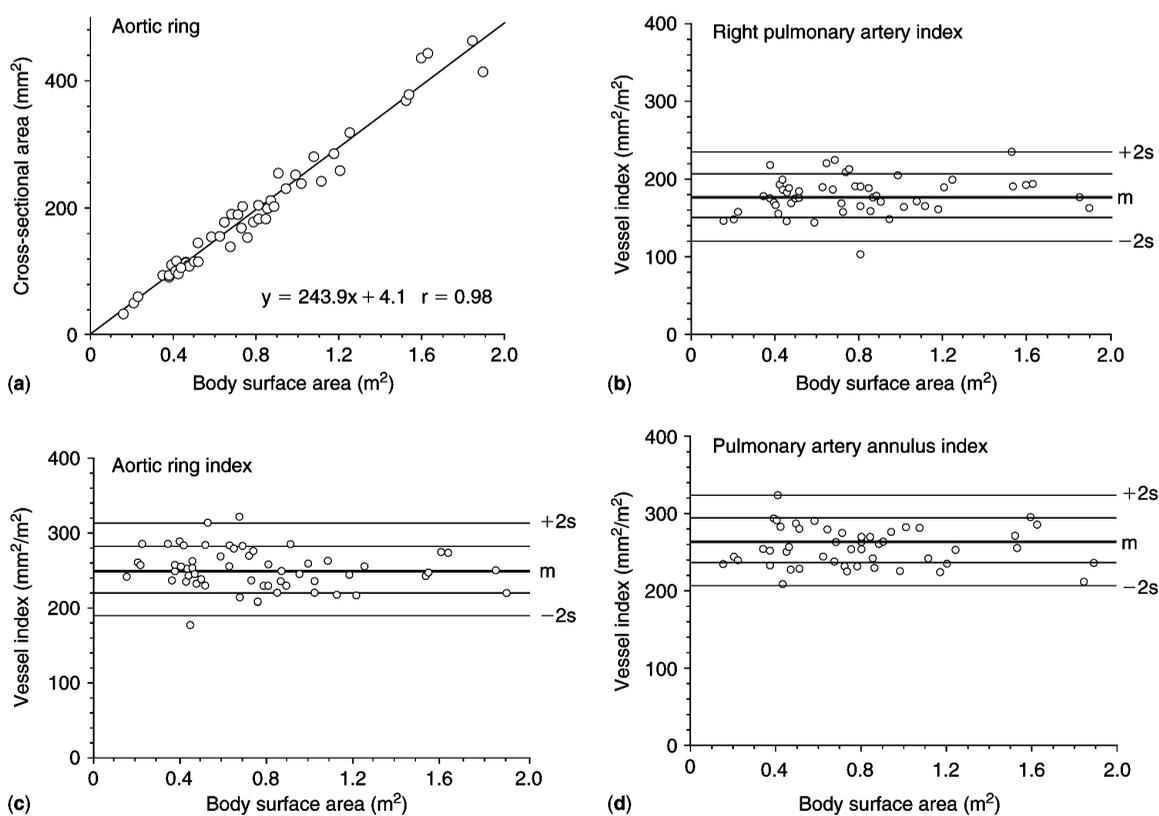
Data are expressed as mean plus or minus standard deviations. Student's paired t-test was used to determine the statistical significance of differences in cross-sectional areas between systole and diastole. Values of less than 0.05 were considered statistically significant. Interobserver variability was determined in 20 angiograms by two independent observers.

## Results

The various indexes for the great vessels, calculated as described above, were constant over a wide range of body surface areas, and their mean values plus or minus the standard deviations are depicted in Figure 2. The index for the aortic ring was 34 percent smaller than that for the aortic sinuses, and 14 percent smaller than that for the aortic sinutubular junction. The index for the pulmonary ring was 2 percent larger than that for the aortic ring, 28 percent smaller than the index for the pulmonary arterial sinuses, and 14 percent smaller than that for the pulmonary sinutubular junction. The index for the right pulmonary artery was 13 percent larger than for the left pulmonary artery. The ratio of the sum of the indexes for the right and left pulmonary arteries, or the pulmonary arteries indexed to the descending aorta at the diaphragm, was 2.5. The difference

between systolic and diastolic diameters of the vessels ranged between 5 percent and 20 percent, and was 13 percent for the pulmonary ring, and 5 percent for the aortic ring. The interobserver error ranged from 0 to 11.3 percent, with a mean of 4.2 percent.

Systolic, diastolic and mean cross-sectional areas were correlated to body surface area ( $r$  0.904–0.980), weight ( $r$  0.897–0.975) and height ( $r$  0.976–0.968). All regressions were linear, and stronger for body surface area. The strongest correlation was found between body surface area and cross-sectional areas of the left pulmonary artery, pulmonary ring, aortic ring, and descending aorta at diaphragm ( $r$  0.97–0.98). Figure 3 shows scatter plots of the mean cross-sectional area of the aortic ring (Fig. 3a), and the indexes of the right pulmonary artery (Fig. 3b), aortic ring (Fig. 3c), and pulmonary ring (Fig. 3d) versus the body surface area.



**Figure 3.** Regression of the cross-sectional area of the aortic ring to body surface area (a). Scatter plots of the right pulmonary arterial index (b), aortic ring index (c) and pulmonary ring index (d), to body surface area.

## Discussion

The anatomy of the arterial roots is complex,<sup>14,15</sup> but its understanding remains crucial in the practice of paediatric and adult cardiology and cardiac surgery. Reference data for dimensions at various sites of the pulmonary and aortic roots, the pulmonary trunk and its branches, and the aorta, as determined using angiography, are scarce in children. Our retrospective angiographic study systematically describes normal cross-sectional areas of the aorta and pulmonary arteries at twelve specific sites, as well as their indexes calculated relative to body surface area.

The pulmonary arterial index as calculated in our study was similar to that previously described,<sup>13</sup> while the remaining indexes have not, as far as we know, previously been reported. The indexes at all the examined sites were remarkably similar over a wide range of body surface areas from infancy to adolescence, thus proving to be parameters applicable for use, and easy to remember, in paediatric cardiological practice.

The changes in the diameters of the vessels between systole and diastole that we observed in our study are also similar to those previously described.<sup>1,7,11</sup> Due to the significant differences noted during the cardiac cycle, we used mean values of the measurements made in our study, in accordance with previous reports.<sup>13</sup> The differences between the indexes calculated for the right and left pulmonary arteries probably reflect the increased flow of blood to the larger right lung. The difference between the indexes for the areas of the aortic and pulmonary roots at the levels of the basal attachments of the leaflets, the so-called "rings", may be due to the muscular nature of the right ventricular infundibulum as opposed to the partially fibrous nature of the left ventricular outflow tract.

The normative data we have produced for the arterial roots and the great arteries are important for decision making in interventional catheterisation during balloon valvoplasty, angioplasty, or placement of stents, as they may provide guidelines for the minimal,<sup>16</sup> optimal and target cross-sectional areas of a vessel or valve in the grow-

ing individual during consecutive interventions. They may also help in choosing between corrective versus palliative surgery in various circumstances, such as in patients with tetralogy of Fallot with or without pulmonary atresia, and those with functionally univentricular physiology. Successful total repair, the choice of a valved versus a nonvalved conduit to be placed between the right ventricle and the pulmonary arteries, and the degree of postoperative right ventricular hypertension and pulmonary insufficiency in tetralogy of Fallot, are all influenced by the pulmonary arterial size and cross-sectional area.<sup>2,16</sup> The surgical approach to patients with functionally univentricular physiology, namely the need for a bidirectional Glenn shunt, and the suitability for the Fontan operation, is also highly dependent on the pulmonary arterial size and capacitance.<sup>3,17</sup> Hypoplastic pulmonary arteries may cause right ventricular hypertension and failure in tetralogy of Fallot, and low cardiac output syndrome in patients put forward for the Fontan operation, both conditions with high postoperative morbidity and mortality.

The ratios between the diameters of the right and left pulmonary arteries relative to the diameter of the ascending or descending aorta have previously been used to predict good or acceptable postoperative results.<sup>2,17</sup> In the setting of congenital cardiac disease, however, the quantity and distribution of flow of blood may differ from normal, making the dimensions of the ascending and descending aorta smaller or larger than in the healthy child. A descending thoracic aorta that is smaller than normal, as is common in tetralogy of Fallot, would lead to an increased ratio between the pulmonary arteries and the descending aorta, thus falsely overestimating the size of the pulmonary arteries.

Our study, and angiographic measurements in general, does have certain limitations. Errors may arise from the assumption that vessels and valves are cylindrical three-dimensional structures that can be measured by taking two-dimensional views in different angiographic planes. The best view would be at a right angle perpendicular to the long axial wall of the vessel, but this view is

not always possible to acquire. Moreover, errors in the correction for magnification must be taken into account, as in all previous angiographic reports. Only a few patients in our study had body surface areas less than 0.4, or more than 1.6 metres squared, so consistency of the indexes for cross-sectional area over the whole range of body surface areas is not proven. Further studies may be needed to assess the indexes for body surface areas outside the range discussed above.

In conclusion, we have shown that the normal cross-sectional areas of the arterial valves and

great arteries are highly correlated to body surface area, and their ratio or index is a consistent parameter applicable throughout congenital cardiac disease. Angiographic quantitation is a useful tool for determination of normal or abnormal growth of cardiac structures in paediatric cardiology and cardiac surgery. This information may assist in electing types of operation, predicting postoperative complications and mortality for a variety of conditions, and choosing the optimal diameters of balloons and stents during interventional catheterisation.

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# Laudatio

Σπυρίδων Α. Ράμμος

Ο Καθηγητής Κ. Αναγνωστόπουλος ιατρός, δάσκαλος, επιστήμονας, καρδιοχειρουργός προσέφερε ανεκτίμητες υπηρεσίες στον τομέα της καρδιοχειρουργικής ενηλίκων και παιδών στην Ελλάδα. Είναι ο οργανωτής 3 δημοσίων καρδιοχειρουργικών τμημάτων στην Ελλάδα: στο Ωνάσειο, στο Πανεπιστήμιο Ιωαννίνων και Αθηνών. Οι κλινικές τις οποίες ίδρυσε και λειτούργησε από το μηδέν, λειτουργούν μέχρι σήμερα με υψηλή απόδοση και ποιότητα υπηρεσιών – κάτι που στην πατρίδα μας είναι σπάνιο.

Δια του παρόντος επιθυμώ να υπογραμμίσω το ήθος, την ποιότητα ενός ιατρού, τη διαρκή και μακροχρόνια δέσμευσή του στον ασθενή, την ιατρική, την εκπαίδευση, τις νοσοκομειακές δομές, την κοινωνία, και το κοινό καλό.

Η αναγνώριση και καταξίωσή του ως ιατρού συνδέεται με 9 πανεπιστημιακούς τίτλους, 10 διευθύνσεις κλινικών, σε Αμερική και Ελλάδα, 10 τιμητικές διακρίσεις και βραβεία.

Ήμουν ένας από τους πρώτους συνεργάτες του στην Ελλάδα. Όχι μόνον εγώ προσωπικά αλλά και κάθε συνάδελφος που συνεργάστηκε μαζί του στη δεκαετή θητεία του στην Ελλάδα εντυπωσιάστηκε από την ακεραιότητα, τον χαρακτήρα, τις γνώσεις σε βάθος και εύρος, την ακατάπαυστη δύναμή του. Ακούραστος με κενोटόμες ιδέες έδινε ουσιαστικές λύσεις, όχι μόνον στις κατ'ιδίαν ή εβδομαδιαίες συναντήσεις, αλλά και ενώπιον της διοίκησης -γνώστης όλων των λεπτομερειών οργάνωσης και λειτουργίας με την μακροχρόνια εμπειρία επτά προηγούμενων νοσοκομειακών δομών.

Παντού, όπου ο κ. Αναγνωστόπουλος εργαζόταν, σε Αμερική ή Ελλάδα, βρισκόταν στην πρώτη μάχιμη γραμμή, ήταν ο ηγέτης και αρχηγός της ομάδας και δεν δίσταζε να αντιμετωπίσει οποιοδήποτε πρόβλημα ακόμα και αγηγώντας τις ιεραρχικές δομές.

Υπό την επίβλεψη και εποπτεία του είχαμε πάντοτε την ευκαιρία να εξετάσουμε τα δεδομένα ακόμα και των προσωπικών του ασθενών, να τους αξιολογήσουμε με κλινικές και παρακλινικές εξετάσεις, και να τους προετοιμάσουμε για τα επόμενα βήματα ή ακόμα και να τους παρακολουθήσουμε μετά την ολοκλήρωση της νοσοκομειακής φροντίδας.

Για το Ωνάσειο Καρδιοχειρουργικό Κέντρο ιδιαίτερα πρέπει να τονισθεί η προσφορά του στην αντιμετώπιση των Συγγενών Καρδιοπαθειών. Σε μικρό χρονικό διάστημα χωρίς ξεχωριστή μονάδα εντατικής θεραπείας, χωρίς να έχει στελεχωθεί παιδοκαρδιοχειρουργικό τμήμα, με βοήθεια από τα τμήματα ενηλίκων, ξεκίνησε το πρόγραμμα με την αντιμετώπιση ασθενών βρεφικής ηλικίας. Σε ελάχιστο χρόνο με θνητότητα που άγγιζε το μηδέν, έχοντας άριστα αποτελέσματά σε παιδιά

και ενήλικες μέ συγγενείς καρδιοπάθειες ξεπέρασε τον αριθμό χειρουργείων άλλων κρατικών ή μη παιδιατρικών νοσοκομειακών δομών της Ελλάδος. Ήταν ο πρώτος στην πατρίδα μας που πραγματοποίησε εγχείρηση Fontan σε ασθενείς με μονήρη κοιλία- που μάλιστα είχαν απορριφθεί από άλλα κέντρα, ο πρώτος που χρησιμοποίησε ομοιομοσχεύματα (Homograft) στη διορθωτική χειρουργική των συμπλόκων συγγενών καρδιοπαθειών, ο πρώτος που τόλμησε την διενέργεια ανατομικής διόρθωσης σε ασθενή με μετάθεση μεγάλων αγγείων και αποτυχημένες προηγούμενες χειρουργικές παρεμβάσεις. Οι δραστηριότητες αυτές και η αναγνώριση των αποτελεσμάτων έδωσαν και το έναυσμα μείωσης εξόδου ασθενών με σύμπλοκες καρδιοπάθειες προς κέντρα της αλλοδαπής για τη χειρουργική τους αντιμετώπιση, μειώνοντας την διασπάθιση δημοσίου χρήματος.

Ο κ. Αναγνωστόπουλος έχει στο ενεργητικό του 21 διαφορετικά ερευνητικά πρωτόκολλα (principal investigator) και είναι συγγραφέας/συντάκτης σε 180 peer reviewed δημοσιεύσεις. Οι δημοσιεύσεις του έχουν εξαιρετική ποιότητα (scopus: h-index: 26, 2067 citations). Γράφει, με σαφή δομή και μήνυμα.

Η διδασκαλία του χαρακτηριζόταν από μια εξαιρετη διδακτική, ενδιαφέρουσα στην παρουσίαση των θεμάτων πρακτική εγγύτητα, υπερεπαρκή χρόνο για συζητήσεις – παρατηρήσεις. Θεωρώ ιδιαίτερα σημαντικό να αναφερθώ στο μεταδοτικό του ενθουσιασμό για γνώση, ούτως ώστε να διεγείρει το ενδιαφέρον των νεώτερων συναδέλφων που είχε υπό την εποπτεία του. Στον κύκλο των «μαθητών του», αλλά και γενικώς όλων των συναδέλφων, ο κ. Αναγνωστόπουλος είναι ένας προικισμένος δάσκαλος, πρόδρομος στην εκπαίδευση και την κατάρτιση νεωτέρων συναδέλφων.

Είναι μια ηγετική φυσιογνωμία ο λαμπρός διοργανωτής 4 νέων καρδιοχειρουργικών κλινικών στην Ελλάδα. Σε κάθε θέση που ανέλαβε, Ωνάσειο, Πανεπιστήμιο Ιωαννίνων, Πανεπιστήμιο Αθηνών δημιούργησε δομές παρουσιάζοντας βασικές ιδέες για τους στόχους, τη βέλτιστη περίθαλψη, την εκπαίδευση με σκοπό τα καλύτερα αποτελέσματα όσον αφορά την θνητότητα, την νοσηρότητα και τη μείωση του κόστους περίθαλψης-αντιμετώπισης.

Ήταν μεγάλη τιμή και εμπειρία η συνεργασία μου με τον συνάδελφο καθηγητή κ. Κ. Αναγνωστόπουλο, ενός ιατρού με διεθνή αναγνώριση, κύρος, γνώσεις σε εύρος και βάθος, ήθος, εργατικότητα, αποδοτικότητα και άριστα χειρουργικά αποτελέσματα.

Αθήνα 30.09.2017

Dr med. habil. Δρ Σπυρίδων Α. Ράμμος

Διευθυντής Τμήματος Παιδοκαρδιολογικού και Συγγενών Καρδιοπαθειών Ενηλίκων ΩΚΚ

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*Reese Anne H. & Reese Peter P.*

# A Little Letter for Dino Anagnostopoulos

*Reese Anne H.<sup>1</sup>, Reese Peter P.<sup>2</sup>*

Dear Dino,

We celebrate you and the honor of this Festschrift. For our contribution, we want to share some memories of what it was like to grow up with you and how your style of doctoring influenced our later lives as adults and physicians.

First, you were always fully engaged. We remember waking up from the fog of sleep when you would kiss us before leaving the house in the early hours of the morning, making sure we were always prepared to be alert in the middle of the night! We knew it often uncertain when you would come home again – maybe that night, maybe a night or even two nights later. But, we had no doubt that when you were gone, you were fully engaged with surgery and patient care and that you would not come home again until all was right at the hospital. We knew you loved surgery and thrived off the intensity of the work. We could hear it in your voice on the phone with your colleagues. You were a parent with a high-minded mission.

When you were home, you might be tired, but then you fully engaged us. Because of your distinctive conversational style – which is kind of like playing an intense game of tennis – we knew that you would want to know our opinions and make us defend them. If we changed our position, you were happy to switch to the other side to continue the conversation! When you weren't talking with us, you were on the phone and looking after your mother or maintaining ties with all of your many cousins in Greece and Europe. Family always mattered deeply to you. We can only hope to keep as engaged with work and extended family as you were.

Second, you were always a full-throated advocate for medicine as a profession. We meet many older physicians who had rewarding careers. Yet, many profess bitterness about changes in medicine, either because of declining reimbursement or impingement on their independence. They refuse to endorse medicine as a career to young people. In contrast, you have always seen medicine as a way to do meaningful work and “create new knowledge.” With direct encouragement - to us, and all of the friends we brought by the house - and by example, you showed us

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that the work of a doctor would be demanding but well worth the effort. We heard your lessons, on long drives in the car, driving in the slow lane, as you made sure we had plenty of opportunity to understand what was expected! As a result, we were not intimidated by the training and sacrifices required when we became physicians. We were well prepared by those early morning wakings!

Third, you always pushed us to aim high. Somehow, you helped inspire all 3 of us kids to seek out the best schools at every step. You helped us to see our individual talents and to achieve without getting burned out. When Peter had his setbacks in college, you told him to learn his lessons, never to look back and to make the most of his time. We are sure our own children will throw us some curve balls, as well, and we will have ample opportunity to reflect this lesson onto them!

Finally, when you faced challenges in your professional life, you found the inner strength to be creative and cultivate new opportunities. You used your inexhaustible energy to start new surgery programs, forge new relationships, inspire a new generation of surgeons, and develop new scientific avenues of inquiry. We do not know what kinds of challenges lie ahead for us, but when those times come, we can call you and call on those memories. We will have an example of what dignity, creativity and tenacity look like.

For these reasons and many more, we want you to know how much we love you and are inspired by your example.

Peter and Annie

**Reese Peter P.**

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# Mortality and Cardiovascular Disease Among Older Live Kidney Donors

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**Abbreviations:** CVD, cardiovascular disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HRS, Health and Retirement Study; NHANES, National Health and Nutrition Examination Survey; OPTN, Organ Procurement and Transplantation Network; RELIVE, Renal and Lung Living Donors Evaluation Study; UNOS, United Network for Organ Sharing

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Over the past two decades, live kidney donation by older individuals ( $\geq 55$  years) has become more common. Given the strong associations of older age with cardiovascular disease (CVD), nephrectomy could make older donors vulnerable to death and cardiovascular events. We performed a cohort study among older live kidney donors who were matched to healthy older individuals in the Health and Retirement Study. The primary outcome was mortality ascertained through national death registries. Secondary outcomes ascertained among pairs with Medicare coverage included death or CVD ascertained through Medicare claims data. During the period from 1996 to 2006, there were 5717 older donors in the United States. We matched 3368 donors 1:1 to older healthy nondonors. Among donors and matched pairs, the mean age was 59 years; 41% were male and 7% were black race. In median follow-up of 7.8 years,

mortality was not different between donors and matched pairs ( $p=0.21$ ). Among donors with Medicare, the combined outcome of death/CVD ( $p=0.70$ ) was also not different between donors and nondonors. In summary, carefully selected older kidney donors do not face a higher risk of death or CVD. These findings should be provided to older individuals considering live kidney donation.

## Introduction

The lower GFR associated with aging has raised concerns about the safety of living kidney donation by older adults. Further, given the strong associations between both older age and chronic kidney disease with cardiovascular disease (CVD), older live kidney donors could have an augmented

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risk of CVD attributable to nephrectomy. Despite these concerns, older individuals ( $\geq 55$  years of age) represent a rapidly growing segment of live kidney donors and two consecutive surveys of transplant center policies suggest that centers are increasingly willing to accept older kidney donors<sup>1,2</sup>.

Epidemiological and physiological studies have demonstrated the loss of kidney function associated with older age, although this loss varies widely among individuals<sup>3-6</sup>. The National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of stages 3-4 chronic kidney disease increased from 0.7% in the 20- to 39-year-age group to 37.8% among individuals  $>70$  years in the general population<sup>7</sup>. Directly measured hemodynamics and clearance reveal that healthy older individuals have lower renal plasma flow, increased vascular resistance and higher filtration fraction compared to their younger counterparts<sup>8</sup>. Pathological examination of kidneys from older patients shows nephrosclerosis, loss of glomeruli and loss of renal mass<sup>9-11</sup>.

For older donors, diminished filtration function at baseline might impair the ability of the remnant kidney to perform adaptive hyperfiltration and promote progressive kidney disease or comorbidities such as CVD. On the other hand, given that older donors have fewer expected years of survival compared to younger donors, older donors will experience a briefer period with a single kidney, which might reduce the opportunity for adverse consequences of nephrectomy<sup>12</sup>.

Prior epidemiological studies have been limited by the small numbers of older live kidney donors, single-center populations, short-term follow-up or a lack of CVD outcomes. In a single-center study of older live kidney donors in the Netherlands, older age was associated with lower GFR both predonation and postdonation, with lower estimated GFR and lesser augmentation of GFR in response to dopamine<sup>5</sup>. In three related studies using US registry data, older kidney donors had similar rates of mortality but higher rates of end-stage renal disease (ESRD) compared to healthy nondonors identified through NHANES. However, the health of the nondonor comparators was determined during an earlier period than when the donors underwent nephrec-

tomy, creating the possibility of a less-healthy comparison group<sup>13-15</sup>. Canadian studies of CVD outcomes among live kidney donors had a small percentage of older donors<sup>16,17</sup>. Therefore, the primary aim of this study was to compare rates of death and CVD in a large cohort of older live kidney donors to contemporary, healthy matched nondonors.

## Methods

### Design

We conducted this matched cohort study after receiving approval from the University of Pennsylvania Institutional Review Board. Using risk-set matching<sup>18,19</sup>, individuals who underwent donor nephrectomy between 1996 and 2006 and were  $\geq 55$  years at the time of donation were matched to similar individuals selected from the Health and Retirement Study (HRS).

### Data sources

This study used registry data on live kidney donors from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS). The OPTN collects demographic and limited clinical data on all live kidney donors in the United States at donation. The donor data set was linked to Medicare Part A, Part B and outpatient records.

The HRS is a National Institutes of Health funded longitudinal cohort study that, since the year 1992, has enrolled a nationally representative sample of  $>25\ 000$  adults  $>50$  years of age in the United States. Through comprehensive interviews, the HRS collects information about physical and mental functioning, comorbidities and quality of life<sup>20,21</sup>. The HRS conducts national probability sampling of the US households, with oversampling of blacks and Hispanics. Participants are re-contacted at regular intervals (currently every 2 years)<sup>22</sup>. The HRS linked interview-data with Medicare claims for participants who provided consent to linkage.

### **Study population**

The index date refers to the cohort entry date when the follow-up began. Each kidney donor's index date was the date of nephrectomy. Each HRS comparator was assigned an index date corresponding to an interview date.

Each donor was matched 1:1 to a nondonor without relevant comorbidities (described below) at an index date close in time to the donor's index date. Kidney donors are carefully selected through an extensive medical evaluation. Multiple consensus guidelines describe diabetes, cancer, coronary artery disease, dementia, poor functional status, chronic serious infections, or major psychiatric or neurological conditions as contraindications to live kidney donation<sup>23,24</sup>. During the study period, some centers accepted donors with obesity<sup>1,2</sup>. A minority of centers accepted donors with hypertension controlled with a single anti-hypertensive medication (<1% of this cohort)<sup>2,25,26</sup>. Because the selection process for kidney donors creates a much healthier group than unselected members of the general population, we used restriction and matching to create a healthy comparator group from the HRS cohort<sup>13,17</sup>. We excluded HRS participants who, by the time of their index date, reported hypertension, diabetes, cancer (except skin), CVD (defined as "heart condition," "angina," "congestive heart failure," "heart surgery" or "stroke"), pulmonary disease (defined as "lung condition"), major psychological or neurological illnesses (defined as "emotional/psychiatric problems"), BMI  $\geq 40$  or who did not self-rate their health as "good," "very good" or "excellent."

### **Outcomes**

The primary outcome was death. Donor deaths were ascertained through center reports and linkage to the Social Security Death Master File. HRS participant deaths were ascertained through linkage to the National Death Index and contacts with participants' surrogates.

For kidney donors and HRS participants with insurance coverage from the Centers for Medicare and Medicaid Service, we obtained claims data through December 31, 2008. A secondary composite outcome was death or, among pairs with Medi-

care coverage, CVD. Medicare claims used to define CVD comprised codes for ischemic cardiac disease, congestive heart failure, stroke and peripheral vascular disease<sup>27</sup>. These CVD codes are listed in Table S1A. In a post-hoc analysis, we examined the risk of diabetes defined by Medicare claims<sup>28</sup>. These claims are listed in Table S1B.

Live donors may be more likely to seek general medical care than members of the general population, creating the possibility for surveillance bias when comparing health outcomes using medical claims data. To evaluate this possibility using Medicare claims, we compared the rate of primary care visits for donors and matched comparators (Medicare codes for primary care are listed in Table S1C). We also compared to the risk of diagnoses for thyroid disease, osteoarthritis and skin cancer, none of which is plausibly related to kidney donation or is a main focus of the donor medical evaluation<sup>24</sup>. Table S1 provides the Medicare claims used to define study outcomes and further information about study methods.

### **Statistical analysis**

Analyses were performed using SAS (SAS Institute, Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). Matches were completed prior to the assessment of any outcome. We performed risk-set matches using R MIPMatch<sup>29-31</sup> with fine balance and a distance defined through the Mahalanobis distance function<sup>18,32</sup>. We matched exactly on race (black/non-black) and sex. Using zip codes, we categorized participants' neighborhoods into four groups based on the percentage of residents living in poverty<sup>33</sup>. Donors and comparators were matched on neighborhood poverty using fine balance<sup>34-38</sup>. Because BMI was not consistently reported to the OPTN until 2001, we did not match on BMI category (<25;  $\geq 25$  to <30;  $\geq 30$  to <35;  $\geq 35$  kg/m<sup>2</sup>) until after the year 2000. A very small percentage (n=15, or <1%) of older donors were categorized as having hypertension. Therefore, we did not match on hypertension, but instead matched donors to nonhypertensive participants in the HRS. We assessed how closely we achieved balance between donors and healthy comparators using the Wilcoxon rank-sum

test for each continuous covariate and Fisher's exact test for binary covariates. We used Cox's proportional hazards model for paired times to estimate hazard ratios (HR) with 95% confidence intervals (CI) for mortality and secondary study outcomes<sup>39</sup>. We used the Prentice-Wilcoxon statistic to test the hypothesis of no difference in study outcomes between donors and nondonors and reported p-values using this method<sup>40,41</sup>.

For analyses of mortality, pairs were followed until one died or end of followup (December 31, 2008). For analyses of the secondary outcome of death or CVD, we measured deaths among pairs until both members entered Medicare, after which we measured deaths or cardiovascular events. We censored both members of pairs at 66 years of age if either member did not enroll in Medicare. Pairs were also censored when either member left Medicare or enrolled in a health maintenance organization.

For analyses of the rates of having Medicare claims for diabetes, hypothyroidism, osteoarthritis and nonmelanoma skin cancer, we censored both members of pairs at death, at 66 years of age if either member did not enroll in Medicare, or if either member left Medicare or enrolled in a health maintenance organization.

To compare differences in the rate of primary care visits between donor and nondonor pairs who were enrolled in Medicare for at least a year, we used Wilcoxon's signed rank test and its associated Hodges-Lehmann estimators<sup>42</sup>. All p-values were two-sided. Any p-value  $\leq 0.05$  was considered significant.

### **Secondary analyses**

We repeated analyses of death and death/CVD in a prespecified subgroup defined by median age at index date ( $\geq 60$  years). For analyses of CVD, we also implemented an alternative, validated set of Medicare codes to ascertain the outcome of CVD<sup>27</sup>. This expanded list of Medicare codes included transient ischemic attack, venous thrombosis and atrial fibrillation, in addition to codes encompassing the four cardiac complications addressed by our primary approach (coronary artery disease, congestive heart failure, stroke and peripheral

vascular disease).

Additional information about study methods is provided in Supplementary Methods.

## **Results**

During the study period, 5717 individuals were  $\geq 55$  years of age at the time of donor nephrectomy. We excluded 560 donors (9.8%) due to missing zip codes and five due to implausible BMI in a live donor ( $>40$  kg/m<sup>2</sup>). The final number of older donors considered for the match was 5152.

There were 25 309 individuals in the HRS cohort. We excluded 17 339 (69%) individuals due to comorbidities, 499 (2%) with low self-rated health status and 152 (0.6%) with missing zip codes or implausible BMIs. There were 7319 nondonor candidates considered for the match.

The final match comprised 3368 donors (65% of the total) and 3368 healthy nondonor HRS participants. Figure 1 shows the process for assembling the matched cohort.

Table 1 shows characteristics of donors and nondonors. After matching, the mean age was 59 years, 41% were male and 7% were African-American. For each pair, the median between the donation date and the interview date was 162 days (interquartile range [IQR]: -4, 358).

Figure 2 shows survival after the index date for matched pairs. In median follow-up of 7.84 years (IQR 5.11, 10.16), there were 115 deaths among donors and 152 deaths among nondonors. The mortality rate was not different between donors and nondonors (4.9 vs. 5.6 deaths per 1000 person years,  $p = 0.21$ ). The HR associated with kidney donation was 0.90 (95% CI 0.71, 1.15).

Sixty percent of donors and 44% of nondonors had any Medicare coverage. A total of 1312 pairs in the primary cohort had simultaneous Medicare coverage and were eligible to have CVD events ascertained. In an analysis of time to death or CVD, the rate of this combined outcome was not significantly different between donors and matched nondonors ( $p = 0.70$ ). The HR associated with kidney donation was 1.02 (95% CI 0.87, 1.20). These results are shown in Figure 3.

The rate of primary care visits was slightly higher among donors than among nondonors (median 1.76 vs. 1.43 per year,  $p = 0.001$ ). As shown in Table 2, kidney donors did not have an increased risk of diabetes ( $p = 0.80$ ), hypothyroidism ( $p = 0.16$ ) or osteoarthritis ( $p = 0.67$ ). Donors did have a greater hazard for having the outcome of nonmelanoma skin cancers alone than nondonors (HR 1.53; CI 1.14, 2.05;  $p = 0.006$ ).

Among the subset of pairs  $\geq 60$  years, donors had a slightly lower mortality risk ( $p = 0.03$ ); the HR for death associated with kidney donation was 0.68 (95% CI 0.49, 0.95). Kidney donors and nondonors had a similar risk of the combined outcome of death or CVD ( $p = 0.72$ ). A secondary analysis of the outcome of death and CVD using an alternative set of Medicare claims revealed no difference in risk between donors  $\geq 55$  years and matched comparators ( $p = 0.72$ ); these results are

not shown.

Additional information about pairs with Medicare data is provided in Table S2.

## Discussion

In this matched cohort study, older kidney donors had similar mortality to healthy participants in the HRS. Similarly, the combined outcome of death and CVD was similar between groups. Donors also did not have an elevated risk of diabetes, a risk factor for CVD and renal disease, compared to matched nondonors. These results should be provided to older individuals considering live kidney donation. This information should be presented in the broader context of other risks attributable to donor nephrectomy, such as perioperative complications, ESRD and quality of life<sup>15,43,44</sup>.

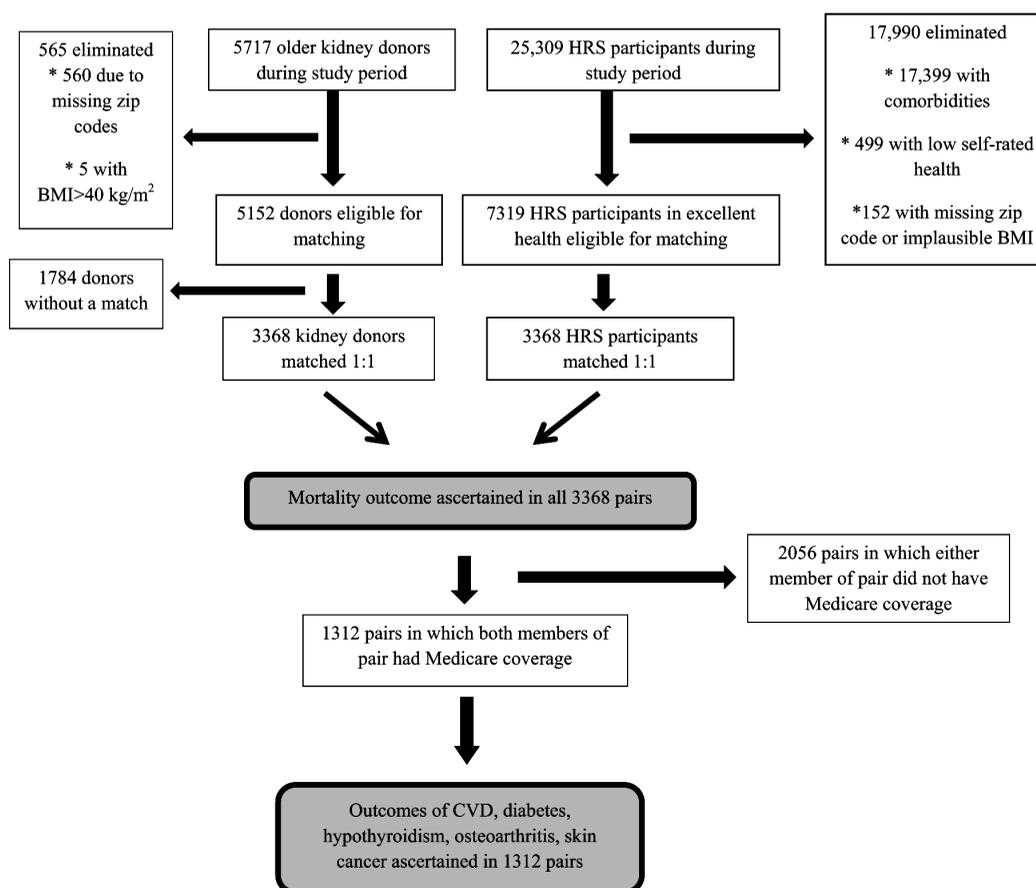


Figure 1: Flow diagram.

The ever-increasing waiting list for a deceased donor kidney has led transplant centers to focus resources on increasing the volume of live kidney donation. In this context, the number and proportion of older live kidney donors has also increased substantially. In the United States in the year 2002, 407 donors (8% of all donors) were  $\geq 55$  years, whereas in 2009, 726 donors (14%) were in this age group<sup>45</sup>. However, the limited empirical data about health outcomes for older live kidney donors makes it difficult for clinicians to evaluate and counsel older individuals considering kidney donation.

The similar rates of death and CVD outcomes between older donors and matched healthy comparators may provide some reassurance to older individuals considering donation and the transplant professionals caring for them. The finding that older donors enjoy longevity similar to healthy older individuals generally confirms the results of prior studies in which donor outcomes were compared to outcomes among demographically and/or comorbidity matched members of the general population<sup>13,14,46,47</sup>. Our finding that CVD rates were not different between donors and matched pairs extends prior results by Garg et al showing no increased risk of CVD in a population of Canadian donors that comprised a small number of older individuals<sup>17</sup>. The similar rates of CVD and diabetes among older donors and matched healthy individuals from our study can also be considered in the context of the Renal and Lung Living Donors Evaluation Study (RELIVE) cohort. RELIVE investigators examined live donors at three large transplant centers and reported that, prior to nephrectomy, older donors were more likely than younger donors to have obesity, hypertension and abnormal glucose tolerance<sup>48</sup>. These findings raised the concern that older donors may be at elevated risk from CVD after donation. However, this observation was not based on the comparison of older donors to healthy nondonors. In our study, we conducted such a comparison by assembling a group of healthy matched older individuals from the HRS by excluding HRS participants with hypertension or diabetes and matching on BMI. Our results suggest that transplant centers are usually able to se-

lect older donors who are not at higher risk of developing CVD or diabetes than healthy members of the general population, despite a possible greater willingness by some centers to accept the presence of metabolic abnormalities among these older individuals.

Our study results should also be evaluated in the context of a higher risk of ESRD associated with donor nephrectomy that has been reported in two important studies by Muzaale et al and Mjvæn et al<sup>15,49</sup>. Muzaale et al<sup>15</sup> matched live donors in the United States to healthy NHANES participants. Notably, while live kidney donors experienced a greater relative risk of ESRD compared to nondonors, the cumulative incidence of this outcome for donors over a 15-year observation period was  $< 1\%$ . Among the 4039 donors  $\geq 60$  years of age, only seven developed the ESRD outcome. In the general public, renal disease is a very strong risk factor for death and CVD events<sup>50</sup>. A potential explanation for our findings of no increased death or CVD rates among older donors and these prior findings of a higher rate of ESRD are that the current evidence suggests that only a small proportion of donors progress to advanced renal disease. Additionally, kidney donors undergo extensive medical screening that typically includes abdominal imaging using computer tomography scan, tests of renal and liver function, electrocardiogram, screening for bloodborne infections including hepatitis and human immunodeficiency virus (HIV) and psychosocial counseling<sup>51</sup>. Thus, most kidney donors may enjoy longevity and low rates of CVD because of careful selection through the donor medical evaluation, which may offset the negative health effects of progressive loss of renal function in a small number of donors.

Our study must be viewed in the context of its limitations and compared to other studies of donor outcomes. First, the OPTN/UNOS does not report on the presence of all relevant comorbidities among donors<sup>25</sup>. Reviews and consensus guidelines indicate that a potential donor would not have been accepted if a major comorbidity such as hepatitis C or diabetes were present<sup>23,24</sup>. Second, for the HRS, comorbidities used to exclude participants as matches were ascertained through interviews rather

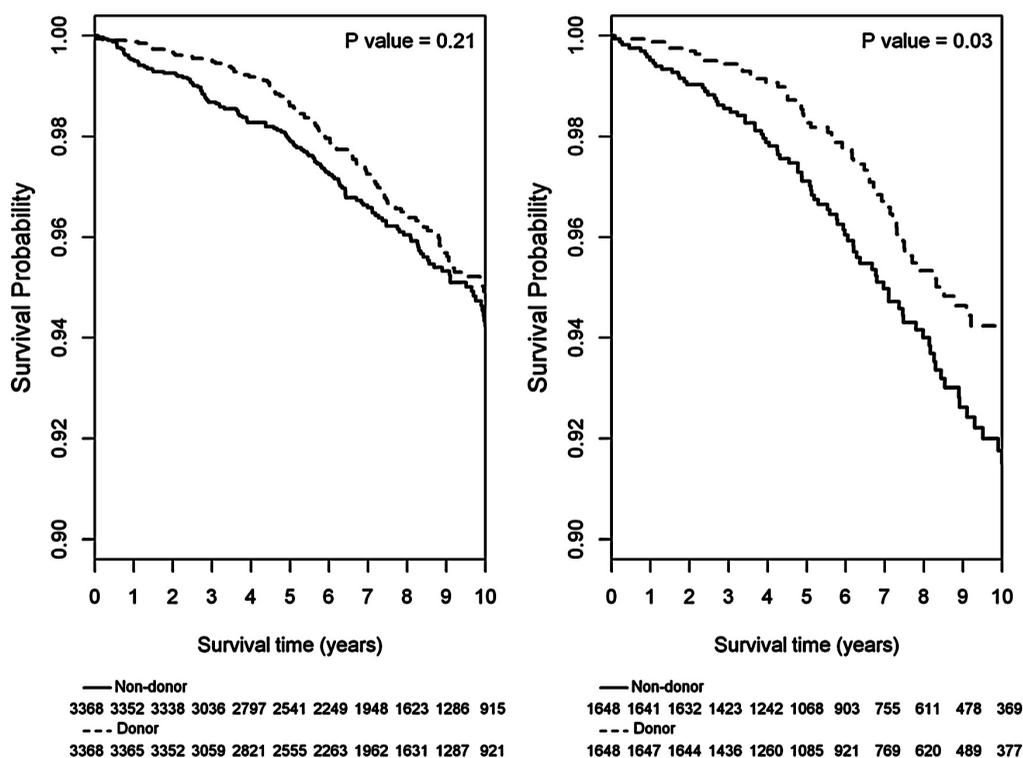
**Table 1:** Subject characteristics of older kidney donors and nondonors, before and after matching<sup>1</sup>

	All donors (n = 5152)	Matched donors (n = 3368)	Matched healthy nondonors (n = 3368)	All nondonors (n = 7319)	p-Value <sup>2</sup>
Age (years)	59.1	59.0	59.0	64.2	0.3423
Male (%)	38	41	41	43	1
Black race (%)	6	7	7	10	1
Neighborhood poverty (%)					
≤12.3%	73	71	71	65	1
12.4–19.9%	18	19	19	21	1
20–39.9%	9	10	10	13	1
≥40%	<1	<1	<1	<1	1
BMI (%)					
Missing <sup>3</sup>	15	3	3	4	1
15–25	32	38	38	42	1
25–30	37	42	42	38	1
30–35	14	14	14	13	1
35–40	2	3	3	3	1

<sup>1</sup>For each kidney donor, the index date was the date of nephrectomy. On that date, each donor was matched to a demographically similar, healthy nondonor from the Health and Retirement Study; the index date for this nondonor was the date of an interview close in time to the donor's date of donation.

<sup>2</sup>For comparison of matched donors and nondonors.

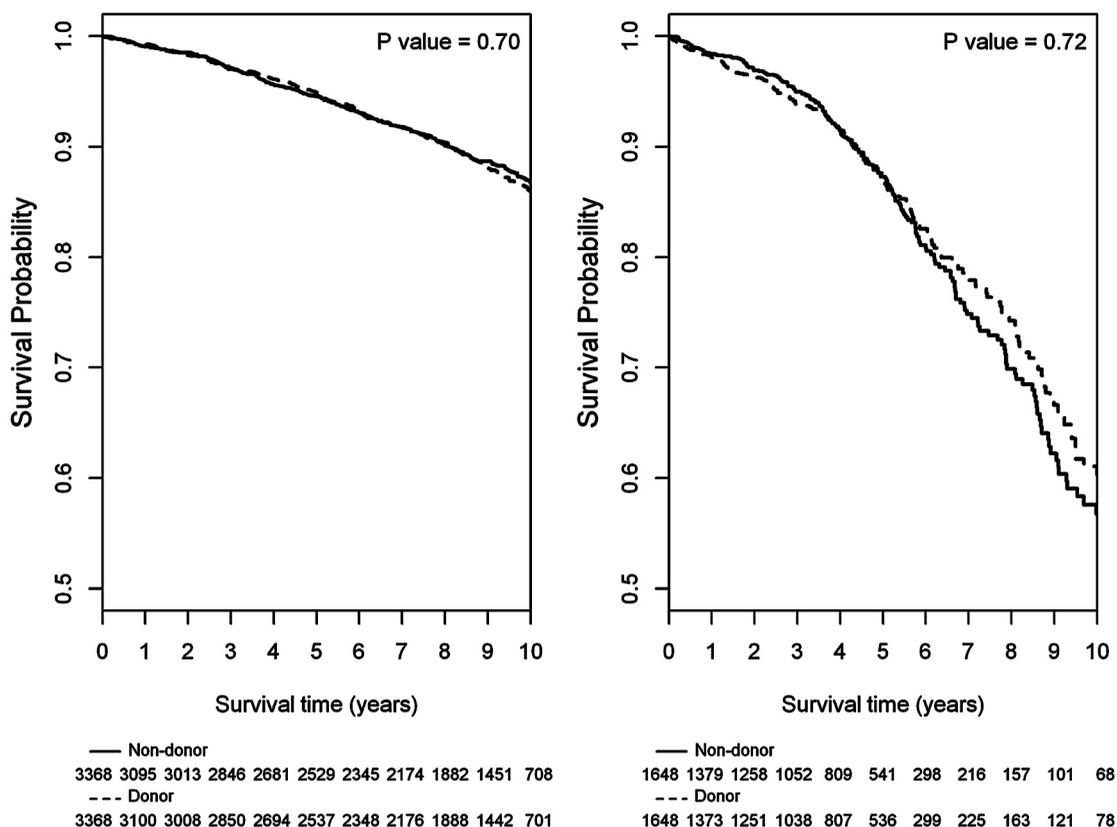
<sup>3</sup>Matches were made on BMI category only after the year 2000 due to a high percentage of missing data on BMI in the donor registry data set before that year.



**Figure 2:** Mortality among kidney donors. (Left panel)  $\geq 55$  years and (right panel)  $\geq 60$  years versus matched healthy older individuals using the Kaplan–Meier method. Note: For this analysis, mortality was ascertained in all matched pairs.

than physical examination or serological testing. The HRS does not record certain important conditions such as HIV or hepatitis C infection that might lead to chronic kidney disease. However, HIV and

hepatitis C infection are rare in the general population. The HRS data set does not allow serological assessment of renal disease. The HRS only directly asked participants about the presence of dia-



**Figure 3:** Mortality and cardiovascular outcomes among kidney donors. (Left panel)  $\geq 55$  years and (right panel)  $\geq 60$  years versus matched healthy older individuals using the Kaplan-Meier method.

**Note:** For this analysis, deaths were measured among pairs until both members entered Medicare, after which the outcome consisted of deaths or cardiovascular events. Pairs without Medicare coverage were censored at age 66 years if either member did not enter Medicare or when either member of the pair no longer had Medicare coverage.

**Table 2:** Hazard ratios for diabetes and other medical conditions among kidney donors  $\geq 55$  years versus matched healthy nondonors

Diagnosis	Hazard ratio	95% CI		p-Value
		Lower	Upper	
Diabetes	1.05	0.83	1.32	0.80
Hypothyroidism	1.08	0.88	1.33	0.16
Osteoarthritis	1.10	0.92	1.30	0.67
Nonmelanoma skin cancer	1.53	1.14	2.05	0.006

Death censored analyses among pairs with Medicare coverage.

betic kidney disease during the first 2 years of the study period. We did restrict our healthy comparison group to HRS participants without diabetes and hypertension; chronic kidney disease in the absence of these conditions is uncommon<sup>52,53</sup>. Despite this restriction, it is possible that some HRS participants had mild or undiagnosed chronic kidney disease.

Third, ascertainment of outcomes using Medi-

care data is limited by the fact that  $<50\%$  of pairs had Medicare insurance coverage and Medicare provides minimal information about individuals before age 65 years. A lower percentage of HRS participants had Medicare claims compared to donors; a likely reason is that in the HRS study, participants had to provide consent for Medicare linkage, whereas no such consent process was required to link donor registry data to Medicare claims. This low percentage of cohort pairs that had simultaneous Medicare coverage may limit generalizability. On the other hand, we assembled a large cohort of older donors, including  $>1300$  pairs with Medicare coverage. Our conservative approach of censoring both members of a pair when either member was not enrolled in Medicare should minimize the potential for bias. At any time when a Medicare claim might record CVD or any other study outcome, both members of the pair were in Medi-

care and capable of having a similar event recorded.

Finally, due to the potential for more frequent contacts with the health system after nephrectomy, it is possible that a comparison of medical conditions ascertained through claims data between donors and healthy comparators might be susceptible to surveillance bias<sup>16</sup>. Our results provided limited evidence of this bias. While kidney donors had a higher rate of primary care visits and claims for nonmelanoma skin cancer than nondonors, non-significant differences were evident in the risk of hypothyroidism, osteoarthritis and diabetes. It is possible that the elevated risk of nonmelanoma skin cancer among donors was due to skin examinations in the peri-operative period.

By comparison to other important studies of live kidney donor outcomes, this study had a number of advantages. Our study design matched donors to HRS participants on index dates when these nondonors had evidence of good health. By contrast, other cohort studies, including those by Muzaale et al and Mjvæn et al, have compared donors to nondonors whose health was not evaluated at the same time as the donor<sup>13-15,49</sup>. The HRS provided a large, national sample of community-dwelling, healthy older adults using a validated sampling methodology. The HRS includes extensive questions about diverse elements of health. Unlike most other studies of donor outcomes, this study adjusted for the psychosocial characteristics of donors by excluding HRS participants with a history of psychiatric disorders and by matching on neighbor-

hood poverty<sup>13,46,49</sup>. Psychiatric disorders and poverty are important predictors of longevity; these attributes would also plausibly be evaluated during the donor nephrectomy work-up<sup>24,54</sup>.

In summary, this study provides valuable new data about outcomes that can be used in decision-making for older individuals considering live kidney donation. In the context of careful medical evaluation and selection, older donors should expect similar medium-term survival and risk of CVD compared to healthy members of the general population.

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#### **Disclosure**

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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Supporting Information Additional Supporting Information may be found in the online version of this article. Supplementary Methods Table S1: Codes for Medicare claims used to ascertain cardiovascular disease and other diagnoses. Table S2: Subject characteristics of older kidney donors and nondonor pairs that did and did not have simultaneous Medicare claims.



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# Single-Stage Extensive Replacement of the Thoracic Aorta: The Arch-First Technique

Chris K. Rokkas, MD Nicholas T. Kouchoukos, MD

**Background:** Single-stage extensive replacement of the thoracic aorta usually involves a period of circulatory arrest with performance of the graft-to-lower descending thoracic aorta anastomosis before performing the anastomosis to the arch vessels. To minimize the period of brain ischemia and reduce the potential for neurologic injury, we developed an alternative technique.

**Methods:** In 6 patients with extensive aneurysms involving the entire thoracic aorta, exposure was obtained via a bilateral thoracotomy in the anterior fourth intercostal space with transverse sternotomy. A 10-mm graft was anastomosed to the aortic graft, opposite the site of the planned anastomosis to the arch vessels. During a single period of circulatory arrest (34-46 minutes), the aortic graft was attached to a cuff of aorta containing the arch vessels. The graft was then clamped on either side, and the arch was perfused with cold blood for 20 to 36 minutes. After the distal aortic anastomosis was completed, antegrade perfusion was established via the 10-mm graft. The proximal aortic anastomosis was performed last.

**Results:** No patient sustained a permanent neurologic deficit. All 6 patients were discharged from the hospital.

**Conclusions:** The "arch-first" technique, combined with a bilateral transverse thoracotomy, allows expeditious replacement of the thoracic aorta with an acceptable interval of hypothermic circulatory arrest and minimizes the risk of retrograde atheroembolism by establishing antegrade perfusion. (*J Thorac Cardiovasc Surg* 1999; 117:99-105)

Aneurysmal disease that involves the ascending aorta, arch, and descending aorta is usually approached in staged operations.<sup>1-3</sup> In certain situations (extensive involvement of the arch, presence of symptoms, impending rupture) a single-stage approach may be preferred.<sup>4-6</sup> Traditionally, single-stage replacement of the thoracic aorta involves a period of circulatory arrest and the performance of the graft-to-lower descending thoracic aorta anastomosis before the anastomosis

to the arch vessels is performed.<sup>7,8</sup> Perfusion is then reestablished in a retrograde fashion via a femoral arterial cannula, and the ascending aortic anastomosis is completed.

Despite advances in anesthetic management and car-diopulmonary perfusion, brain injury remains an important source of morbidity and mortality in operations on the thoracic aorta. In operations requiring the use of profound hypothermia and circulatory arrest, perioperative stroke with a focal neurologic deficit is related to the presence of concurrent distal aortic disease and to the duration of circulatory arrest.<sup>9</sup> Temporary neurologic dysfunction is related to the cerebral ischemia time although permanent neurologic dysfunction is the result of embolic strokes.<sup>10</sup> To minimize the time of circulatory arrest and to reduce the duration of retrograde aortic perfusion, we developed a technique that involves anastomosis of the aortic graft to the arch vessels first and hypothermic perfusion of these vessels while reconstruction of the descending thoracic aorta is performed. We report our experience with 6 consecutive patients in whom the arch-first technique in combination with a bilateral anterior thoracotomy and transverse sternotomy was used for single-stage, extensive replacement of the thoracic aorta.

## Patients and methods

**Patients.** From January 1996 to May 1998, 6 patients (mean age, 60.5 years; range, 39-74 years) underwent repair of the aortic arch and varying

lengths of the ascending and descending thoracic aorta with the arch-first technique (Table I). Four of these patients, all men, had undergone previous operations for acute type A dissection (patients 2, 3, 5, and 6; mean interval, 8.1 years; range, 16 months–11 years). Patient 1 had a chronic type A dissecting aneurysm, and patient 4 had a degenerative fusiform aneurysm. None of the patients had Marfan's syndrome or other known microfibrillar disease. All patients had been treated for hypertension, and patients 2, 3, 4, and 5 had moderate or severe chronic obstructive pulmonary disease. In patients 5 and 6, the dissection involved the thoracoabdominal aorta, but without aneurysmal enlargement of the infradiaphragmatic segment. The indications for operation were progressive enlargement of the involved aortic segments documented by tomographic studies (all patients) and the presence of symptoms (patient 5, chest pain). All patients underwent preoperative cardiac catheterization and chest and abdominal computed tomographic scanning. Aortography was used selectively (Fig 1).

**Operative technique.** Hemodynamic monitoring includes bilateral radial artery cannulation for the monitoring of arterial pressure and placement of a pulmonary artery catheter. Electroencephalographic monitoring is used. Two lines for arterial perfusion are connected to the main arterial line of the pump-oxygenator to provide control of selective flow using an occluder and a flowmeter (HT 109; Transonic Systems, Inc, Ithaca, NY). Provisions are also made for retrograde brain perfusion. After endotracheal intubation with a double-

**Table I.** Demographic data, clinical pathologic findings, surgical procedures, and outcome

Patient	Age (y)	Sex	Previous operation	Type of disease
1	74	M	None	Chronic type B dissection
2	72	M	Acute type A dissection repair: tube graft, AVR (10 y)	Chronic type A dissection
3	69	M	Acute type A dissection repair: tube graft, AVR (11 y)	Chronic type A dissection
4	60	F	None	Degenerative aneurysm
5	49	M	Acute type A dissection repair: tube graft (10 y)	Chronic type A dissection
6	39	M	Acute type A dissection repair: composite graft (15 mo)	Chronic type A dissection

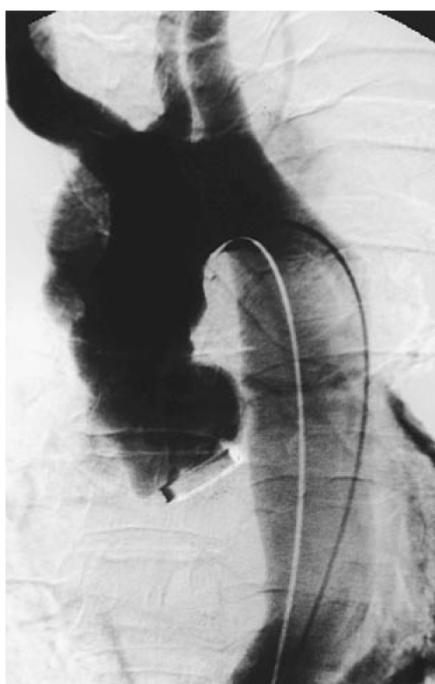
AA, Ascending aorta; AVR, aortic valve replacement; DTA, descending thoracic aorta.

lumen tube to permit deflation of the left lung, the patient is positioned on the operating table with the chest rotated 20 to 30 degrees from supine toward the right. The right arm is secured at the side, and the left arm is abducted on an armrest (Fig 2, *inset*).

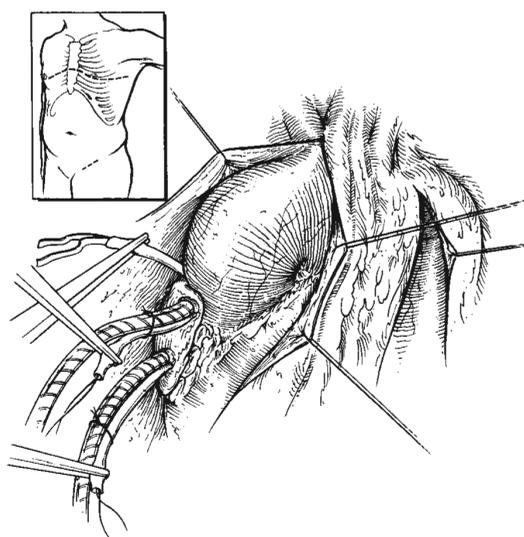
Bilateral submammary anterior thoracotomy incisions are made with the left incision extending laterally to the midaxillary line and the right, to the anterior axillary line. The pleural spaces are entered; the internal thoracic vascular pedicles are ligated and divided bilaterally, and the sternum is divided transversely with an oscillating saw. Chest retractors are placed bilaterally. A common femoral artery is isolated through an oblique incision

in the skin crease of the groin and is cannulated with a 20F or 22F cannula. The anterior mediastinal structures are exposed sufficiently to allow venous cannulation. Heparin is administered to achieve and maintain activated clotting time of greater than 500 seconds. Both venae cavae are cannulated separately through the right atrium, and cardiopulmonary bypass is established. A left ventricular vent is placed through the right superior pulmonary vein; a retrograde cardioplegia cannula is positioned within the coronary sinus, and the superior vena cava is encircled with a tape. If possible, an antegrade cardioplegia cannula is placed low in the ascending aorta. Perfusion cooling is initiated; and exposure of the ascending aor-

<i>Extent of lesion</i>	<i>Procedure</i>	<i>Ventilatory support</i>	<i>Major complications</i>	<i>Outcome</i>
Arch, proximal 2/3 DTA	Replacement of diseased segments, CABG	1 day	Transient postoperative neurologic deficit	Alive and well
Distal AA, arch, proximal 2/3 DTA	Replacement of diseased segments	2 days	None	Alive and well
Distal AA, arch, proximal 2/3 DTA	Replacement of diseased segments	2 days	None	Alive and well
Entire AA, arch, proximal 2/3 DTA	Replacement of diseased segments	1 day	None	Alive and well
Distal AA, arch, entire thoracoabdominal aorta	AVR, CABG, replacement of entire thoracic aorta	15 days	Temporary left vocal cord paralysis; tracheostomy	Alive and well
Arch, entire thoracoabdominal aorta	Replacement of arch and entire thoracic aorta	1 day	None	Alive and well



**Fig 1.** Preoperative aortogram from patient 3.



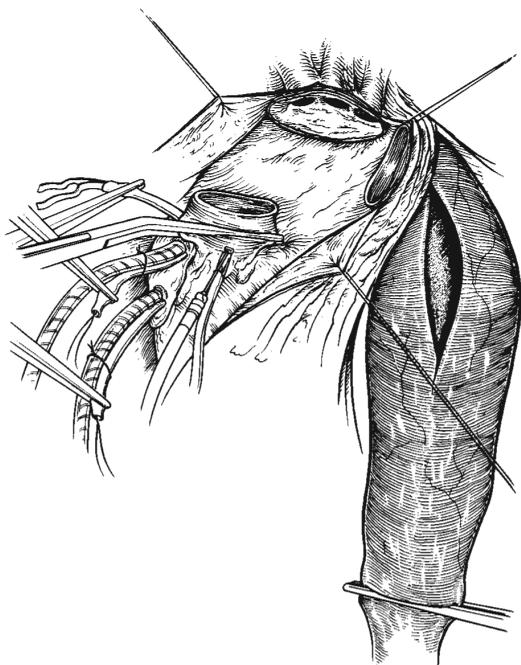
**Fig 2.** Patient positioning, incision, exposure of the mediastinal structures, and cannulation.

ta, the arch, and the descending aorta is obtained (Fig 2). The inferior pulmonary ligament is divided. The fat pad containing the vagus and phrenic nerves is identified and protected. As soon as the heart fibrillates, the ascending aorta is clamped and antegrade cardioplegia is administered. If clamping of the aorta is not possible, only retrograde cardioplegia is used as soon as the ascending aorta is opened after circulatory arrest is established and every 20 minutes thereafter. While cooling is being effected, a long collagen-impregnated woven Dacron aortic graft (Hemashield; Meadox Medicals, Inc, Oakland, NJ) is selected, and a 10-mm graft (Hemashield; Meadox Medicals, Inc) is anastomosed to the aortic graft opposite the site of the planned anastomosis to the arch vessels with a continuous 4-0 polypropylene suture. When coronary bypass grafts are required, the distal anastomoses are performed during the period of cooling. Aortic valve replacement or reconstruction of the aortic root is also performed at this time, if indicated. Methylprednisolone (7 mg/kg) and thiopental (10 to 15 mg/kg) are given during cooling. Cooling is continued until electroencephalographic silence is achieved, usually at a nasopharyngeal temperature of 15°C to 17°C. Ice packs are placed around the patient's head; the head is placed in a dependent position; the tape around the superior vena caval cannula is secured; the cannula is clamped; the intracardiac vent is occluded, and 1000 to 1500 mL of blood is drained into the venous reservoir.

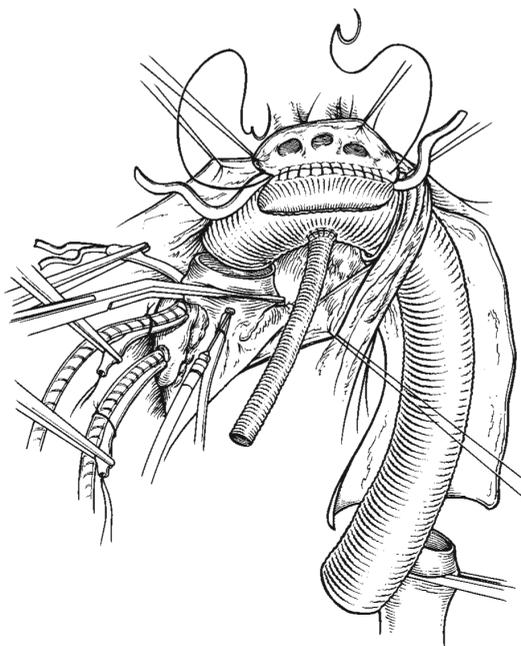
With the circulation arrested, an aortic clamp is placed on the distal descending thoracic aorta to minimize blood loss into the operative field. The ascending aorta is incised, and a cuff of aortic tissue containing the arch vessels is prepared (Fig 3). The descending aorta is incised distal to the arch, and the previously prepared graft is passed down through the opening under the pedicle containing the vagus and phrenic nerves (Fig 4). An opening is made on the graft opposite the site of insertion of the 10-mm graft, and the anastomosis to the arch vessels is performed (Fig 4). All aortic anastomoses are constructed with continuous 3-0 or 4-0 polypropylene suture, buttressed with a strip of Teflon felt. Graft-to-graft anastomoses are not

buttressed. As the anastomosis to the brachiocephalic arteries is being completed, cold retrograde brain perfusion through the superior vena caval cannula is initiated at a flow of 600 to 900 mL/min, maintaining a central venous pressure of less than 30 mm Hg.<sup>11</sup> The aortic graft is clamped just distal to the arch anastomosis with a straight clamp (Atraumax G-5030; Applied Medical, Laguna Hills, Calif) fitted with 61-mm inserts (G-6150; Applied Medical). The second arterial line from the pump-oxygenator is attached to the 10-mm graft, and antegrade arterial perfusion is established to evacuate air from the open, proximal part of the graft. Retrograde head perfusion is discontinued, and the aortic graft is clamped proximal to the aortic arch with a large angled clamp (CV 5050; V Mueller ZA) fitted with 86-mm inserts (G-8650; Applied Medical). Antegrade head perfusion then is established at 800 to 1200 mL/min at a temperature of 20°C (Fig 5), and the superior vena caval occlusion clamp or tape and the clamp on the inferior vena cava are removed.

During the interval of hypothermic flow to the upper body, the distal clamp on the aorta is removed, and the graft is cut to the appropriate length. The distal aortic anastomosis is then performed with an open technique (Fig 5). The graft is beveled posteriorly, when possible, to preserve the origins of the lower intercostal arteries. In the presence of chronic dissection, the septum between the true and the false lumina is identified, and a large segment is removed to permit perfusion of both lumina. As this anastomosis is being completed, perfusion through the femoral arterial line is initiated to remove air and debris, and a small angled clamp (Atraumax G-5045, 61-mm inserts; Applied Medical) is placed on the graft to test the integrity of the anastomosis. The lower clamp on the aortic graft is removed, and the graft is deaired via several puncture holes opened with a 21-gauge needle. Perfusion via the femoral arterial cannula is discontinued; the distal arch clamp is removed, and flow is established in an antegrade direction via the 10-mm graft, increasing flow to allow perfusion of the lower body (Fig 6). Rewarming is commenced at this

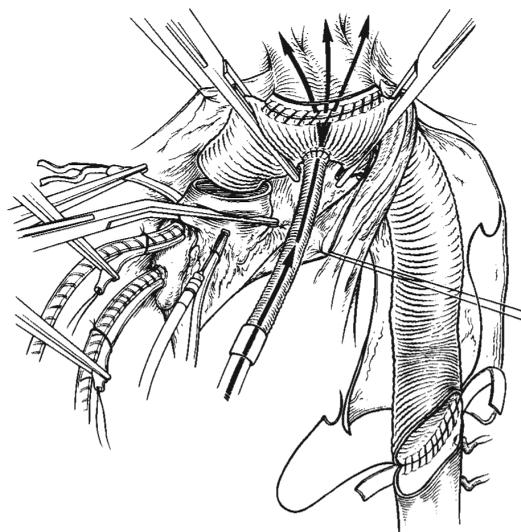


**Fig 3.** Circulatory arrest, exposure of the aorta, and resection of the aneurysm.



**Fig 4.** Anastomosis to the arch vessels.

time. Alternatively, if the distal anastomosis is technically difficult, it can be constructed with a separate piece of graft, which is then sutured to the upper aortic graft in an end-to-end fashion (patients 5 and 6). After reperfusion of the lower body is established, the upper intercostal and bronchial arteries are ligated.

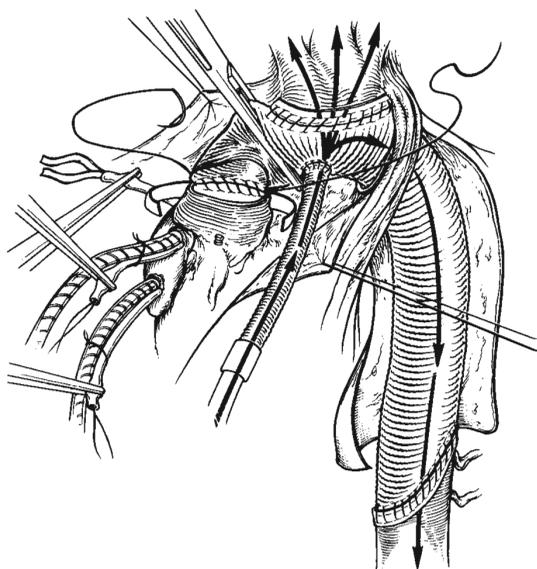


**Fig 5.** Antegrade cold arch perfusion; distal aortic anastomosis.

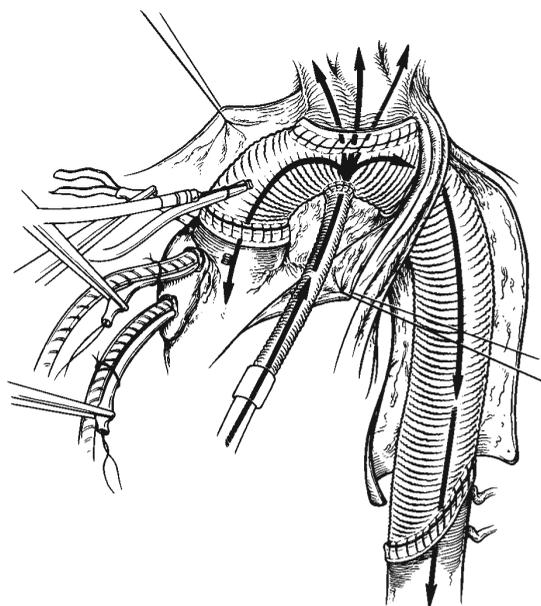
The proximal end of the aortic graft is sutured end to end to the proximal ascending aorta or the existing ascending aortic graft (Fig 6). The saphenous vein bypass grafts are anastomosed to the aortic graft at this time. Routine maneuvers to deair the heart are completed. A needle vent is placed on the proximal portion of the graft and connected to suction; the clamp proximal to the arch is removed (Fig 7). Hemostasis is effected, and the patient is weaned from cardiopulmonary bypass. The 10-mm graft is divided and is suture ligated close to the aortic graft. Two thoracostomy tubes are placed in each pleural space.

## Results

There were no hospital deaths. Five patients were extubated within 48 hours of operation. Postoperative pneumonia developed that required temporary tracheostomy and assisted ventilation for 2 weeks in patient 5, who had pre-existing chronic obstructive pulmonary disease and a large aneurysm that involved the entire thoracic aorta. This patient also experienced the development of transient left vocal cord paralysis. One patient had a delayed postoperative neurologic deficit consisting of left hemiparesis from which he recovered completely. The perioperative mean transfusion



**Fig 6.** Antegrade perfusion and rewarming; proximal aortic anastomosis.



**Fig 7.** All clamps removed; weaning from cardiopulmonary bypass.

**Table II.** Perfusion data (in minutes)

Patient	Circulatory arrest*	Retrograde brain perfusion	Arch perfusion	Lower body ischemia	Cooling	Rewarming	Myocardial ischemia	Total CPB
1	34	7	27	61	50	56	137	159
2	38	11	36	74	50	60	164	184
3	46	11	23	69	46	63	164	162
4	26	5	20	46	30	55	122	115
5	44	9	36	80	35	80	218	248
6	40	6	29	69	39	48	121	155
Mean	38	8	28	66	41	60	154	170

CPB, Cardiopulmonary bypass.

\*Includes duration of retrograde brain perfusion.

requirement was 5.6 units of packed red cells (range, 4-9 units). All patients received fresh frozen plasma and platelet concentrates. None received cryoprecipitate. Aprotinin was not used. None of the patients had evidence for spinal cord ischemic injury. Renal function was preserved in all patients without the elevation of the serum creatinine level above baseline levels. There were no wound-related complications. One patient required re-exploration for the evacuation of a retained intrapleural clot. The mean duration of post-operative hospital stay was 15 days (range, 8-36 days). All patients are alive and well 2 to 26 months after the operation (mean follow-up, 9.5 months).

Perfusion data are summarized in Table II. The mean duration of circulatory arrest was 38 minutes (range, 34-46 minutes). Selective cold perfusion of the brachiocephalic vessels averaged 28 minutes

(range, 20-36 minutes). The sum of these 2 periods represents the duration of lower body ischemia, which could be considered synonymous with the duration of spinal cord ischemia. This interval ranged from 46 to 80 minutes (mean, 66 minutes).

## Discussion

Replacement of the thoracic aorta in stages may not be feasible when extensive aneurysmal disease in the arch makes staging technically challenging or when the presence of symptoms may be related to more than one diseased aortic segment. Single-stage replacement of the thoracic aorta with a bilateral anterior thoracotomy "clamshell" incision has been previously used with an operative risk

comparable with that of the 2-stage approach.<sup>6,7</sup> This incision provides an excellent exposure facilitating control of the distal aorta and the intercostal arteries.<sup>5</sup>

We believe the clamshell incision is particularly advantageous in reoperative procedures because it permits easier access to the mediastinal structures. Bicaval cannulation eliminates the need for central pulmonary artery cannulation and makes the administration of retrograde brain perfusion possible without the use of separate percutaneous catheters.<sup>12</sup> Furthermore, it allows clear exposure of the phrenic and recurrent laryngeal nerves, reducing the possibility of injury.

Previously described techniques for single-stage replacement of the thoracic aorta involve a period of circulatory arrest during which the distal aortic and the arch anastomoses<sup>6,7</sup> or the arch and the proximal aortic anastomoses<sup>12</sup> are performed. A technique of hypothermic selective antegrade cerebral perfusion has been described by Ergin and associates.<sup>13</sup> This technique involves perfusion of the head vessels via a separate graft that is later anastomosed to the aortic graft. Our technique reduces the duration of circulatory arrest by constructing the anastomosis to the arch vessel first and immediately reestablishing antegrade brain perfusion without further interruptions in cerebral blood flow. Furthermore, there is no need for separate cannulation of the head vessels.<sup>14</sup> After retrograde head perfusion to evacuate particulate debris and air from the arch vessels, antegrade perfusion is established until cardiopulmonary bypass is discontinued. This should minimize the risk of retrograde atheroembolism.

Our technique does not allow adequate exposure of the infradiaphragmatic aorta. None of our patients required resection of this segment of the aorta. When indicated, the infradiaphragmatic

aorta could be replaced either concurrently via a separate thoracoabdominal or abdominal incision or at a later time. We do not advocate the routine use of this technique for acute type A aortic dissection, unless extensive aortic replacement beyond the arch is planned.

The "arch-first" technique allows single-stage extensive replacement of the thoracic aorta to be performed with the shortest interval of circulatory arrest and minimizes the duration of retrograde aortic perfusion. Our initial experience justifies further clinical evaluation of this technique.

### Addendum

Since submission of the manuscript, the technique has been used in 4 additional patients with large aneurysms (1) and chronic type A dissections (3). Patient 7 underwent composite graft replacement of the aortic root and replacement of the ascending aorta, aortic arch, and most of the descending aorta. After an uneventful initially postoperative course, he had a sudden cardiac arrest and died on postoperative day 4. Autopsy findings were unremarkable. Patients 8, 9, and 10 recovered uneventfully.

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# Transaortic Video Assisted Removal of a Mobile Left Ventricular Thrombus: a Safe and Effective Technique

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## ABSTRACT

Pedunculated and mobile thrombus of left ventricle is a rare but life-threatening complication of myocardial infarction. The indications, the mode of removing and the strategy of management of this complication are still debated. We describe for first time in the European literature a case of a patient with a mobile left ventricular thrombus following acute myocardial infarction, successfully treated through an ascending aorta incision and by using VATS technique.

**Keywords:** Post infarction LV thrombus, intracardiac mobile thrombus, VATS in cardiac surgery

## INTRODUCTION

Left ventricular thrombus is a well-known complication of acute myocardial infarction (AMI), reported in the literature in an incidence between 4% and 60%<sup>1,2</sup>. Mostly it is a thrombotic mass, well-attached (with a wide base) to the trabeculated ventricular surface. The intracardiac thrombi are potentially lethal as a result of valvular obstruction, peripheral embolization and disturbances of rhythm or even, a sudden death. All these complications are possible, especially for a mobile thrombus<sup>3</sup>. The recent aspects about the

treatment of a patient with a left ventricular thrombus are debated. Some advocate an aggressive strategy including emergency surgery for remove the thrombus, while some others mostly recommend a conservative treatment<sup>5,6,7</sup>. In addition, in the case of surgical management, the indicated approach for thrombectomy is still debated. We describe a case of a patient with post-AMI left ventricular mobile thrombus, treated by a transaortic video-assisted thrombectomy, combined with a CABG and as far as we know it is the first case in the European literature.

## PATIENT – METHOD

A 45-year-old man was admitted in the Cardiology Department suffered from an AMI after successful thrombolysis in another hospital. He underwent an emergency coronary angiography which revealed a two-vessel disease: 80% stenosis of LAD, and 80% stenosis of left circumflex artery (LCx). Echocardiography revealed hypokinesis of the anterior wall and the apex, with a low left ventricular EF (30%). On the 5<sup>th</sup> post-infarct day, the ECHO revealed an irregular, LV mobile mass 2x2 cm, originated from the apical segment of the lateral wall. The finding was consistent with an intracavitary mobile thrombus. Continuous heparin infusion started, combined with simultaneous oral anticoagulation. On the 9<sup>th</sup> post-infarct day, the mobile thrombus (Fig.1) showed increased diameter (2 x 2, 5 cm). Surgical treatment was considered to prevent a life-threatening embolization and we planned a simultaneous thrombus removing and coronary artery revascularization.

### Operation

Under general anaesthesia, an intraaortic balloon pump was inserted to support the marginal hemodynamic condition of the patient. After a median sternotomy the LIMA and left great saphenous vein were harvested. Ascending aortic and bicaval cannulation were accomplished and cardiopulmonary bypass with moderate systemic hypothermia (32°C) was instituted. To avoid any manipulation to the left ventricle, vent was introduced after aortic cross-clamping and cold blood cardioplegia administration. An oblique aortotomy was performed and a video-thoracoscope (Karl-Storz Endoskope 26003AA, 0°,  $\psi$  10mm) was advanced through the aortic valve in the left ventricle. The ventricular cavity was continuously vented and additionally an external sucker was used to obtain a clean intracardiac surgical field. The pedunculated thrombus was visualized at the lateral wall and was removed by using ring forceps (Fig. 2). The whole cavity of left ventricle was thoroughly inspected and residual pieces of mural thrombus were also removed. The aortotomy was closed, cardioplegia was reinfused and two distal anastomoses to the 1<sup>st</sup> obtuse marginal branch (vein graft) and to the LAD (LIMA) were

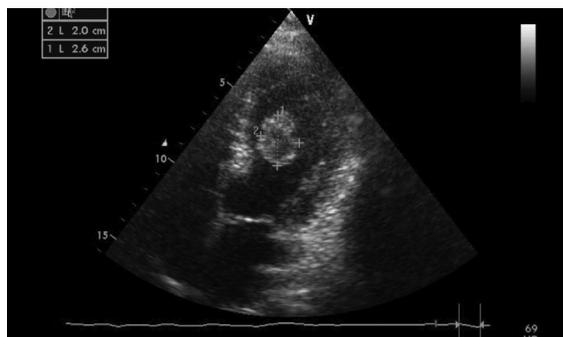


Figure 1. Thrombus in the LV cavity

sequentially constructed. The proximal anastomosis of vein graft was done during rewarming. The patient was successfully weaned from cardiopulmonary bypass, drains were placed, and after sternotomy closure he was transported in the ICU. He was extubated after 12 hours and the TTE confirmed the complete removal of the thrombus, and verified the normal function of the aortic valve. The patient had an uneventful course, was discharged on the 7<sup>th</sup> postoperative day, and till today-5 years- he is in good condition with no recurrence of thrombus and EF of 55%.

## DISCUSSION

The treatment of choice for LV thrombus is anticoagulation with intravenous heparin followed by a minimum of 3-6 months of warfarin if an embolic event has already occurred or if the patient has a large anterior infarction or if a thrombus is detected<sup>5,9</sup>. However, recurrent embolization during anticoagulation treatment has been reported,



Figure 2. The thrombus was removed successfully.

and this risk is even higher in case of a mobile thrombus<sup>2,4</sup>.

Surgical removal in these cases has not yet received clear recommendations due to: a) the unknown real incidence of this complication, b) the lack of randomized studies comparing surgical and conservative treatment, and c) the influence of higher surgical mortality after a ventriculotomy. The deterioration of an already poor LV function, the increased risk of bleeding, the postoperative arrhythmia, the aneurysm or a new thrombus formation after a ventriculotomy, are some of the possible complications which hesitate the surgical management.

According to the proposed David – Komeda procedure the ventriculotomy is combined with the infarction exclusion technique in order to prevent a post-ventriculotomy aneurysm formation<sup>6</sup>.

The approach through the mitral valve after a left atriotomy has been also proposed<sup>7</sup>. However, organized thrombi adherent to ventricular trabeculae might be difficult to be removed through the papillary muscles and chordate tentinae. Potential complications related to the above techniques are mitral valve apparatus laceration; ventricular or atrial wall perforation and conduction system contusion.

The transaortic approach of the LV thrombus using a VATS-equipment which has been first described in 1999 by Tsukube T, et al<sup>8</sup> is in our opinion a non-traumatic and safe surgical choice. In the cases of an atherosclerotic ascending aorta the transaortic approach should be abandoned. In our opinion for these cases a transatrial approach (through the left atrium) using VATS-equipment could be an alternative approach.

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# Vascular Trauma in Orthopaedic Surgery

*Panagiotis N. Soucacos*

## Introduction

There are various situations in which the orthopaedic surgeon may be faced with vascular injuries. The most common of these are complete or incomplete nonviable amputations and open injuries/fractures of the upper or lower extremities. In addition, injuries to major vessels during trauma or reconstructive orthopaedic procedures are known to occur and need to be addressed immediately by the operating team.

Prior to the development of microsurgery, vascular surgeons were usually called upon to take over and manage these very serious limb, or even life-threatening injuries. Microvascular repair by an orthopaedic team well-schooled in microsurgical techniques enhances the chances of limb salvage with satisfactory function.

With the introduction of the operating microscope and other means of magnification (Le. loupes) along with micro-instruments and micro-sutures, orthopaedic surgeons were able to achieve successful anastomoses of small vessels less than 1 mm in diameter, including the digital arteries in complete and incomplete nonviable digital amputations<sup>29,31,32</sup>. Although the use of microsurgery by orthopaedic surgeons, at least initially, was almost exclusively applied to revascularization and replantation, the growing expertise in microsurgical techniques has evolved towards a role in the management of other traumatic injuries, including type IIIb and IIIc compound fractures.

## Basic Principles in Microvascular Surgery

Fine work with reliable accuracy is made possible in microsurgery with the aid of an operating microscope or magnifying loupes, and the refined techniques and skills can be acquired only by many hours of practice. In this regard, training in the laboratory has proven a key factor before a surgeon can make a successful clinical contribution. Before participation in complex cases of complete or incomplete nonviable amputations,

surgeons need to demonstrate adequate experience and skills acquired in the laboratory, where devotion of adequate time, practice and patience are prerequisite to performing small vessel anastomosis.

Microsurgical procedures are performed on small structures that require magnification. Magnification can be achieved with an operating microscope or ocular loupes. Although several types and models of operating microscopes are currently available, similar general principles

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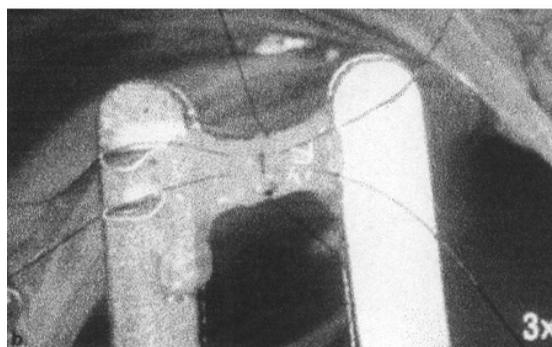
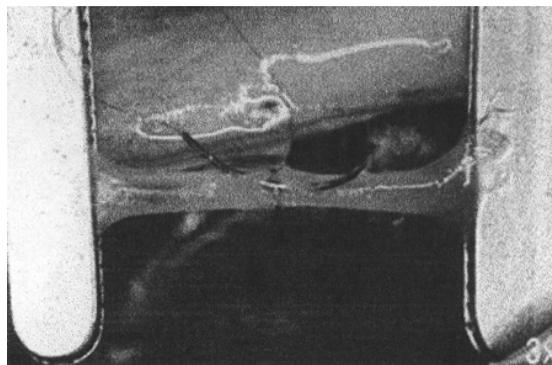
apply to the use of most. In general, a magnification of 6x and 10x is used for dissection and exposure of small nerves and vessels, while microsurgical repair of vessels and nerves requires 16x and 25x magnification.

While magnification from 16x to 40x is provided by the microscope and is essential when working with structures less than 1 mm in diameter, many procedures may be performed using magnifying loupes of up to 5x. Ocular loupes are invaluable tools for anastomosis of large vessels (diameter 2-3 mm) or for the initial dissection.

Microvascular instruments are extraordinarily delicate so as to allow the surgeon to execute very precise procedures. Although a variety of specialized instrumentation exists, for the most part microvascular procedures require three or more straight and curved jewellers forceps for manipulating fragile tissues:

- Fine suture, microscissors with blunt edges for fine dissection
- Microscissors with serrated blades for cutting without crushing the intima of the vessel
- Microvascular clamps with a closing pressure of less than 30 g per square millimetre to avoid damaging the vascular intima of small vessels and causing subsequent thrombosis.

The patency rate obtained in microvascular anastomosis is dependent upon the skills learned in the laboratory and upon careful attention and awareness of factors that influence the success of patency<sup>64</sup>. Minimal, no more than 1-2 mm, adventitial stripping is recommended in order to visualize the lumen and avoid an excess of adventitia that can invert and occlude the lumen. On the other hand, extensive stripping of the adventitia can lead to necrosis of the adventitial wall at the anastomosis site (Fig. 14.3.2). Interrupted suturing is the technique of choice in contrast to a running suture that can cause unacceptable constriction of the lumen. A few interrupted sutures are preferable to an excessive number, as the latter may produce increased areas of vessel wall necrosis that could subsequently lead to scar formation and intimal proliferation and necrosis. Furthermore, excessive suturing may cause added deformation of the ends



*Fig. 1 a,b End-to-end microvascular anastomosis. a Once the vessel ends are placed in a bar clamp, the two-stay sutures can be placed 120° apart. A suture is then placed in between the stay sutures in the anterior wall, followed by the even placement of subsequent sutures. The clamped vessel is then turned 180° to show the posterior wall. b A stitch is placed 120° from the initial stay sutures in the posterior wall, followed by evenly spaced sutures in between. Common technical errors during microvascular anastomosis include sutures catching on the back of the vessel, suturing the side wall of the vessel, sutures which are poorly placed and fail to fully penetrate the vessel wall, and uneven spacing of sutures with poor approximation of intima. The figure shows correctly placed sutures*

of the vessel, causing exposure of more collagen of the tunica media to blood flow and, in turn, producing clot aggregation and thrombus formation<sup>1</sup>.

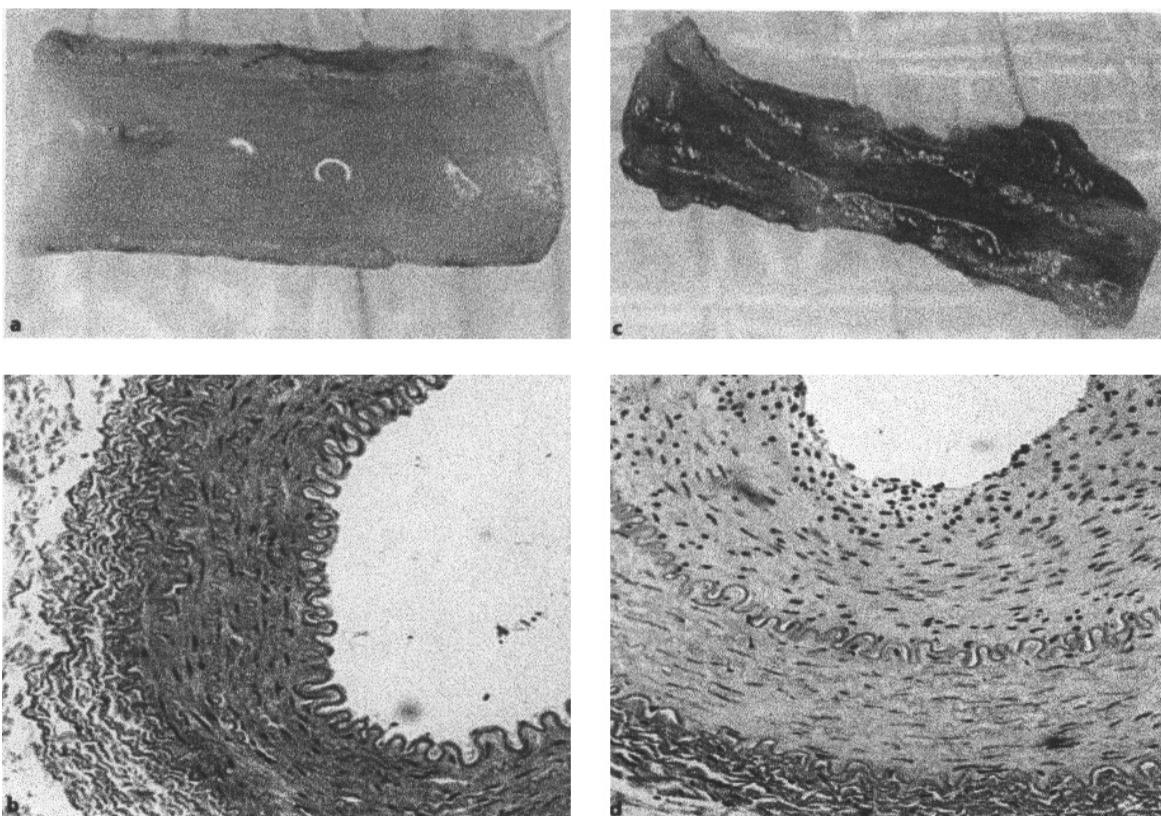
Suturing of the vessels must be done on healthy tissue and under no tension. In general, correct tension can be indicated by a small loop of suture visible through the opposed vessel walls. In addition, the tension should be such that the suture does not break while knotting. The diameter of this loop should be equal to the thickness of the

wall<sup>11</sup>. Although perfusion of the lumen of the vessel is not always necessary since it may induce damage to the intima, irrigation of the edges of the vessel to remove any residual traces of blood is helpful.

Once anastomosis has been achieved, patency is evaluated. A simple patency test is to inspect the fullness and pulsation of the vessel or to gently palpate the site of anastomosis. However, the most reliable patency test is the “empty-and-refill” or “milking test” performed by clamping the artery proximal to the anastomosis site with forceps and then milking the vessel distal to the anastomosis site using different forceps, thus creating an empty vessel pocket. Once an empty segment has been obtained, then the proximal forceps are released. If the vessel is patent, then the empty space should show blood flow and rapid filling.

### Basic Microvascular Techniques End-to-End Microvascular Anastomosis

Careful microvascular dissection under magnification is used to expose the selected vessel (Fig. 14.3.1). Magnification by a microscope is required when working with vessels less than 2 mm in diameter, while ocular loupes are valuable for the initial dissection and anastomosis of vessels greater than 2-3 mm in diameter. Proper exposure entails clearing enough room to perform the procedure and to be able to visualize enough of the proximal recipient vessel to verify its condition. Once the loose connective tissue surrounding the vessel has been removed, each end of the vessel is mobilized to obtain an adequate length to approximate both ends with no tension. This can be achieved by ligation of side branches that



*Fig. 2a-d Histological examination of the anastomosis site has demonstrated unequivocally that extensive stripping of the adventitia or suturing under tension can seriously damage the vascular wall. a The appearance of the normal lumen in longitudinal section of an intact vessel (the femoral artery of a rabbit) as it appears under the operating microscope. b Histological appearance of the normal vascular wall cytoarchitecture (H&E, 50x). c A longitudinal section of the rabbit femoral artery following incorrect suturing technique with 8-0 suture. Anastomosis under tension and on damaged intima of the vessel result in an abnormal vessel lumen. d The histological picture of the lumen following incorrect suturing technique shows extensive (8 layers) proliferation of the intima (H&E, 50x)*

tether the vessel. The area is continuously irrigated with heparinized lactated Ringer solution throughout the procedure to keep the vessel moist and pliable and to prevent the suturing material from becoming sticky. Adventitia is removed from the vessel ends by circumferential trimming or applying traction to the adventitia, pulling it over the vessel stump and then transecting it ("sleeve amputation"). By doing this, all layers of the vessel wall should be exposed. Upon inspection of the intima under high magnification (25-40x), the vascular wall can be cut until the normal tissue ends appear. Afterwards, the vessel ends can be apposed with a clamp approximator.

Interrupted sutures that go through the full thickness of the vessel wall are used. The first two sutures (stay sutures) are placed about 120° apart on the vessels circumference and the ends are left long so that they can be used for traction. Once the clamp approximators are rotated to expose the posterior wall, a stitch 120° from the initial two stitches can be placed. Additional stitches are placed in the remaining spaces. In general, arteries 1 mm in diameter usually need five to eight stitches, while veins need 7 to 10 sutures. Once the anastomosis is complete, the clamp distal to the anastomosis is removed first, followed by the upstream clamp. Some minimal bleeding between stitches is of no concern. A patency test should be performed as described above, and soft tissues are closed over the vessels so as to avoid exposure and drying of the vascular wall.

### **End-to-Side Microvascular Anastomosis**

Dissection and vessel mobilization is performed as for end-to-end anastomosis. Once dissection and mobilization has been done, a small elliptical portion is carefully excised from the recipient vessel using microscissors. The vessel that is to be connected is then cut at a 45° angle. Sutures with long suture ends for traction are placed in the proximal and distal ends of the ellipse of the receiving vessel, followed by placing sutures evenly between the traction sutures. Once anastomosis is complete, the procedures followed are similar to those described above.

### **Microvascular Vein Suturing and Grafting**

The techniques used for the suturing of a vein are similar to those applied for suturing of an artery. However, as the vessel wall of the vein is considerably thinner and more frail than that of the artery, great care is necessary in handling the vein wall to avoid tearing. In addition, finer suture material should be used when suturing veins.

Vein grafting is performed when end-to-end microvascular anastomosis cannot be performed. In revascularization and replantation procedures, this may also entail bone shortening. There are several candidate veins available for grafts so that the graft can approximate the diameter of the recipient vessel. Close approximation of sizes between vein graft and recipient avoids thrombosis resulting from turbulence. Vein grafts are generally harvested from the upper and lower extremities. Upper extremity veins tend to be more flimsy because of the lower muscle content in the upper extremity vessels, but as a result they also demonstrate fewer spasm problems. The foot and forearm are sources for veins 1-2 mm in diameter, although grafts can frequently be obtained from amputated parts. The graft should be handled minimally during harvesting.

When the vein is harvested, the small side branches are either ligated or cauterized with bipolar cautery far from the vein wall. A suture is placed on the proximal end. This provides an arbitrary convention for the surgeon to orient the graft knowing that the blood flow is always in the direction from the unmarked end of the graft towards the end with the suture. For arterial reconstruction using interposition graft, the vein graft should be reversed end from end in order to avoid obstruction of blood flow by the valves in the veins. This is not necessary for venous reconstruction. The suturing technique is similar to that used for end-to-end anastomosis described above, although often size differences in the vessel diameters need to be overcome by cutting the vessel ends obliquely or in a fish-mouth pattern. First the proximal anastomosis is performed, once the vein graft has been gently perfused with heparinized Ringer solution. Afterwards, the distal anastomosis can be performed.

## Application of Microvascular Surgery to Trauma Orthopaedics

Orthopaedic surgery has witnessed exponential growth in the role of microsurgical techniques to a wide variety of traumatic injuries. Major contributions of microvascular surgery in orthopaedic trauma include revascularization and replantation of complete or incomplete nonviable amputated digits and extremities, type IIIb and IIk open fractures, as well as free compound tissue transfer.

### Replantation

In 1968, Komatsu and Tamai [30] reported the first successful replantation of an amputated thumb. Since then, innumerable revascularization and replantation procedures for amputated digits have taken place with the indications, procedures and results being assessed in relation to complete and incomplete nonviable amputations, as well as in conjunction with the severity of the injury, the number of the amputated digits, and the various modalities and techniques included in the revascularization and replantation procedures. Today, the accumulated experience has made revascularization and replantation surgery a fairly routine procedure which can be performed in a number of hospitals worldwide, provided that they house surgeons who are well-trained in microsurgical techniques.

Well-documented selection criteria have been established to assist the surgeon in screening patient eligibility for replantation. The goal of all revascularization and replantation efforts is targeted not only towards the survival of the amputated part, but mainly towards producing as close as possible normal functional ability. Well-defined selection criteria enable the surgeon to avoid procedures that lead to a surviving, but nonfunctioning part, as well as a plethora of secondary reconstructive procedures [50]. Fundamental to the success in revascularization and replantation is not only a solid microsurgical technique for vascular microanastomosis, nerve coaptation and tendon repair, but also a deep understanding of the selection criteria.

At its start, orthopaedic microsurgery focused

on replantation. The tendency to replant virtually every amputated part eventually gave way to attempts to define strict selection criteria and optimize the functional results. Today, however, the major concern is not “how to replant an amputated part”, but rather “how to make it functional”. In this regard, revascularization and replantation of amputated parts without sensation and function are no longer considered acceptable [47].

### Selection Criteria

The surgeon must consider various factors in determining whether to replant an amputated part, including survival of the replanted part and functional outcome. The functional outcome should be superior to that of a prosthesis or revision of the amputation. The criteria which aid the surgeon in predicting outcome can be divided into: (1) those factors related to the type of amputation and its characteristics; and (2) general factors related to the patient

Three main categories of amputations are recognized and graded, based on the viability of the amputated part. Amputations are classified as: (1) complete amputations; (2) incomplete nonviable amputations; (3) incomplete viable amputations.

- **Complete amputation** is defined as full detachment of the amputated part from the proximal stump.
- **Incomplete nonviable amputation** is defined as when all of the major and vital arteries and veins have been severed, however the distal amputated part is connected with the proximal stump with an islet of skin or tendon. The latter are, of course, inadequate to provide the necessary blood supply to the distal part.
- **Incomplete viable amputations** is a grey zone type of amputation which stands true only if, after visualization under the operating microscope, a major feeding artery is intact or some venous return is present. For example, in the case of a digit, if one digital artery is intact or venous return is assisted by an intact piece of skin.

### **General Indications and Contraindications**

In addition to selection criteria related to the type, level and severity of the amputation, other general factors related to the patient need to be considered before replantation is attempted. These include: the age, mechanism of injury, interval between amputation and time of replantation (ischaemic time), patient's general health, predicted rehabilitation and vocation.

#### ***Age***

In children, an attempt should always be made to revascularize and replant almost any amputated digit or body part. If the reattached part survives, useful function can be predicted. Although digital replantation in very young patients is technically demanding regarding microanastomosis of digital vessels that are often less than 0.5 mm, we have found good functional results [7]. In contrast, poor nerve regeneration and joint stiffness pose problems for good functional outcome in the elderly. In general, good sensibility, strength and coordination are rarely achieved in the older patient, despite the satisfactory function of the replanted digit.

#### ***Mechanism of Injury***

Clean-cut "guillotine" type amputations are good candidates for revascularization and replantation. Usually a satisfactory functional result can also be anticipated in minor crush or avulsion amputations that have minimal vascular injury. Severely crushed or avulsed digits or extremities have extensive vascular, nerve and soft tissue damage and the predicted outcome is usually poor. Segmental injuries at multiple levels are usually associated with severe vascular damage, often too extensive to warrant replantation.

#### ***Time of Ischaemia***

Ischaemia remains a key factor in determining the success of replantation [8]. However, because the duration of ischaemia allowable varies from tissue to tissue, for didactic purposes ischaemia time is divided for digits and major limbs. Since digits consist of mostly skin, bone and subcutaneous tissue and contain no muscles, warm

ischaemia is tolerated for a longer period of time. After adequate cooling, we have experienced successful replantation even up to 24 h postinjury and it has been reported up to 36 h. However, major limbs that consist of a high percentage of muscle can tolerate only 4-6 h of ischaemia following amputation. Due to the size of the amputated extremity, even when wrapped and immersed in an ice box for cooling, only the outer section of the amputated part is adequately cooled. The inner muscles remain in relative warm ischaemia and, thus, the allowable 6 h of ischaemia cannot be extended [24].

#### ***General Health of the Patient***

If the patient has sustained other major life-threatening injuries at the time of trauma, then replantation of digits may need to be postponed or even cancelled. Certain diseases that can adversely affect peripheral circulation, such as diabetes mellitus, some autoimmune diseases, collagen vascular diseases or atherosclerosis, among others, may also produce a condition which contraindicates replantation.

#### ***Preoperative Care of the Patient and Amputated Part***

After other major injuries have been stabilized, bleeding from the stump should be controlled using pressure. The patient should be transported with a pressure dressing and no attempt to ligate or clamp vessels should be made. In cases where bleeding is persistent, a pneumatic tourniquet or cuff can be used.

The amputated part, if contaminated during trauma, should be gently rinsed in normal saline or other physiological solutions. The part can then be wrapped with gauze, moistened in normal saline or Ringer's lactate. The wrapped part should then be placed in a plastic bag and placed on ice. Alternatively, the part can be immersed in normal saline or Ringers lactate in a plastic bag and the bag placed on ice. The latter method is preferable as it is less likely for the part to become frozen by coming in contact with the ice or to be strangled by the wrappings.

In incomplete amputations, the amputated part

should be left attached to the stump with care taken to avoid rotation or pinching of the soft tissues which might further compromise any remaining blood flow. Sterile gauzes moistened in normal saline should be applied to the stump and amputated part and an ice pack applied to the amputated part. The limb may be supported with padded splints.

### **Surgical Sequelae and Techniques**

Simple reattachment of the amputated segment in patients who have sustained complete amputations does not ensure survival of the amputated part. The survival and function of the replanted part, and in turn the success of the surgery, depend on various parameters and the appropriate management of the specific tissue components. For digit replantation, survival and function of the replanted digit are intimately related to the successful anastomosis of both of the digital arteries, as well as two dorsal veins per patent digital artery (Fig. 14.3.3).

The surgical sequelae in replantation may vary somewhat according to the level of the amputation and type of injury. After thorough cleansing and debridement, structures are identified and repair is performed. Structures are repaired serially from the skeletal plane outwards, so that the deeper structures are repaired first, avoiding the sites of vascular anastomosis. In most cases, the repair of digits follows the following operative sequence: (1) tissue debridement; (2) neurovascular identification and labelling in the amputated part and stump; (3) bone shortening and stabilization; (4) extensor tendon repair for digits; (5) arterial anastomoses; (6) venous anastomoses; (7) flexor tendon repair for digits; (8) nerve repair; and (9) soft-tissue and skin coverage. All of the structures are repaired primarily, including nerves, unless a large nerve gap is present which necessitates a secondary nerve grafting procedure. Secondary reconstruction of structures would entail operating through already repaired structures of the replanted part.

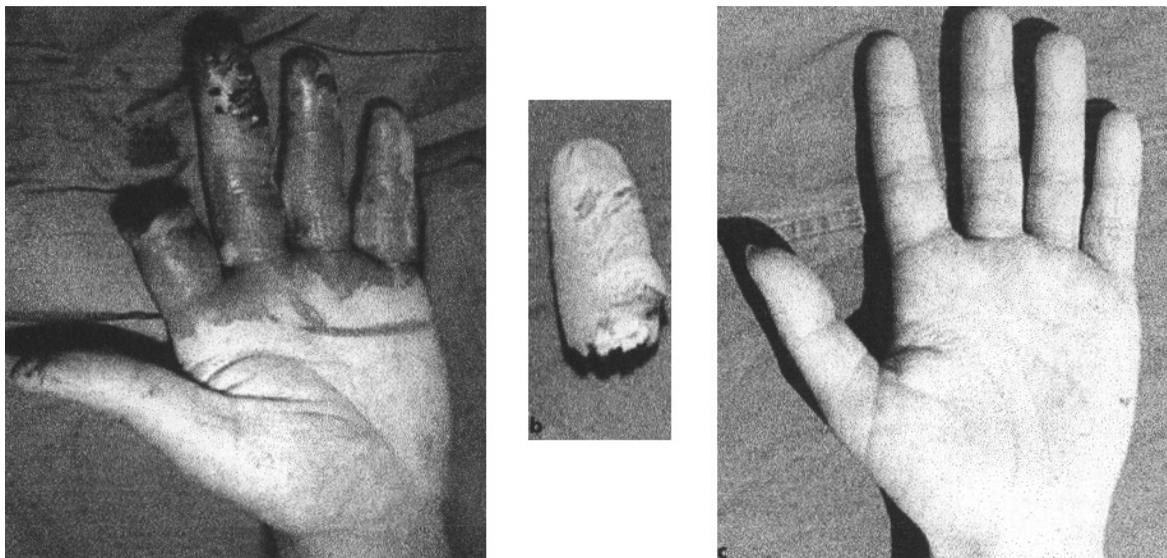
### **Surgical Preparation of Amputated Part and Patient**

Revascularization and replantation procedures require two teams. One surgical team prepares the amputated part, while the other prepares the patient and the amputated stump. The amputated part is cleaned with normal saline. The part should be kept cool by placing it on a bed of ice draped by a sterile drape sheet and plastic drape. Depending on the size of the amputated part, debridement should be performed using the operating microscope or magnifying loupes. The amputated part is carefully debrided and dissected to expose and identify arteries, veins, nerves, tendons, joint capsule, periosteum and soft tissues, which will save considerable time during replantation later.

Once the patient has undergone a complete clinical evaluation, the second team initiates surgical preparation of the patient. Most digital replantations can be performed under axillary brachial plexus block with bupivacaine, a long-acting local anaesthetic. Regional anaesthesia is preferred because of the increased vasodilation and peripheral blood flow due to the peripheral autonomic block. The stump is first cleansed with an antiseptic, such as povidone-iodine solution, and irrigated with normal saline. Then the stump is debrided and neurovascular structures are identified and labelled with 8-0 or 9-0 nylon under magnification and tourniquet ischaemia. Subcutaneous veins on the stump are often very difficult to locate, but to avoid venous congestion, it is critical that an adequate number of veins are identified for later patent anastomosis. Additionally, the harvesting of veins in the digit is usually tedious, requiring meticulous and gentle dissection. However, once one good vein is located in the subcutaneous layer, it may serve to guide the surgeon to similar veins in the same plane. Another useful guide for finding veins in the stump are small red blood clots. These small thromboses form at the open ends of the veins and can be very helpful for the surgeon in pin-pointing the vein.

### **Bone Shortening and Fixation**

Bone shortening almost always proceeds osteosynthesis and vessel anastomosis. Shortening



*Fig. 33a-c. Revascularization and replantation of a complete single digit amputation, a Complete amputation of the right index finger at the level of the middle phalanx slightly distal to the insertion of the flexor digitorum superficialis. b Appearance of the amputated part, c One year postoperative view showing successful revascularization and replantation. Good function of the proximal interphalangeal (PIP) joint was attributed to the intact superficialis.*

of the digital skeletal framework before replantation appears to be one of the best alternatives in achieving good end-to-end vessel anastomosis on healthy tissue and without tension. In general, the procedure entails the careful resection of the bone ends to ensure ease of approximation of the vessels and nerves with minimal stripping of the periosteum. The amount of bone removed varies according to the type of injury and the level of the amputation. It is usually preferable to remove bone from the amputated part, so that if the replantation fails, length of the stump has not been sacrificed. A greater amount of bone must be removed in an avulsion or crush injury until normal intimal coaptation without tension is possible, as compared to clean-cut or guillotine-type injuries. Excessive bone resection should be avoided in children, as it may result in the excision of, or potential damage to, the epiphyseal plate. Bone resection is followed by osteosynthesis, which allows for the healing of microvascular anastomoses and nerve sutures, as well as repaired tendons.

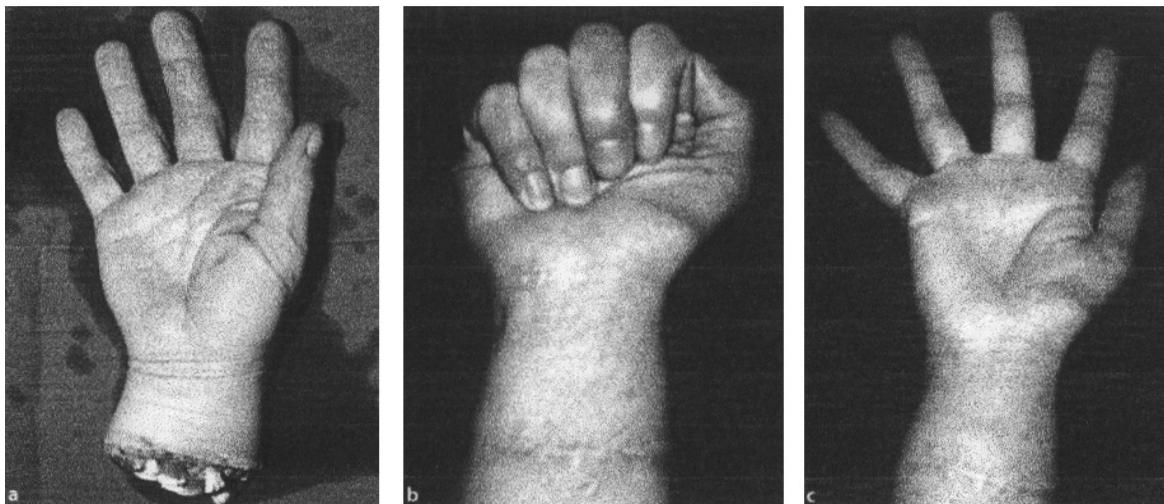
#### ***Skin Coverage***

Once all of the structures have been repaired, haemostasis is imperative. Then the skin can be

loosely approximated with a few interrupted nylon sutures. Potentially necrotic skin is excised and the skin is closed without tension. It is of paramount importance that the anastomosis site is covered, otherwise adventitial necrosis will ensue, with subsequent thromboses formation. A local flap, split thickness graft, z-plasty, two-stage pedicle flap or free flap may be required to ensure coverage of the anastomosis site, as well as the area of nerve and tendon repair. Fasciotomies are indicated if pressure or constriction occurs.

#### ***Postoperative Management***

The wound should be covered with strips of gauze moistened with antibacterial grease. It is essential that the strips are not placed in a continuous or circumferential manner, which can potentially constrict the replanted digit. A bulky dressing is applied, with the fingertips remaining exposed for clinical observation and temperature probes. Plaster splints are usually applied to the palmar aspect of the hand so that the dorsum can be inspected, but if the flexor tendons have been repaired, the splints need to be placed dorsally to prevent pull of the flexors against the plaster. The extremity is then elevated to avoid oedema. The



*Fig. Revascularization and replantation of a complete amputation of the distal third of the forearm, a Preoperative view following clean-cut amputation of the distal third of the forearm. One year postoperative views showing successful revascularization and replantation (b) with good flexion (c) and extension.*

dressing is left in place for about 2 weeks. However, dressing changes should be done every other day to ensure that dried blood or other materials do not collect, which can act as a constricting factor on the replanted part.

## **Major Limb Revascularization and Replantation**

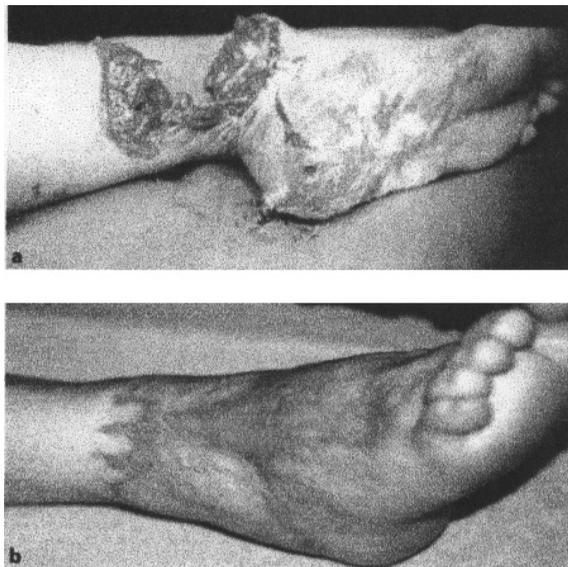
### **Upper Limb**

Complete or incomplete nonviable amputations of the wrist or distal third of the forearm are ideal for revascularization and replantation because with success hand function is restored, since both flexion and extension of the digits can be achieved by the proximal uninvolved muscles (Fig. 14.3.4). Good protective sensation of the hand is also readily achieved with primary or secondary repair of the median and ulnar nerves. In contrast, amputations at the upper third of the forearm and level of the elbow are more challenging due to the severity of injury and soft tissue damage. Although above-elbow amputations are easier from the technical perspective as only one artery of large diameter (brachial) needs to be anastomosed, they are associated with extensive bone, muscle and nerve damage. This makes the preoperative evaluation and management more demanding and postoperative treatment more difficult with a high rate of infection.

In addition, nerve recovery has a relatively low potential at this level, requiring multiple reconstructive procedures to provide functional use to the extremity. Amputations at the shoulder level are more severe than global brachial plexus injuries and a detailed evaluation taking into account various factors has to be considered before replantation can be attempted.

### **Lower Limb**

In general, lower limb replantation is met with a lower rate of success compared to upper limb replantation. This is because most of these injuries are related to motor vehicle accidents which tend to be more serious in nature (Fig. 14.3.5). Severe tissue avulsion, multiple level damage and heavy contamination of the wounds usually characterize these amputations, which weaken the indications for replantation. Early complications include extensive blood loss, possible acidosis, renal insufficiency, infection and systemic toxicity. Late complications are related to considerable bone shortening, bony nonunion, chronic osteomyelitis, restrictive joint motion, foot deformity secondary to Volkman contracture, and plantar trophic ulcers because of inadequate nerve regeneration. For these reasons and since prosthetic devices, particularly for below-knee amputations, are able to achieve excellent rehabilitation, replantation of lower limbs



*Fig. 5a,b Revascularization and replantation of an incomplete nonviable amputation of the foot, a Preoperative view showing relatively clean-cut incomplete nonviable amputation of the distal third of the leg. b Nine-month postoperative view showing successful revascularization and replantation*

should be considered carefully.

### Replantation in Children

The selection criteria applied to adults do not always apply to children, since in virtually all cases an attempt at revascularization and replantation in children should be made [5]. Children have a higher regenerative potential in as far as peripheral nerves are concerned. The only contraindication for attempts at replantation in children are severely damaged and/or mutilated parts, when the general condition of the child may prohibit a long surgical procedure or when other systemic injuries are present.

### Postoperative Management

Careful postoperative management is essential for a successful outcome. The patient's vital signs and vascularity of the area should be monitored continuously. The room should be warm, as cooling can lead to cold-induced vasospasm. In addition, the patient should be left in a quiet room with limited visitations, to avoid stress-induced vasospasm. Cigarette smoking by the patients and visitors is strictly forbidden, as nicotine is a potent

inducer of vasospasm. Finally, cold drinks, as well as those with caffeine are restricted.

Broad-spectrum antibiotic (cephalosporins) are generally indicated for 5-10 days for patients with open injuries. The parenteral or oral route, and the duration of antibiotic treatment depend upon the patient's clinical situation. For vessel repair in open injuries, antibiotic administration is considered therapeutic and the duration of administration can be somewhat longer.

Sharp lacerations of vessels usually require minimal anticoagulant therapy. In contrast, high energy crush or avulsion-type injuries with extensive vessel damage depend upon adequate anticoagulant therapy for better patency. Among the agents commonly used are heparin, aspirin and low molecular weight dextran (Dextran 40) [69]. Usually, heparin is administered intraoperatively from the time that the initial anastomosis is performed until the dressing is applied. A dose of 2500-5000 units of heparin is given immediately after removal of the clamp per anastomosed artery. The role of heparin has diminished over the years, as it has become dear that patency is more a factor of suturing on healthy tissue and without tension. The use of heparin postoperatively is also avoided because of potential excess bleeding.

Several methods of monitoring after microvascular surgery have developed over time. Regardless of the method used, the most valuable and essential tool is regular clinical evaluation by the surgeon and nurses. Clinical evaluation should include colour, capillary refill, temperature and turgor. Clinical evaluation should be performed continuously for the first 3 days postoperatively. Skin temperature monitoring probes have been found the simplest and most reliable adjunct to clinical evaluation. Continuous temperature monitoring is now widely used to assess temperature changes in replanted digits and vascularized free flaps. This method, which assesses the changes in relative and absolute temperature, requires three probes, one each being placed on the revascularized area, the normal adjacent area and the dressing. If the temperature of the revascularized area drops below 30°C or differs by more than 3°C from the adjacent normal tissue, then vascular compromise is likely present.

## Complications

### *Acute Complications*

Inadequate perfusion is responsible for acute complications. When signs of inadequate perfusion are present, postoperative efforts must be intensified to improve the chances of survival. In difficult replantations, heparin may be beneficial. If a catheter is present, a regional sympathetic block may help alleviate vasospasm. Decreased skin temperature, loss of capillary refill, diminished turgor and or abnormal colour in the immediate postoperative period indicate that the replanted digit is in jeopardy. Following most micro vascular procedures used in replantation, the rule of thumb is that when the part or area has developed pallor and loss of turgor (e.g. the area is pale with loss of capillary refill), then arterial insufficiency is present. In contrast, when the area is cyanotic, congested and turgid, then venous insufficiency is present. If the problem is minor, it sometimes can be managed without having to re-operate. Otherwise the anastomosis site needs to be evaluated surgically, to determine if there is thrombosis formation at the anastomosis site, which may require the vascular anastomosis to be redone or even the insertion of a vein graft. Venous congestion can be effectively relieved with the use of medicinal leeches.

### *Late and Chronic Complications*

Although late complications due to infection are fairly frequent in digital replantations, they rarely result in the loss of the replanted part. Pin tract infections are the most common and occur about 4 weeks after surgery. They can be managed by pin removal and administration of antibiotics.

The most common chronic complications include cold intolerance, tendon adhesions and malunion.

- Cold intolerance is a common complaint in patients with digital replantation. It is related to the adequacy of digital reperfusion, and provides an argument for maximizing the number of arteries repaired. Cold intolerance improves over time.
- Tendon adhesions are frequent, resulting in

limited motion. In severe cases, tenolysis or a two-staged tendon reconstruction can be performed after a few months.

### *Management of Venous Congestion with Leeches*

Venous congestion is a frequent and significant problem of various microsurgical procedures, including revascularization and replantation, as well as free skin flaps. Venous congestion can be the result of various factors including an inadequate anastomosis of a vein, an effect secondary to arterial insufficiency, venous spasm, venous occlusion and the absence of venous repair. It has been generally recognized that venous congestion and engorgement can potentially lead to necrosis of the replanted part or flap. In fact, clinical experience indicates that necrosis, particularly in flaps, is more frequently associated with venous congestion than arterial insufficiency. The major therapeutic effect of the leech is the relief of venous congestion. Recent recognition of the clinical efficacy of leech, in this regard, has produced a continuous increase in its use [2, 15-17,23,43,49,52,58]. Overall, venous insufficiency is the most important indication for leeching.

A state of venous insufficiency can be recognized by the bluish colour of the tissue, as well as by tissue tension and oedema. In our experience, the leech was effective in the treatment of venous congestion in skin flaps and trauma, in the treatment of venous insufficiency following replantation of digits and hands, and in distal phalanx replantation without venous drainage due to the absence of adequate veins for anastomosis. The effectiveness of leech therapy becomes particularly apparent in view of the extremely rapid in colour of an engorged flap following the application of the leech (Fig. 14.3.6). Relief is accomplished both immediately with the decongestion that is produced with the leech is attached, and afterwards due to the continued flow of blood from the site of attachment. Bleeding can continue from the wound for a long as 24-48 h. Ultimately, the venous decongestion produced by leeching acts to prevent any potential arterial occlusion. 'The earlier that the diagnosis of venous congestion is made, the better the result.

Although medicinal leeches appear to be an ef-



*Fig. 6a-c Vascularized tensor fascia lata flap was used to cover a large pelvic defect in a young male patient, a Postoperative view showing that the flap is extremely cyanotic, oedematous, indicative of venous congestion secondary to insufficient venous drainage, b Rapid improvement of the appearance of the flap was noted after the application of leeches, c The flap was successfully salvaged over its entire surface.*

fective method for treating venous insufficiency following certain microsurgical procedures, it should be noted that alternative methods are also available to the surgeon. These include revision of the venous anastomoses, as well as wound decompression by incisions in patients who have undergone revascularization/replantation or by removal of the stitches in free flaps, and by maintaining egress by stimulating the flow of blood with the aid of heparinized gauzes to wipe the area.

The most significant contraindication to leeching is arterial insufficiency. It should be noted that in cases of arterial insufficiency the leech does not attach. Due to the relative increased risk of bacterial infection, immunosuppressed patients are also not considered appropriate candidates for leech therapy [66]. Thus, patients who are in an immunodeficient state, either primary or secondary to immunosuppressive drug therapy, should have venous congestion treated with an alternative method.

The application of leeches can potentially result in a significant loss of blood. The amount of blood lost is dependent upon the number of leeches applied and the duration of their use. However, the continuous oozing of blood from the site of attachment makes it difficult to precisely measure the total amount of blood loss due to the leech. In general, although each leech consumes only about 5-15 ml, from the subsequent oozing from the leech bite, each leech induces about 50 ml blood loss. In this regard, it is essential to closely monitor the vital signs of the patient, as well as perform frequent blood and laboratory tests, since any drop has detrimental effects not only for the patient, but also for the survival of the free flap and reattached part. Hence, the use of leeches can result in a significant loss of blood which is directly dependent upon the number of leeches applied and the duration of their use [13, 52, 55].

The use of medicinal leeches can have various complications [66]. These include persistent bleeding, anaphylaxis and local allergic reactions to biologically active substances within the leech's saliva, the transmission of viral-borne infections and excessive scarring from the leech bites. In our own experience, we have noted no significant complications that could be associated with leech therapy [52,55].

Although the risk of infection is always there, in our experience the use of leeches has not been associated with infection in any patients. Studies indicate that *Aeromonas hydrophila* is a predominant leech enteric organism that is responsible for digestion [67], and that there is always the concern for infection [34,48]. However, it should be

noted that leeches have been increasingly used without report of infection problems. According to some reports, the incidence of infection ranged from 0% to 20% [40]. We have found that when patients are treated with a combination of aminoglycosides and third-generation cephalosporin antibiotics for prophylaxis infections can be effectively avoided. Another factor that may contribute to the lack of infection is the use of each leech only once [52, 55]. Furthermore, the continuous bleeding following the application of the leech may act to rinse the wound and, thus, play a role in limiting infection.

Overall, leeches have been found to be effective in the treatment of venous congestion following microsurgical procedures such as replantations and free skin flaps. Since venous engorgement is a frequent cause of necrosis, the efficacy of leech therapy is of clinical significance where their application can avoid expected partial or complete loss of Ae replanted part or flap. The usefulness of the leech appears to be related to not only the immediate removal of congested venous blood, but also to the continuous flow of blood which ensues, as well as the local state of anticoagulation produced by the antithrombotic agent hirudin.

### **Open Fractures - Type IIIb and IIIc**

Open type IIIb and especially type IIIc fractures of the upper and lower extremities are extremely severe injuries that can often lead to amputation of a limb. These types of fractures are usually caused by high energy impact, resulting in extensive bony comminution or segmental bone loss, as well as severe soft tissue injury including extensive skin loss, tendon and nerve damage, muscular and periosteal stripping from the bone, and severe circulatory compromise secondary to heavy trauma of the major vessels. The gravity of this fracture is emphasized by the high rate of amputation, which has been reported to occur from 60% up to 100% [44,68]. Today, efforts are no longer aimed at simply salvaging the limb that has sustained a serious compound injury, but rather at producing a functional extremity free of pain which has, at the very least, protective sensation.

The functional outcome and success of preserving a limb following the treatment of these severe open fractures depends on several variables. These include the extent and severity of vascular injury, the extent of bony and soft tissue injury, the duration and type of ischaemia to the limb, the patient's age, time since the initial injury and finally any concomitant organ injuries which may be present [20,21].

Microsurgical techniques with the use of vein grafts are able to restore arterial blood flow in the injured limbs and, thus, contribute to salvaging the limb. On the other hand, microsurgical methods, such as free flaps, vascularized bone grafts and nerve grafting, utilized in the secondary reconstructive procedures have helped tremendously in achieving better results and in improving the functional outcome of the severely injured extremity, as well as diminishing the need for secondary amputation. Thus, microsurgery plays a decisive role in augmenting the treatment of open type IIIb and IIIc fractures by: (1) restoring the circulation of the injured extremity; and (2) improving the function of the limb using free tissue transfers such as nerve grafts, free skin flaps and vascularized bone grafts [60].

The treatment for patients with types IIIb and IIIc open fractures is an extremely demanding procedure that requires a highly specialized medical team and a hospital centre with outstanding emergency and surgical facilities. Even with today's sophisticated scoring systems for evaluating the extent of injury, it still is difficult for the surgeon to determine which limb to preserve and which to amputate [26]. Mangled extremity syndrome and the mangled extremity severity scores are scoring systems designed to aid in the decision-making process by predicting the viability and salvageability of the mangled limb part [19, 22,60].

For open fractures of the lower extremity, the combination of damage to both posterior and anterior tibial arteries and popliteal arteries at the trifurcation level that is often seen in open tibial fractures bears the worst prognosis [28]. In our own experience, none of our patients with open type IIIb injuries have undergone amputation [60]. This must be attributed, at least in part, to the use of

microsurgical techniques which permit better restoration of arterial damage, and to the fact that most of our cases involved isolated arterial injuries, which are known to have a better prognosis [39]. The use of vein grafts is a time-consuming procedure, as it doubles the surgical time for vascular anastomosis. However, vein grafting does offer the benefit of doing the vessel anastomoses without tension and on healthy intima.

Microsurgical techniques and the use of vein grafts to restore arterial blood flow in the injured extremities are also related to the relatively high rate of limb salvage in patients with type HIC injuries. Microsurgical skills applied in secondary reconstructive procedures such as free flaps, vascularized bone grafts and nerve grafting help achieve better results and to improve the functional outcome of the severely injured extremity. Microsurgery aids the treatment of these injuries by improving the circulation of the injured extremity using fine surgical techniques, restoring limb function, and solving other complex problems such as replacing unstable scar tissue with free skin flaps.

### **Vascular Complication in Orthopaedic Patients**

Damage to major arterial structures during various orthopaedic procedures related to both trauma and reconstruction is well-known and has been documented extensively in the orthopaedic literature [4, 12, 14, 37, 45, 46, 60]. Injuries to the major vessels may be of several types, involving either partial or complete interruption of normal blood flow. They can be the product of continuous pressure resulting in thrombosis or false aneurysm [3] or the result of acute complete or partial laceration from a sharp instrument, such as a surgical scalpel, resulting in massive bleeding [14, 46]. These are very serious intraoperative vascular injuries that may not only jeopardize the viability of a limb, but even the life of the patient. In all cases, further injury is related to some extent to varying degrees of ischaemia and local bleeding.

The orthopaedic surgeon should be aware of potential complications inherent to the procedure

that they are performing. This along with solid knowledge of the anatomy of the area is the best preventive factor. In the face of these serious complications, however, the orthopaedic surgeon must have the skills to recognize and manage the emergency promptly. If there is any doubt concerning the extent of the arterial complication, a thorough clinical examination of the viability of the limb should be performed without hesitating to use objective testing controls, such as the Doppler ultrasound or contrast media for intraoperative arteriography. No matter what the severity of the complication, if it is treated promptly and correctly, the devastating potential for limb or nit loss can be successfully avoided.

There are various vulnerable anatomical sites susceptible to vascular complications during orthopaedic procedures [60]. Among these include major vessels, for example the femoral artery or popliteal artery which are susceptible to injury during reconstructive surgical procedures, such as total arthroplasties or osteotomies of the hip and knee, respectively. Surgical management of pseudoarthrosis or heterotopic ossification around the hip, knee or elbow joint is also associated with a high risk of vascular injury.

Prior to the development of microsurgery, vascular surgeons were usually called upon to take over and manage these very serious intraoperative complications by repairing the damaged vessel either by end-to-end anastomosis or interposition of a vein graft. Today, these serious vascular complications during orthopaedic procedures can be met with a successful outcome when there is immediate recognition of the complication, and when there is an orthopaedic surgeon present who is well-trained in microsurgical techniques who is able to immediately manage the emergency. The presence of a vascular surgeon or an orthopaedic surgeon trained in microvascular technique represents an invaluable attribute to the orthopaedic team, and minimizes, if not eliminates, the potentially disastrous outcome from serious intraoperative vascular complications.

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**Swistel Daniel G.**

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# Management of Patients with Complex Hypertrophic Cardiomyopathy: Resection/Plication/Release

*Daniel G. Swistel, MD, Joseph J. DeRose, Jr., MD, and Mark V. Sherrid, MD†*

Left ventricular outflow tract narrowing or obstruction due to asymmetric septal hypertrophy can cause high intraventricular pressure and chamber hypertrophy with subsequent symptoms of sudden death or heart failure. Brock first described muscular hypertrophy of the left ventricular outflow tract in 1957.<sup>1</sup> The obstruction was felt to be analogous to right ventricular infundibular narrowing and hence was labeled subaortic stenosis. The surgical relief of this problem was described as early as 1958 by Cleland<sup>2</sup> and evolved into the classic Morrow procedure after careful studies of the pathological substrate and resultant hemodynamic compromise.<sup>3</sup> Our understanding of the pathophysiology of this disorder, now known as hypertrophic cardiomyopathy (HCM), has progressed further and has led to the understanding that systolic anterior motion (SAM) of the mitral valve and certain abnormal anatomic variations of mitral valve structure are greatly involved in the generation of this outflow tract gradient.<sup>4</sup> In fact, the commonly performed resection of the muscle bar just under the aortic valve annulus is now understood to not only be of little use, but probably leads to an unnecessary incidence of iatrogenic ventricular septal defects. Briefly stated, the sur-

gical management of this disorder involves not only dealing with an area of septal hypertrophy deep within the ventricular cavity where mitral septal contact occurs, but also with altering the mitral valve apparatus in a way that minimizes the chances of that mitralseptal contact.

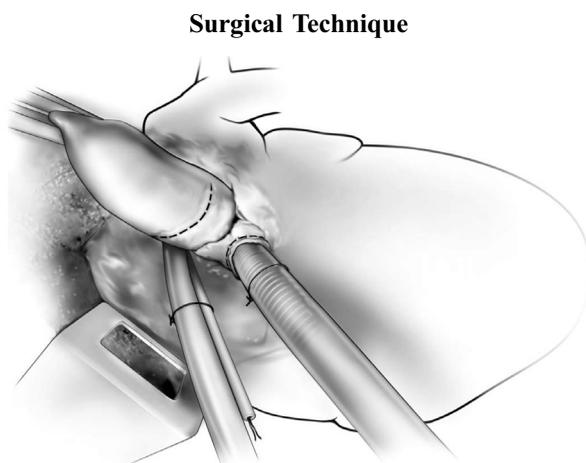
## Indications and Evaluation for Surgery

It is important to understand that the majority of HCM patients are not obstructed, but can still have symptoms and be at risk for sudden cardiac death.<sup>5-7</sup> Symptoms are due to LV diastolic dysfunction and myocardial ischemia in the absence of epicardial coronary narrowing. Surgery is not indicated in the absence of significant left ventricular outflow tract obstruction. Medical therapy frequently involves the use of Bblockers and calcium channel blockade. Disopyramide, a negative inotrope, can be used in cases with persistently high resting gradients. To prevent sudden cardiac death, implantable cardioverter-defibrillators are used aggressively.

Obstructed patients usually have more severe symptoms and a murmur that brings them to medi-

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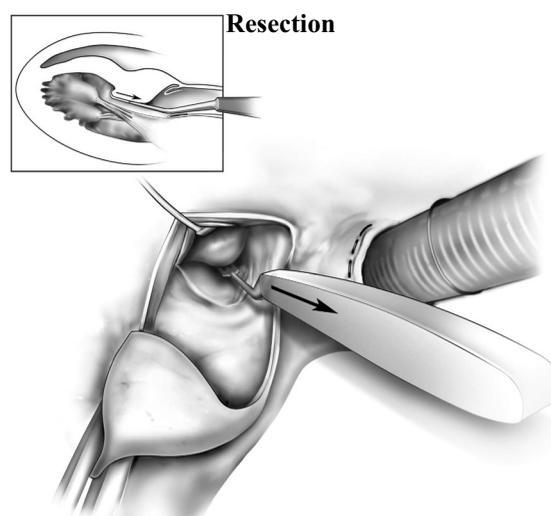
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**Figure 1** Exposure is obtained via a partial upper sternotomy through the third or fourth interspace on the right side. If coronary bypass grafting or mitral valve surgery through the left atrium is required or in reoperative cases, a standard median sternotomy is performed. Standard venous and aortic cannulas are used. A 28F vent cannula is introduced into the left ventricle at the right superior pulmonary vein-left atrial junction. This provides both excellent venting and a bloodless field during the subsequent myectomy stage of the procedure. A retrograde cardioplegia catheter is introduced into the coronary sinus and is used only if its position is confirmed by palpation or echocardiographic guidance. Alternatively, cardioplegia is subsequently delivered via handheld cannulas directed into the coronary ostia. After institution of cardiopulmonary bypass, the temperature is lowered to 32°C and a cross clamp is applied and a transverse aortotomy is performed. Traction sutures of 4-0 prolene are used to hold open the edges of the aorta, but no traction sutures are used on the aortic leaflets themselves.

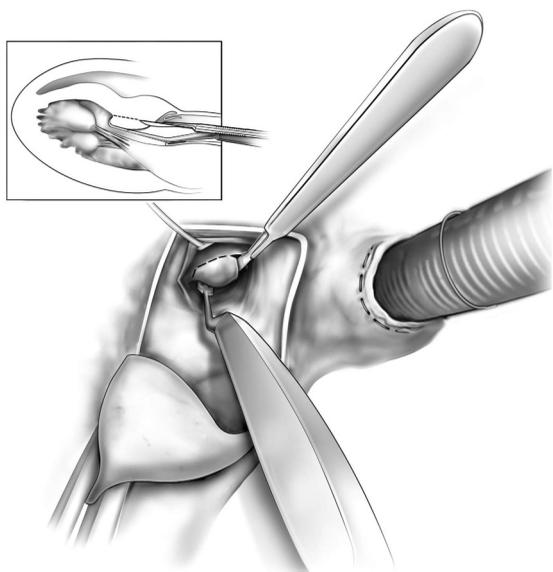
cal attention.<sup>8</sup> Again, the overwhelming majority of these patients at our institution are treated medically under the care of cardiologists specializing in the care of HCM. Diligent analysis is necessary to identify the presence of moderate or severe mitral insufficiency, and consistent monitoring is necessary to identify symptoms of vasodilatation, hypotension, and heart failure.

Only those patients with symptoms refractory to medication and obstruction either at rest or with provocation are generally referred for surgery. This constitutes a little less than 10% of the total patients who present at our HCM clinic for care. The vast majority of these patients have had severe mitral regurgitation as one of their primary prob-



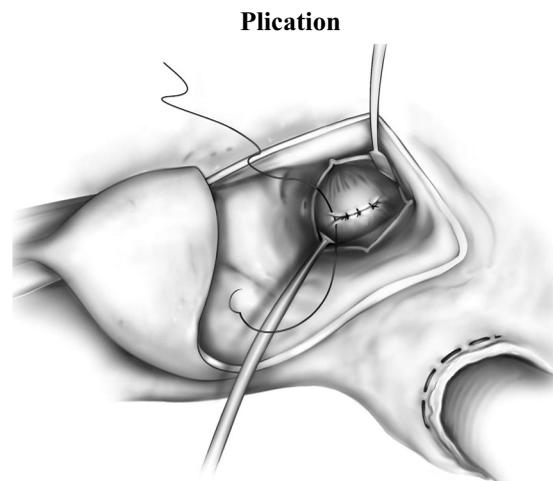
**Figure 2** The aortic leaflets are retracted by the assistant who stands on the patient's left, using two blunt, flat leaflet retractors. Often, at least one of these retractors is introduced into the left ventricular cavity itself to elevate this part of the septum. The trefoil hook is introduced into the ventricular cavity and care is taken not to tangle the hooks in the mitral valve apparatus, as both the leaflet and chords are frequently quite redundant. Elevation of the septum with the leaflet retractor aids in this process. The trefoil hook is engaged as deeply as possible into the septal muscle deep within the ventricular cavity between the right coronary ostia and the commissure of the left and right aortic leaflets. The hook must engage the septal muscle at or beyond the point of mitral-septal contact. This distance was previously calculated from the preoperative transesophageal echo. With outward and posterior traction, the septal bulge is accentuated.

lems. At initial evaluation for possible surgical intervention, the preoperative echocardiogram is carefully analyzed to calculate the thickness of the myocardium in general, the specific thickness of the septum, both anteriorly and posteriorly, the exact distance of the area of mitral-septal contact from the aortic annulus, and the morphology of the leaflets of the mitral valve. A judgment is made regarding the pathology, whether septal hypertrophy and an outflow tract gradient, a floppy, redundant mitral leaflet with valvular insufficiency, or a combination of both, is primarily responsible for the symptoms. If the septum is less than 1.8 or 2.0 cm, then septal resection can still be considered, albeit to a somewhat limited extent, and careful consideration of the mitral leaflet pathology will



**Figure 3** A standard long handled #15 blade is used. While maintaining traction on the engaged portion of septum, as large a segment as possible is excised. It is difficult to excise a portion much more than 1.0 to 1.5 cm in thickness, so if the predetermined septum is around 3.0 cm, there is no danger of creating a ventricular septal defect. The trefoil hook serves two purposes. First, it defines, in the anterior-posterior direction, the point toward which the #15 scalpel blade is pushed, and second, it stabilizes the muscle to be resected and prevents it from being pushed out and away from the blade and surgeon. If the septum is less than 1.5 cm, then care must be taken to resect a thinner portion. This is easily accomplished. It is important to remove the right amount of thickness in the first attempt. Secondary resections are difficult because the muscle tissue tends to shred and the surface becomes irregular. Once the deepest resection is completed, additional segments are resected toward the base of the papillary muscle and outwards in the direction of the aortic annulus, being careful not to resect any muscle closer than 3 to 5 mm from the annulus. This area is not involved in the pathogenesis of SAM and spares the AV node and avoids postoperative heart block.

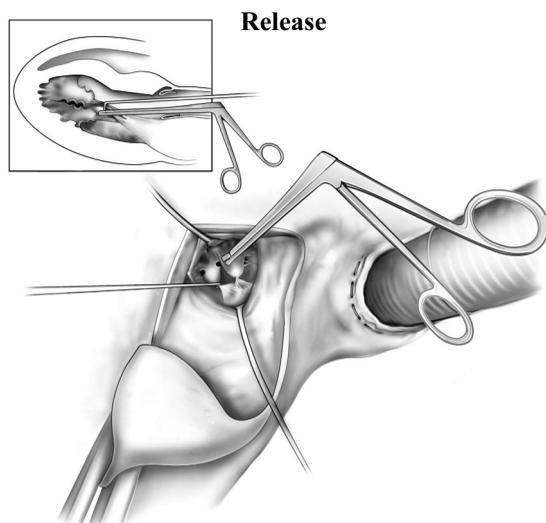
be required. In these situations, it is all the more important not to resect any muscle bar just under the aortic annulus because the septum here is usually quite thin and the risk of creating a ventricular septal defect and aortic insufficiency is high. When the ventricular chambers are collapsed, the weight of the right ventricle pushes on the septum and a septal bulge is easily mistaken to exist just beyond



**Figure 4** In selected patients with large floppy valves, we plicate the anterior mitral leaflet. In general, patients are at risk for a suboptimal hemodynamic result due to residual SAM because of increased mobility, size or length of the anterior mitral leaflet. Visualization is easiest from the left side of the operating table. The leaflet retractors are repositioned to facilitate exposure of the anterior mitral leaflet. Three or usually four sutures of 5-0 prolene are used in a vertical mattress technique to shorten the leaflet. The amount of shortening is dependent on the degree of leaflet elongation. In some instances, with extremely floppy valves, as much as 4.0 mm have been shortened with these mattress sutures. It is not uncommon to identify small jets of mitral insufficiency during evaluation of the immediate postbypass transesophageal echo. This is felt to be a result of the needle holes left by the plication stitches. This has never persisted, in our experience, once the heparin is reversed with protamine.

the aortic annulus. We have found circumferential narrowing of the outflow tract in this area to be extremely rare and not, in general, involved in the pathophysiology of HCM. By avoiding this area for resection, the AV node is preserved and the patient is spared subsequent heart block.

Occasionally, a patient will have SAM, mitral septal contact, and a high gradient without severe hypertrophy. Malposition and enlargement of the valve are implicated and papillary muscle mobilization<sup>9</sup> will displace the valve posteriorly and anterior leaflet plication<sup>10,11</sup> will shorten the excursion of that leaflet into the outflow tract. These processes will become critical to abolish the outflow tract gradient and mitral regurgitation. Using the methodology described herein and using the tre-



**Figure 5** It is necessary to sever the abnormal connections that bind the papillary muscles to the anterior wall. The mitral valve then assumes its more normal posterior position, out of the outflow tract. After the septum is resected, it becomes much easier to visualize structures within the ventricular cavity. The leaflet retractors are pushed deeper into the ventricular cavity and the anterior papillary muscle is gently grasped with a long broad toothed forceps and pushed medially. The abnormal attachments are divided with either a knife or scissors. A nerve hook can also be used to retract the papillary muscle if it is too thick to grasp. Alternatively, we have used a long papillary rongeur to divide these attachments and also thin out the papillary muscles, which are so thick in these patients that with a medium sized device, it is unlikely one can resect too much.

foil hook, we proceed with resection of a septal bulge in the area of mitral-septal contact even if the septum in this area is as little as 1.5 cm thick. Resection of 0.5 cm of thickness in this area along with the mitral valve manipulations has resolved these individuals' hemodynamic problems.

Mitral valve replacement is rarely needed, but is necessary if structural abnormalities are identified during the preoperative echo. A central or anteriorly directed mitral regurgitation jet is a clue to the presence of structural mitral abnormalities. If prolapse is identified, the valve is repaired if possible. If calcification with severe immobility is identified, then no amount of septal resection and papillary muscle mobilization will cure the mitral insufficiency, and mitral valve replacement is performed.

## Comments

Durable long-term results can be achieved with an aggressive approach to mitral valve pathology in addition to myectomy for patients with complex HCM disease. We have utilized this three-part approach (extended myectomy resection, anterior mitral leaflet plication, and papillary muscle release) in the management of our patients with complex obstructive pathology. Over the last six years, sixteen patients have undergone this repair. Their mean preoperative left ventricular outflow tract obstruction (LVOTO) was  $137 \pm 45$  mm Hg and their degree of mitral regurgitation (MR) was  $3.1 \pm 0.8$ , with all patients exhibiting SAM. Initial postoperative TEE demonstrated marked reduction in LVOTO to  $10 \pm 17$  mm Hg ( $P < 0.0001$ ) and significant improvement in mitral valve regurgitation to  $0.2 \pm 0.4$  ( $P < 0.0001$ ). Mean follow-up was  $2.4 \pm 2.1$  years, at which time LVOT gradient remained low at  $6 \pm 14$ , and mitral regurgitation remained mild at  $0.4 \pm 0.5$  (both:  $P < 0.0001$ ). Follow-up was 100% and there were no deaths, reoperations, or any other adverse consequences. Others have suggested mitral valve replacement for those patients with complex HCM pathology usually defined as mitral valve regurgitation.<sup>12</sup> But these patients are usually young and would require a mechanical prosthesis and the need for life-long anti-coagulant therapy. McIntosh has described his technique for mitral valve plication consisting of sutures placed in an anterior-posterior (AP) orientation.<sup>10</sup> This approach seems contrary to our understanding of the floppy leaflet, which is too long in the AP dimension. By placing the plication sutures in a medial-lateral orientation, the leaflet is not only shortened, but also stiffened enough to limit its excursion into the outflow tract. This approach is analogous to the triangular segment resection sometimes performed during mitral valve repairs from the left atrial side. By plicating the leaflet as described herein, a counter incision in the left atrium is unnecessary, and this becomes a much simpler procedure and provides a more reproducible result. Others have advocated approaching the entire procedure from the left atrium for this reason. As difficult as it is to resect the area of mitral-sep-

tal contact from the trans-aortic incision, it is much more problematic trying to identify the proper area for resection from in between the chords and papillary muscles of the mitral apparatus.

Our resection, plication, and release methodology is easy to learn, comparatively simple to perform and has provided excellent, durable results.

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# Αλληλεπιδράσεις Φαρμάκων

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## Abstract

Increased medication use by people can lead to significant interactions, where the pharmacological effect of a drug can be altered under the co-administration of another drug, plant remedy and even food.

These interactions result to a cumulative or antagonistic effect and to an increase or decrease of the activity of the medications and a potential change in the therapeutic target.

Clinical implications in fact are to be concerned about, only in case of narrow therapeutic index drugs, such as theophylline, lithium, anticoagulants.

## Περίληψη

Σήμερα η αυξημένη διάθεση φαρμακευτικών προϊόντων και η πολυφαρμακία μπορεί να οδηγήσουν σε σημαντικές και επικίνδυνες αλληλεπιδράσεις φαρμάκων.

Αλληλεπιδράσεις παρατηρούνται όταν οι δράσεις ενός φαρμάκου μεταβάλλονται από την συγχρόνηση κάποιου άλλου φαρμάκου ή εναλλακτικού φυτικού προϊόντος ή ακόμα και τροφών.

Το τελικό αποτέλεσμα μπορεί να είναι αθροιστικό δηλαδή αύξηση της δράσης ενός ή περισσότερων φαρμάκων ή ανταγωνιστικό δηλαδή ελάττωση της δράσης ενός ή περισσότερων φαρμάκων.

Φάρμακα με στενό θεραπευτικό πλάτος όπως θεοφυλίνη, λίθιο, διγοξίνη, αντιπηκτικά, αντιεπιληπτικά μπορούν να εμφανίσουν ιδιαίτερα κλινικά προβλήματα.

## Επηδημιολογία φαρμακευτικών αλληλεπιδράσεων

Σε συγχορήγηση φαρμάκων μπορούν να συμβούν αλληλεπιδράσεις μεταξύ τους, οι οποίες οδηγούν σε μεταβολές της δραστηριότητας και κατά περίπτωση και του θεραπευτικού αποτελέσματος.

Σε κλινικά δεδομένα από το Πανεπιστήμιο Harvard το 20% των εισαγωγών στα θεραπευτικά ιδρύματα σχετίζεται με ανεπιθύμητες δράσεις φαρμάκων και προσαγωγή ασθενών σε μονάδα επείγοντων οφείλεται κατά 3,8% σε αλληλεπιδράσεις φαρμάκων. Στις ΗΠΑ σε διάστημα 8 ετών εντοπίστηκαν 2341 αλληλεπιδράσεις φαρμάκων που σχετίζονται με θάνατους. Θάνατοι από αλληλεπιδράσεις παρατηρούνται σε άτομα ηλικίας άνω των 55 ετών. Ο κίνδυνος ήταν μεγαλύτερος με την πάροδο της ηλικίας (75 ετών και άνω) λόγω διαταραχής των ομοιοστατικών μηχανισμών. Οι θάνατοι ήταν σε υψηλότερο ποσοστό στους άνδρες σε σχέση με τις γυναίκες.<sup>1</sup>

Ασθενείς με ηπατική και νεφρική νόσο ή ασθενείς με μακροχρόνια αγωγή φαρμάκων, ασθενείς με HIV, διαβητικοί, επιληπτικοί, ασθενείς εντατι-

κής μονάδας, μεταμοσχευμένοι ή που πρόκειται να υποστούν σοβαρές χειρουργικές επεμβάσεις και λαμβάνουν άνω του ενός φαρμάκου είναι υψηλού κινδύνου για την ανάπτυξη ανεπιθύμητων ενεργειών από αλληλεπιδράσεις.<sup>2,3</sup>

## Φαρμακοκινητικές και φαρμακοδυναμικές αλληλεπιδράσεις

Μετά την απορρόφηση τα φάρμακα και οι μεταβολίτες τους συνδέονται με υψηλή συγγένεια με τις πρωτεΐνες του αίματος και των ιστών και κατανομονται στους ιστούς συμπεριλαμβανόμενου και του οργάνου στόχου.<sup>4</sup>

Η σύνδεση των φαρμάκων (D) με τις πρωτεΐνες (P) του αίματος και των ιστών είναι μη ειδική και ανατάξιμη.



Ολική συγκέντρωση του φαρμάκου στο πλάσμα  $[D_t] = [D_f] + [DP]$

Το σύμπλοκο [DP] παριστά τη συγκέντρωση του συνδεδεμένου φαρμάκου ενώ το [D<sub>f</sub>], το ελεύθερο που είναι φαρμακολογικά δραστικό και δύναται να κατανεμηθεί, να μεταβολισθεί, να δράσει στο όργανο στόχο και να αποβληθεί.<sup>5</sup>

Το συνδεδεμένο φάρμακο έχει ρόλο σιωπηλής αποθήκης και είναι ανενεργό. Η πρωτεϊνική σύνδεση των φαρμάκων (υποδοχείς, πρωτεΐνες φορείς, ένζυμα) είναι σημαντική παράμετρος σχετικά με τον καθορισμό των φαρμακοκινητικών και φαρμακοδυναμικών ιδιοτήτων τους και ευθύνεται για την εμφάνιση αλληλεπιδράσεων.

Η αλβουμίνη είναι η κύρια πρωτεΐνη στην οποία συνδέονται κυρίως όξινα φάρμακα, όπως η βαρφαρίνη και τα μη στεροειδή αντιφλεγμονώδη.<sup>6</sup>

Αντίθετα τα αλκαλικά φάρμακα όπως τα τρικυκλικά αντικαταθλιπτικά, η λιδοκαΐνη, η δισοπραμίδη και η προπρανολόλη συνδέονται με την α1-όξινη γλυκοπρωτεΐνη.

Η α1-όξινη γλυκοπρωτεΐνη και διάφορες λιποπρωτεΐνες συνδέονται με αλκαλικής αντίδρασης ουσίες (pKa < 7,5). Η α1-όξινη γλυκοπρωτεΐνη είναι πρωτεΐνη οξείας φάσης και αυξάνεται σε εμφραγμα του μυοκαρδίου, νεοπλάσματα, ρευμα-

### Συχνές φαρμακευτικές αλληλεπιδράσεις

<b>Αντιβιοτικά</b>	<b>Φάρμακα καρδιαγγειακού</b>
Σιπροφλοξασίνη	Αμιοδαρόνη
Κλαριθρομυκίνη	Δελτιαζέμη
Ερυθρομυκίνη	Κινιδίνη
Μετρονιδαζόλη	Βεραπαμίλη
<b>Αντικαταθλιπτικά</b>	<b>Φάρμακα γαστρεντερικού</b>
Δουλοξετίνη	Σιμετιδίνη
Φλουοξετίνη	Εσομεπραζόλη
Φλουβοξαμίνη	Ομεπραζόλη
Νεφαζοδόνη	
Παροξετίνη	
Σερταλίνη	
<b>Αντιμυκητιασικά</b>	<b>Διάφορα</b>
Φλουκοναζόλη	Απρεπιτάνη
Ιτρακοναζόλη	Βουπροπιόνη
Κετοκοναζόλη	Δισουλφιράμη
Μικοναζόλη	Χυμός grape fruit
Βορικοναζόλη	Ιματινίβη
	Βαλπροϊκό νάτριο

τοιδή αρθρίτιδα. Ειδικά όσον αφορά την φαρμακευτική αγωγή νεοπλασμάτων τα αντικαρκινικά φάρμακα είναι συνήθως αλκαλικά με υψηλή σύνδεση με την α1-όξινη γλυκοπρωτεΐνη. Με την πάροδο όμως της αγωγής η συγκέντρωση της α1-όξινης γλυκοπρωτεΐνης ελαττούται και μεγαλύτερο ποσοστό ελεύθερου κλάσματος αποδίδεται στην κυκλοφορία με πιθανή τοξική δράση και είναι πιο πρόσφορο για αλληλεπιδράσεις με τα ισοένζυμα του P450 του ήπατος και του γαστρεντερικού σωλήνα.<sup>7,8</sup>

Κατά την φάση της κατανομής μπορεί να παρατηρηθούν αλληλεπιδράσεις φαρμάκων ως αποτέλεσμα εκτόπισης ενός φαρμάκου από τη θέση σύνδεσής του με τις πρωτεΐνες από κάποιο άλλο με μεγαλύτερη συγγένεια ως προς την θέση σύνδεσης με αποτέλεσμα να αυξάνεται το ελεύθερο φαρμακολογικά δραστικό κλάσμα του εκτοπισμένου φαρμάκου και αν πρόκειται για φάρμακο με στενό θεραπευτικό πλάτος να παρατηρείται τοξικότητα. Δηλαδή οι διεργασίες σύνδεσης και εκτόπισης των φαρμάκων παριστούν μηχανισμούς φαρμακοκινητικών και φαρμακοδυναμικών αλληλεπιδράσεων. Φαρμακοδυναμικές αλληλεπιδράσεις παρατηρούνται όταν οι δράσεις ενός φαρμάκου για κάποιο στόχο μεταβάλλονται από την παρουσία κάποιου άλλου φαρμάκου με δράση στον ίδιο στόχο.<sup>5,9</sup>

#### Ανταγωνιστικές αλληλεπιδράσεις

Ένα βρογχοδιασταλτικό-αγωνιστής των β2 αδρενεργικών υποδοχέων όπως η σαλβουταμόλη δρα ανταγωνιστικά με τους ανταγωνιστές των β-αδρενεργικών υποδοχέων.

Ειδικοί ανταγωνιστές χρησιμοποιούνται για να αναστρέψουν τη δράση κάποιου φαρμάκου στον υποδοχέα όπως η ναλοξόνη για τα οπιοειδή και η φλουμαζενίλη για τις βενζοδιαζεπίνες.<sup>10,11,12</sup>

Κλινικά οι περισσότεροι σημαντικές αλληλεπιδράσεις φαρμάκων παρατηρούνται στη φάση μεταβολισμού. Ο μεταβολισμός αναφέρεται στις διεργασίες κατά τις οποίες ένα φάρμακο ή άλλες ουσίες μεταβάλλονται βιοχημικά ώστε να επιτραπεί η διάσπασή και η απομάκρυνση τους από τον οργανισμό. Το κύριο όργανο μεταβολισμού είναι το ήπαρ αλλά συμμετέχουν και άλλα όργανα όπως ο γαστρεντερικός σωλήνας, οι νεφροί το δέρμα

και ο πλακούντας. Ο μεταβολισμός των φαρμάκων στο ήπαρ υπόκειται σε δύο φάσεις, αντιδράσεις φάσης I όπως οξείδωση, υδρόλυση, και αναγωγή και φάσης II που κυρίως πρόκειται για συζεύξεις του φαρμάκου με άλλες ουσίες όπως γλυκουρονικό καιθειικό οξύ. Στον μεταβολισμό της φάσης I συμμετέχει κυρίως το κυτόχρωμα P450 (CYP 450). Το ήπαρ είναι το κυριότερο όργανο όπου λαμβάνει χώρα μεταβολισμός μέσω κυτοχρώματος P450 αλλά και τα επιθηλιακά κύτταρα του λεπτού εντέρου είναι επίσης σημαντικά.<sup>13</sup>

Το σύστημα του CYP 450 περιλαμβάνει 57 ισοένζυμα. Υπάρχουν πολλές διαφορετικές μορφές αυτών των ενζύμων. Κάθε ισοένζυμο του κυτοχρώματος P450 μεταβολίζει μια ομάδα ουσιών. Τα γονίδια που κωδικοποιούν τα ισοένζυμα του κυτοχρώματος 450 μπορεί να διαφέρουν μεταξύ των ατόμων αλλά και μεταξύ εθνοτήτων. Οι διαφοροποιήσεις αυτές (πολυμορφισμός) δύνανται να επηρεάσουν τον μεταβολισμό πολλών φαρμάκων.<sup>14,15</sup>

Οι περισσότερες λοιμώξεις εντοπίζονται στον εξωκυττάριο χώρο στα διάφορα όργανα ή συστήματα και η επιτυχία της αντιμικροβιακής αγωγής εξαρτάται από τη συγκέντρωση του χορηγούμενου φαρμάκου στο όργανο στόχο. Σειρά μελετών έδειξε παρόμοια ευρήματα όσον αφορά τη συγκέντρωση του φαρμάκου στον εξωκυττάριο χώρο με το πλάσμα. Επιπλέον μελετήθηκαν οι αλληλεπιδράσεις φαρμάκων του τύπου της εκτόπισης πχ αντιμικροβιακά εκτοπιζόμενα από μη στεροειδή αντιφλεγμονώδη, λιδοκαΐνη από προπρανολόλη υπό την αλβουμίνη σε φυσιολογικές καταστάσεις και σε νόσους. Πιθανόν τα προβλήματα που απαντούν in vivo να αποδίδονται στην παρουσία ενδογενών ουσιών που λειτουργούν ως ανταγωνιστές στις θέσεις σύνδεσης της αλβουμίνης.<sup>16,17</sup>

#### Αλληλεπιδράσεις φαρμάκων και τροφών

Έχει πλέον γίνει σαφές ότι οι τροφές μπορεί να επιδράσουν σημαντικά στην απορρόφηση των φαρμάκων λόγω δράσης στην απορρόφηση ή στην κινητικότητα του ΓΕΣ.

### Παραδείγματα αλληλεπιδράσεων λόγω ενζυμικής επαγωγής

Φάρμακο που υπόκειται σε επαγωγή	Επαγωγέας	Κλινικές παρατηρήσεις
Per os αντισυλληπτικά	Ριφαμπικίνη Ριφαμπουτίνη Μοδαφινίλη	Αποτυχία αντισυλληπτικών Απαιτείται επιπλέον αντισυλληπτική προστασία Απαιτείται αυξημένη δόση οιστρογόνων
Κυκλοσπορίνη	Φαινοτοΐνη Καρβαμαζεπίνη Υπερικό το διάτρητο*	Ελάττωση κυκλοσπορίνης κίνδυνος απόρριψης μοςχεύματος
Παρακεταμόλη	Χρόνιοι αλκοολικοί	Ηπατοτοξικότητα και σε μικρές δόσεις
Κορτικοστεροειδή	Φαινοτοΐνη Ριφαμπικίνη	Αυξημένος μεταβολισμός, κίνδυνος θεραπευτικής αποτυχίας

\* Βαλσαμόχορτο, σπαθόχορτο, St John wort

### Παραδείγματα αθροιστικών ή συνεργικών αλληλεπιδράσεων

Αλληλεπιδρώντα φάρμακα	Φαρμακολογική δράση
NSAIDs, βαρφαρίνη, κλοπιδογρέλη Αναστολείς μετατρεπτικού ενζύμου (ACEI), καλιοπροστατευτικά διουρητικά Βεραπαμίλη, β-ανδρενεργικοί ανταγωνιστές Νευροπληγικά και αμινογλυκοσίδες Αιθανόλη, βενζοδιαζεπίνες Πιμοζίδη, σοταλόλη Κλοζαπίνη, co-τριμεθοξαζόλη	Αυξημένος κίνδυνος αιμορραγίας Αυξημένος κίνδυνος υπερκαλιαιμίας Βραδυκαρδία και ασυστολία Αυξημένος νευρομυϊκός αποκλεισμός Αυξημένη καταστολή Παράταση QT Αυξημένος κίνδυνος καταστολής του μυελού των οστών

Ο χυμός grape fruit αναστέλλει το CYP3A4 στο έντερο και έχει μικρή δράση στο CYP3A4 του ήπατος. Αυτό αποδείχθηκε από το γεγονός ότι ο μεταβολισμός ενός φαρμάκου από το CYP3A4 όταν χορηγείται ενδοφλεβίως δεν επηρεάζεται από το ρόφημα ενώ επηρεάζεται με χορήγηση από του στόματος του ίδιου φαρμάκου.<sup>18,19</sup>

#### Αλληλεπιδράσεις φυτικών παρασκευασμάτων και φαρμάκων

Πολλά φυτικά παρασκευάσματα από την ημεδαπή και άλλες χώρες (π.χ. Κίνα) χρησιμοποιούνται καθημερινά. Το 24% των νοσοκομειακών ασθενών αναφέρει χρήση φυτικών ιαμάτων. Τα προϊόντα αυτά περιέχουν ουσίες που μπορεί να αλληλεπιδρούν με τα συμβατικά φάρμακα.<sup>20</sup>

Αναφέρονται κλινικές περιπτώσεις σοβαρής τοξικότητας από φυτικά σκευάσματα παρά την επικρατούσα αντίληψη ότι είναι αθώα και αβλαβή.<sup>21-24</sup>

Πολλά φυτικά παρασκευάσματα περιέχουν αντιπηκτικές ουσίες και αυξάνεται η αιμορραγική τάση της ασπιρίνης ή της βαρφαρίνης σε περίπτωση συγχορήγησης. Φυτικά εκχυλίσματα που περιέχουν ουσίες όμοιες των κουμαρινικών είναι Alfalfa (*Medicago sativa*), Αγγελική (*Angelica archangelica*), Dong Quai (*Angelica polymorpha*, *A. dahurica*, *A. atropurpurea*), χαμομήλι, ιππουρίδα, κόκκινο τριφύλλι (*red clover-Trifolium Pratense*) που εν δυνάμει μπορεί να αλληλεπιδρούν με την βαρφαρίνη. Φυτικά προϊόντα με αντιαμοπεταλιακή δράση είναι το μποράγκο (*Borago officinalis*) ή βρωμαλεΐνη (*Ananas comosus*) και κουρκουμάς (*turmeric*).<sup>25</sup>

Οι περισσότερες συζητημένες αλληλεπι-

δράσεις αφορούν το Υπερικό το διάτρητο (βαλσαμόχορτο, St John's wort) που χρησιμοποιείται στην Ευρώπη στη θεραπεία της κατάθλιψης.<sup>26,27</sup>

### Συμπεράσματα

Πάντα κατά την λήψη ιστορικού από τον άρρωστο πρέπει να συλλέγονται πληροφορίες και για την λήψη φυτικών προϊόντων ώστε να προλαμβάνονται κατά το δυνατόν θεραπευτικές αστοχίες.<sup>28</sup>

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# Statins Reduce Neurologic Injury in Asymptomatic Carotid Endarterectomy Patients

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**Background and Purpose**—Statins are neuroprotective in a variety of experimental models of cerebral injury. We sought to determine whether patients taking statins before asymptomatic carotid endarterectomy exhibit a lower incidence of neurological injury (clinical stroke and cognitive dysfunction).

**Methods**—A total of 328 patients with asymptomatic carotid stenosis scheduled for elective carotid endarterectomy consented to participate in this observational study of perioperative neurological injury.

**Results**—Patients taking statins had a lower incidence of clinical stroke (0.0% vs 3.1%;  $P=0.02$ ) and cognitive dysfunction (11.0% vs 20.2%;  $P=0.03$ ). In a multivariate regression model, statin use was significantly associated with decreased odds of cognitive dysfunction (odds ratio, 0.51 [95% CI, 0.27–0.96];  $P=0.04$ ).

**Conclusions**—Preoperative statin use was associated with less neurological injury after asymptomatic carotid endarterectomy. These observations suggest that it may be possible to further reduce the perioperative morbidity of carotid endarterectomy.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00597883 (*Stroke*. 2013;44:1150-1152.)

**Key Words:** carotid stenosis ■ cognitive dysfunction ■ statins ■ stroke

The introduction of statins has reduced the natural history risk of asymptomatic carotid artery stenosis to such a level that the benefit of carotid endarterectomy (CEA) for those with high-grade stenosis is almost of negligible benefit.<sup>1</sup> It remains unclear whether statins are actually neuroprotective in humans.

The Asymptomatic Carotid Surgery Trial suggested a reduction in the perioperative risk of stroke and death from 6% to 2% for those “on lipid-lowering agents.”<sup>2</sup> However, administrative data from Canada on 1252 asymptomatic CEAs failed to demonstrate a protective effect for statins.<sup>3</sup> The effect of statins on postoperative cognitive dysfunction has not been studied previously. The aim of this study was to determine whether statins are neuroprotective in a cohort of asymptomatic CEA patients by evaluating statin use and neurological injury, defined by both clinical stroke and significant cognitive dysfunction.

## Materials and Methods

### Patients

A total of 328 asymptomatic elective CEA patients with high-grade carotid artery stenosis were enrolled with written informed consent in this institutional review board-approved observational study. Two-hundred patients were taking statins at the time of surgery, and 124 were not. A reference group was used to account for trauma of

surgery, effects of general anesthesia, and practice effect associated with repeated neurocognitive testing, as described previously.<sup>4</sup> Patients were examined with a previously described battery of neuropsychometric tests preoperatively and 1 day postoperatively.<sup>4</sup> Four patients had a perioperative clinical stroke defined by significant clinical manifestations and radiographic infarcts detected by magnetic resonance imaging ( $n=2$ ) or computerized axial tomography ( $n=2$ ) and were excluded from neuropsychometric analysis. A total of 324 asymptomatic patients completed the entire battery of neuropsychometric tests at both time points. The neuropsychometric tests evaluate a variety of cognitive domains, including verbal memory, visuospatial organization, motor function, and executive action, as described previously.<sup>4</sup>

A variety of factors affect the neuropsychometric performance of patients after CEA, but only age  $>75$  years and diabetes mellitus have been shown previously to significantly and independently affect performance.<sup>5</sup> Other factors that might also affect performance, but have not been shown to independently affect performance, were evaluated as well. These included years of education, body mass index, history of smoking, extensive peripheral vascular disease, hypertension, and duration of cross-clamping of the carotid artery. We have included these factors in our univariate and multivariate analyses.

### Anesthesia and Surgery

As described previously,<sup>4</sup> the surgical technique, anesthetic management, and indications for CEA have remained constant at this institution over the duration of this study, as described previously.<sup>4</sup>

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Drs Heyer and Connolly had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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### Statistical Analyses

Neuropsychometric performance was calculated, as described previously.<sup>4,6</sup> Patients were considered to have cognitive dysfunction based on 2 criteria to account for both focal and global/hemispheric deficits:  $\geq 2.0$ -SD worse performance than the reference group in  $\geq 2$  cognitive domains or  $\geq 1.5$ -SD worse performance than the reference group in all 4 cognitive domains.

Statistics were performed using R environment (R Development Core Team, Vienna, Austria). For univariate analyses, Student *t* test, Wilcoxon rank-sum test, Fisher exact test, Pearson  $\chi^2$  test, and simple logistic regression were used where appropriate. The  $\alpha$  level was adjusted for multiple hypotheses using the Benjamini and Hochberg method to control for the false discovery rate.<sup>7</sup> A multiple logistic regression model was constructed to identify independent predictors of cognitive dysfunction. All of the factors with  $P < 0.20$  in a simple univariate logistic regression were entered into the final model. Model fit and calibration were confirmed with the likelihood ratio test, Hosmer-Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. The sample mean was imputed in the event of missing values for predictor variables.  $P \leq 0.05$  was considered significant.

### Results

There were no differences in patient characteristics between those taking and not taking statins (Table 1). Patients taking statins had a significantly lower incidence of perioperative stroke (0.0% vs 3.1%;  $P = 0.02$ ) and a significantly lower incidence of cognitive dysfunction (11.0% vs 20.2%;  $P = 0.03$ ) compared with patients not taking statins. The final logistic regression model included statin use and body mass index (Table 2). Statin use was associated with significantly decreased odds of cognitive dysfunction (odds ratio, 0.51 [95% CI, 0.27–0.96];  $P = 0.04$ ). No other variables were significant in the model.

### Discussion

Although some preliminary data suggest that preoperative and perioperative statin use may be associated with a lower incidence of perioperative stroke in symptomatic patients undergoing CEA, the data for asymptomatic patients are nearly nonexistent.<sup>2,3</sup> This study demonstrates for the first time that statin use is associated with a lower incidence of perioperative neurological injury in asymptomatic patients, as defined by both clinical stroke and cognitive dysfunction. Our previous studies in CEA patients have confirmed that the degree

**Table 1. Patient Characteristics: No Statin and Statins**

Characteristic	No Statins (n=124)	Statins (n=200)	P Value
Age >75 y	33.1%	25.5%	0.18
Education, y	14.7 $\pm$ 3.1	14.7 $\pm$ 3.5	0.09
BMI	26.3 $\pm$ 3.8	27.5 $\pm$ 4.9	0.07
History of smoking	65.3%	73.5%	0.15
Hypertension	44.4%	56.5%	0.04
Diabetes mellitus	16.1%	20.5%	0.41
PVD	25.8%	32.0%	0.29
Cross-clamp duration, min	41.3 $\pm$ 16.6	45.5 $\pm$ 18.5	0.05
Cognitive dysfunction	20.2%	11.0%	0.04

Data show the mean $\pm$ SD unless otherwise specified.

BMI indicates body mass index; and PVD, peripheral vascular disease.

**Table 2. Univariate and Multivariate Logistic Regression Models**

Characteristic	Univariate		Multivariate	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age >75, y	1.01 (0.98–1.05)	0.51		
Education, y	0.97 (0.88–1.06)	0.46		
BMI	0.94 (0.87–1.01)	0.13	0.96 (0.88–1.03)	0.24
History of smoking	0.99 (0.51–2.00)	0.99		
Hypertension	1.30 (0.70–2.46)	0.41		
Diabetes mellitus	0.87 (0.36–1.88)	0.73		
PVD	0.69 (0.32–1.38)	0.31		
Cross-clamp duration, min	1.00 (0.98–1.02)	0.99		
Statin use	0.49 (0.26–0.91)	0.02	0.51 (0.27–0.96)	0.04

BMI indicates body mass index; and PVD, peripheral vascular disease.

of cognitive dysfunction reported in this study is associated with actual brain injury,<sup>8</sup> and studies by other groups suggest that postoperative cognitive dysfunction can be predictive of not only disability and early retirement but even early death.<sup>9</sup> Thus, we feel that the witnessed protection is clinically significant.

Finally, we recognize the limitations of our study. The reasons for prescription and duration of statin use were not recorded. Although there are advantages of a single-center study in terms of consistency in surgical/anesthetic technique, as well as neuropsychometric evaluation, there are limitations associated with the applicability of our results to a generalized population. Therefore, all of these weaknesses would be addressed by a multicenter trial, which is critical in determining the clinical significance of these findings.

### Conclusions

Statin use is associated with less neurological injury, as defined by both clinical stroke and cognitive dysfunction, after asymptomatic CEA. These observations, if confirmed in prospective trials, suggest that it may be possible to further reduce the perioperative morbidity of CEA.

### Sources of Funding

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### Disclosures

None.

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# Stroke

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**Statins Reduce Neurologic Injury in Asymptomatic Carotid Endarterectomy Patients**  
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# Differential Expression of Collagen Type V and XI a-1 in Human Ascending Thoracic Aortic Aneurysms

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## Abstract

**Background.** The molecular mechanisms leading to ascending thoracic aortic aneurysms (ATAAs) remain unknown. We hypothesized that alterations in expression levels of specific fibrillar collagens occur during the aneurysmal process.

**Methods.** Surgical samples from ascending aortas from patients with degenerative ATAAs were subdivided by aneurysm diameter: small, 5 to 6 cm; medium, 6 to 7 cm; and large, greater than 7 cm; and compared with nonaneurysmal aortas (mean diameter, 2.3 cm).

**Results.** Histology, immunofluorescence, and electron microscopy demonstrated greater disorganization of extracellular matrix constituents in ATAAs as compared with control with an increase in collagen a1(XI) within regions of cystic medial degenerative lesions. Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) showed collagens type V and a1(XI) were significantly and linearly increased in ATAAs as compared with control ( $p < 0.001$ ). There was no change in the messenger ribonucleic acid (mRNA) expression levels of collagens type I and III. Western blot analysis showed collagens type I and III were significantly decreased and collagens a1(XI) and V were significantly increased and were linearly correlated with the size of the aneurysm ( $p < 0.001$  for both).

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**Conclusions.** These results demonstrate that increased collagen  $\alpha 1(XI)$  and collagen V mRNA and protein levels are linearly correlated with the size of the aneurysm and provide a potential mechanism for the generation and progression of aneurysmal enlargement.

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Ascending thoracic aortic aneurysms (ATAAs) pre-dominately affect the elderly population with an incidence of 5.9 new cases per 100,000 persons/year<sup>1</sup>. It is expected that the incidence of ATAAs will continue to increase with the potential of severe clinical consequences, including rupture, dissection, and the possibility to cause aortic valve insufficiency<sup>2</sup>.

There are two broad categories of ATAAs; namely those associated with genetic syndromes such as Marfan, Ehlers-Danlos, and Loeys-Dietz, and those without genetic involvement, which predominantly occur in the aging population<sup>3</sup>. The pathogenesis of ATAAs, not associated with known genetic syndromes, remains poorly understood. However, previous research has suggested that alterations in the extracellular matrix (ECM), the major constituent of the aortic wall, may play an important role in the formation and expansion of ATAAs<sup>3-5</sup>. The aortic wall is primarily composed of collagen types I and III, the major fibrillar collagens, responsible for the tensile strength of the aortic wall<sup>6,7</sup>. Under normal conditions collagen types I and III form heterotypic fibrils with collagen type V<sup>6</sup>. Collagen type V is a minor fibrillar collagen, but plays a critical role in the regulation of the size/diameter of the heterotypic fibrils<sup>5</sup>. Greater proportions of collagen type V have been shown to significantly decrease the diameter of the heterotypic fibrils, and in turn decrease tensile strength; however, other minor fibrillar collagens may also be involved. One of these is collagen  $\alpha 1(XI)$ .

Collagen  $\alpha 1(XI)$  is structurally and biologically

related to collagen type V and has the same large globular amino-terminal domain<sup>5</sup>. Experimental data have shown that collagen  $\alpha 1(XI)$  is expressed in the mouse embryonic aortic tunica media and that the messenger ribonucleic acid (mRNA) of collagen type  $\alpha 1(XI)$  may be present in human abdominal aortic aneurysms<sup>8,9</sup>.

However, there have been no data to show the involvement of collagen  $\alpha 1(XI)$  in the normal thoracic aorta or in thoracic aortic aneurysms in humans. The purpose of the present study was to determine the mRNA and protein expression levels of fibrillar collagens I, III, V, and  $\alpha 1(XI)$  in the aortic wall of ATAAs and to compare these results with control nonaneurysmal aortas during the progression of the aneurysmal enlargement.

## Material and Methods

### Clinical Data and Aortic Specimens

Research protocols were approved by the Institutional Review Boards in all participating hospitals and informed consents were obtained. Clinical data and aortic specimens were collected during a 2-year period (April 2006 to April 2008) from patients with nonaneurysmal ascending thoracic aortas undergoing heart transplantation (n = 7) and patients undergoing replacement of ATAAs (n = 25). All patients had tricuspid aortic valves and patients with ATAAs were subdivided into three groups according to the maximal diameter

Table 1. Primers Used for Real Time RT-PCR Reactions

mRNA Target	Forward Primer	Reverse Primer
$\beta$ -actin	5'-AGCATTGCTTTCGTGTAATTATG-3'	5'-GTGTGCACTTTTATTCAACTGGTC-3'
Collagen $\alpha 1(I)$	5'-CTCTGACTGGAAGAGTGGAGAGTA-3'	5'-TTGGTGGTTTTGTATTCAATCACT-3'
Collagen $\alpha 1(III)$	5'-AGTGACCGACAAAATCCAGTTAT-3'	5'-CTTTACTGGTGAGCACAGTCATT-3'
Collagen $\alpha 2(V)$	5'-TGAGTTGTGGAGCTGACTCTAATC-3'	5'-TAACAGAAGCATAGCACCTTTCAG-3'
Collagen $\alpha 1(XI)$	5'-GAAATTGTACCTTGGTGCCACCAAC-3'	5'-GGATGGATGAGAATGAGCACCATAT-3'

mRNA = messenger ribonucleic acid; RT-PCR = reverse transcription-polymerase chain reaction.

of the aneurysm: small ATAAs (n = 9) with diameters between 5 and 6 cm; medium ATAAs (n = 8) between 6 and 7 cm; and large ATAAs with diameters greater than 7 cm. Full-thickness biopsies containing all three layers of the aorta were collected from the right-lateral aspect of the ascending aorta (the greater curvature, roughly in line with the commissure between the right and noncoronary sinuses) in the operating room and fresh frozen in liquid nitrogen and stored at -80°C until analysis.

All patients with ATAAs underwent elective surgery and required graft replacement of the ascending aorta. Aortic samples from relatively young patients (<50 years of age) or from patients with aneurysms secondary to genetic syndromes such as Marfan, Ehlers-Danlos, and Loeys-Dietz syndrome or from patients with bicuspid aortic valves were excluded from this study.

#### *Histology, Immunofluorescence, and Transmission Electron Microscopy*

Tissue samples from the site of the maximal diameter of the ascending aorta were used for histological, immunofluorescence, and transmission electron microscopy analysis. For histology, frozen tissue was sectioned (1.5 µm thickness). Thirty sections from each specimen were mounted on glass slides and divided sequentially for Masson's trichrome staining and Movat's pentachrome staining using standard techniques and reagents<sup>10</sup>. Some sections were stained with collagen type I (ab292, 1:200 dilution; Abcam Inc, Cambridge MA). Primary antibodies were detected with species-appropriate Alexa 568 conjugated secondary antibodies (Molecular Probes, Invitrogen; Carlsbad, CA) prior to mounting and visualization on a multipoint spinning disk confocal system (Atto; BD Biosciences, Rockville, MD) attached to a Zeiss Axiovert 200M microscope (Zeiss, Thornwood, NY)<sup>10</sup>. For immunohistochemistry, tissue samples were fixed in 5% zinc buffered formalin, embedded in paraffin, cut to 1 µm thickness, and heat fixed onto glass slides. Sections were deparaffinized in xylene, rehydrated through graded ethanol, and incubated for 30 minutes in 0.01 mg/mL hyaluronidase (Sigma-Aldrich Cor-

poration, St. Louis, MO)<sup>11</sup>. Primary antibody to collagen a1(XI) was diluted 1:400 and applied to tissue section for 1 hour at 25°C<sup>12</sup>. An antirabbit secondary antibody conjugated to horseradish peroxidase was applied and incubated for 30 minutes, followed by development with substrate chromogen (DakoCytomation, Dako, North America). Slides were subsequently counterstained with hematoxylin. For transmission electron microscopy tissue samples were fixed with 1.25% formaldehyde, 2.5% glutaraldehyde, and 0.03% picric acid in 100 mM cacodylate buffer, and embedded in resin<sup>10</sup>. Thin sections (1 µm) were stained with 1% uranyl acetate and examined with transmission electron microscopy by an independent pathologist.

#### *Real-Time Quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR)*

Frozen tissue was ground in liquid nitrogen and total RNA extracted by homogenization in Trizol reagent (Invitrogen Corporation, Carlsbad, CA) according to the manufacturer's protocol. Real-time qRT-PCR was performed using a Chromo 4 continuous fluorescence detector and Opticon monitor 3 software (MJ Research, Waltham, MA) using an iScript one-step RT-PCR kit with SYBR green solution (Bio-Rad, Hercules, CA) according to manufacturer's instructions. In brief, 100 ng of total RNA and 600 nM of both forward and reverse primer were added to each reaction. Primers are shown in Table 1. Control samples and ATAAs samples were run for each primer set in duplicate. Control reactions without reverse transcriptase were performed for each reaction. Reaction kinetics were optimized for each primer set: reverse transcription 30 minutes at 60°C, denaturation 2 minutes at 94°C, followed by 60 cycles of denaturation 15 seconds at 94°C; annealing for 30 seconds at 58°C a1(I), 60°C a1(III), 61°C a2(V), 65°C a1(XI), and 60°C -actin; extension for 2 minutes at 68°C. The RT-PCR products were stored at 4°C until further analysis. Melting curves were constructed for each reaction at the conclusion of the cycling parameters from 60°C to 95°C. Fold changes in gene expression were calculated using the Pfaffl method<sup>13</sup>. Real-time RT-PCR

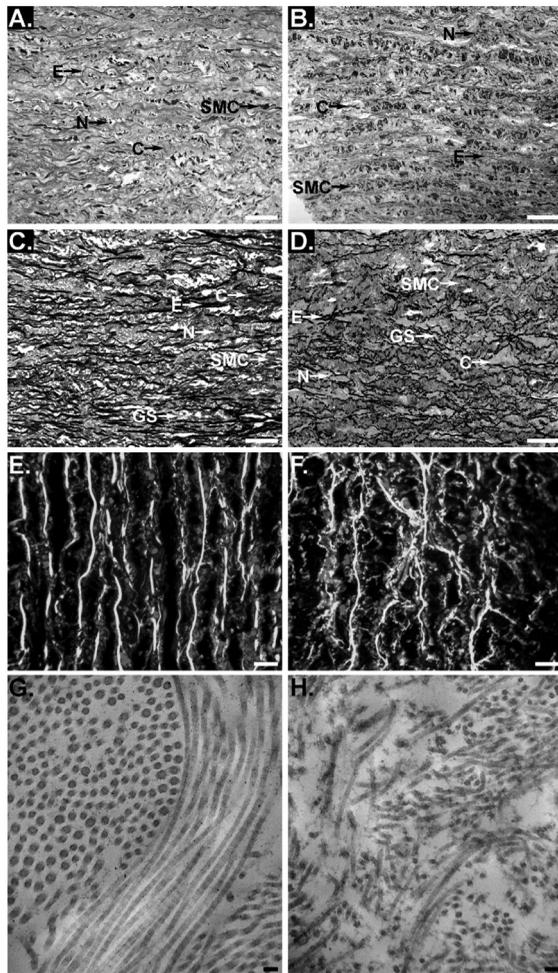


Fig 1. Histological analysis using Masson's trichrome (A and B) and Movat's pentachrome (C and D). Representative serial sections of the tunica media of the aortic wall from control (A and C) and ascending thoracic aortic aneurysms (ATAA) (B and D) are shown. Collagen (C), smooth muscle cells (SMC), elastin (E), nuclei (N), and ground substance (GS) are shown. Scale bars represent 50  $\mu$ m. Representative serial sections of the tunica media of the aortic wall from control (E) and ATAA (F) are shown. In E and F elastin auto-fluorescence is shown in green and collagen type I is shown in red. Scale bars represent 10  $\mu$ m. Transmission electron microscopy collagen fibrils are shown in longitudinal and cross sections. Representative serial sections of the tunica media of the aortic wall from control (G) and ATAA (H) are shown. Collagen fibrils in ATAA are fragmented and disorientated as compared with control aorta. Scale bars represent 100 nm.

products were validated by agarose gel electrophoresis and sequencing.

#### Western Blotting

Full-thickness aortic tissue from the site of the maximal diameter containing all three layers (tunica adventitia, tunica media, and tunica intima) was pulverized under liquid nitrogen and protein extraction was performed using the T-PER reagent (Pierce, Rockford, IL). Protein concentration estimation was performed by using the BCA protein assay (Pierce). Total protein (40  $\mu$ g) was used for standard denaturing 10% sodium-dodecyl-sulphate polyacrylamide gel electrophoresis under non-reducing (collagen types I and V) or reducing conditions (collagen type III, collagen  $\alpha$ 1(XI), and  $\beta$ -actin). Protein transfer and blocking was performed as previously described<sup>10</sup>. Immunoblotting was performed using the following antibodies: collagen type I (ab292, 1:2000 dilution; Abcam Inc, Cambridge, MA); collagen type III (ab6310, 1:1000 dilution; Abcam Inc); collagen type V (ab19812, 1:200 dilution; Abcam Inc); collagen  $\alpha$ 1(XI) (kind gift of Dr J. T. Oxford, Boise State University, Boise, ID) [14]; and  $\beta$ -actin (ab8227, 1:2000 dilution; Abcam Inc). Antibodies were diluted in trisbuffered saline-Tween and incubated with the membranes at 4°C overnight. Membranes were washed and appropriate secondary antibodies (dilution 1:5,000) (Santa Cruz Biotechnology Inc, Santa Cruz, CA) were used<sup>10</sup>. Blots were detected using ECL

Plus (Amersham Pharmacia Biotech, Piscataway, NJ) with species-appropriate secondary antibodies. Densitometric analysis was performed using the ImageJ analysis software (Rasband WS, ImageJ; <http://rsb.info.nih.gov/ij>).

#### Statistical Analysis

All continuous variables were expressed as mean  $\pm$  SD. Discrete variables were summarized by percentages. Independent sample *t* tests and one way analysis of variance were used for mean comparisons between two or multiple groups, respectively. The Spearman rank correlations,  $\chi^2$  test, and Fisher exact test were also performed to describe association between different outcome variables. The Bonferroni correction was used to

adjust for both multiple comparisons and correlated outcome variables. Two-tailed probability values of  $p$  less than 0.01 were considered statistically significant for each test to ensure an overall study significance level of  $p$  less than 0.05. All statistical analyses were performed in SPSS 15.0 (SPSS, Inc, Chicago, IL).

## Results

### *Aortic Specimens and Patient Characteristics*

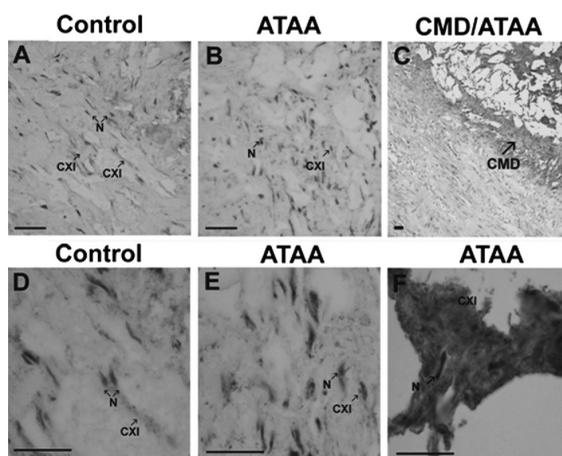
Thirty-two surgical ascending aortic samples were analyzed. Seven specimens from patients who underwent heart transplantation procedures with normal ascending aortic diameters (mean diameter, 2.3 cm) were used as controls. Twenty-five patients underwent ascending aortic replacement for ATAAs (mean diameter, 6.8 cm,  $p < 1.1$  vs controls). This subgroup of patients was fur-

ther divided into small ( $n = 9$ , mean diameter 5.6 cm), medium ( $n = 8$ , mean diameter 6.5 cm), and large aneurysms ( $n = 8$ , mean diameter 8.4 cm) (all  $p < 0.001$  vs controls). Patients with ATAAs had no differences in age, smoking, hypertension, or gender distribution. Patients with control aortas were younger, with decreased percentages of hypertension. All ATAAs specimens analyzed in this study were from patients with tricuspid aortic valves having degenerative ATAAs. None of the specimens analyzed was atherosclerotic and none were lined with thrombus. Control specimens were taken from donors in order to ensure that these aortas would have minimal alterations in matrix composition.

### *Histology, Immunofluorescence, and Transmission Electron Microscopy*

Histological analysis using both Masson's trichrome and Movat's pentachrome staining, and transmission electron microscopy demonstrated that both elastin and collagen showed greater disorganization and fragmentation in ATAA samples as compared with controls (Figs 1A–1H). These results were consistent in all samples.

Immunohistochemical staining demonstrated that collagen a1(XI) was detectable in both control and ATAA samples (Figs 2A, B, D and E). Collagen a1(XI) was more uniformly distributed through the matrix in control tissues while the staining pattern in the ATAA samples appeared more punctuate. Collagen a1(XI) staining intensity was increased in areas of cystic medial degenerative lesions (Figs 2C and 2F).



**Fig 2.** Immunohistological analysis of collagen a1(XI). (A) Control tissue and (B) ascending thoracic aortic aneurysms (ATAA) tissue, at X200 original magnification. (C) Cystic medial degenerative (CMD) lesion at X50 original magnification. (D) Control tissue, (E) ATAA tissue, and (F) CMD lesion from ATAA at X630 original magnification. Tissue sections stained with antibody directed to collagen a1(XI) demonstrated staining within the tunica media in both control tissues and ATAA. Presence of collagen a1(XI) is indicated by brown staining (indicated by arrow CXI). Tissues were counterstained briefly with hematoxylin to stain nuclei (blue, indicated by arrow N). An increase in staining for collagen a1(XI) is shown within regions of CMD lesions. Scale bars in A to F are 100  $\mu$ m.

### *Real-Time qRT-PCR*

The qRT-PCR showed only one product per primer set was produced at the predicted molecular size. Sequence analysis confirmed that the products corresponded to the genes analyzed (Fig 3 and results not shown). There was a significant increase in collagens a2(V) and a1(XI) in ATAAs as compared with controls ( $p < 0.001$ ). Collagen a2(V) expression levels were increased 1.9-, 2.7-, and 5.0-fold and collagen a1(XI) was increased 5.2-, 9.5-, and 16.1-fold in small, medium, and large aneurysms, respectively, as compared with

control aortas. There was no significant difference in the expression levels of collagens  $\alpha 1(I)$  and  $\alpha 1(III)$  or that of  $\beta$ -actin within or between groups (Fig 3).

*Western Blotting*

Western blots (Fig 4) of collagen type I showed two bands at 138 kDa and 129 kDa corresponding to the two  $\alpha 1$  and  $\alpha 2$  chains, respectively, of collagen type I. Collagen  $\alpha 1(I)$  protein levels were significantly decreased in all ATAAs categories as compared with control aortas ( $p < 0.001$ ) while collagen  $\alpha 2(I)$  protein levels were significantly decreased in

small and large aneurysms as compared with controls ( $p < 0.001$ ). Collagen type III protein levels were significantly decreased in all ATAAs groups as compared with control aortas ( $p < 0.001$ ). Collagen type V protein levels were significantly increased in all ATAAs groups as compared with control aortas ( $p < 0.001$ ). Western blots of  $\alpha 1(XI)$  protein showed two bands, at 55kDa and 45kDa, corresponding to the two different isoforms. Both isoforms were significantly increased in ATAAs as compared with control aortas ( $p < 0.001$ ).

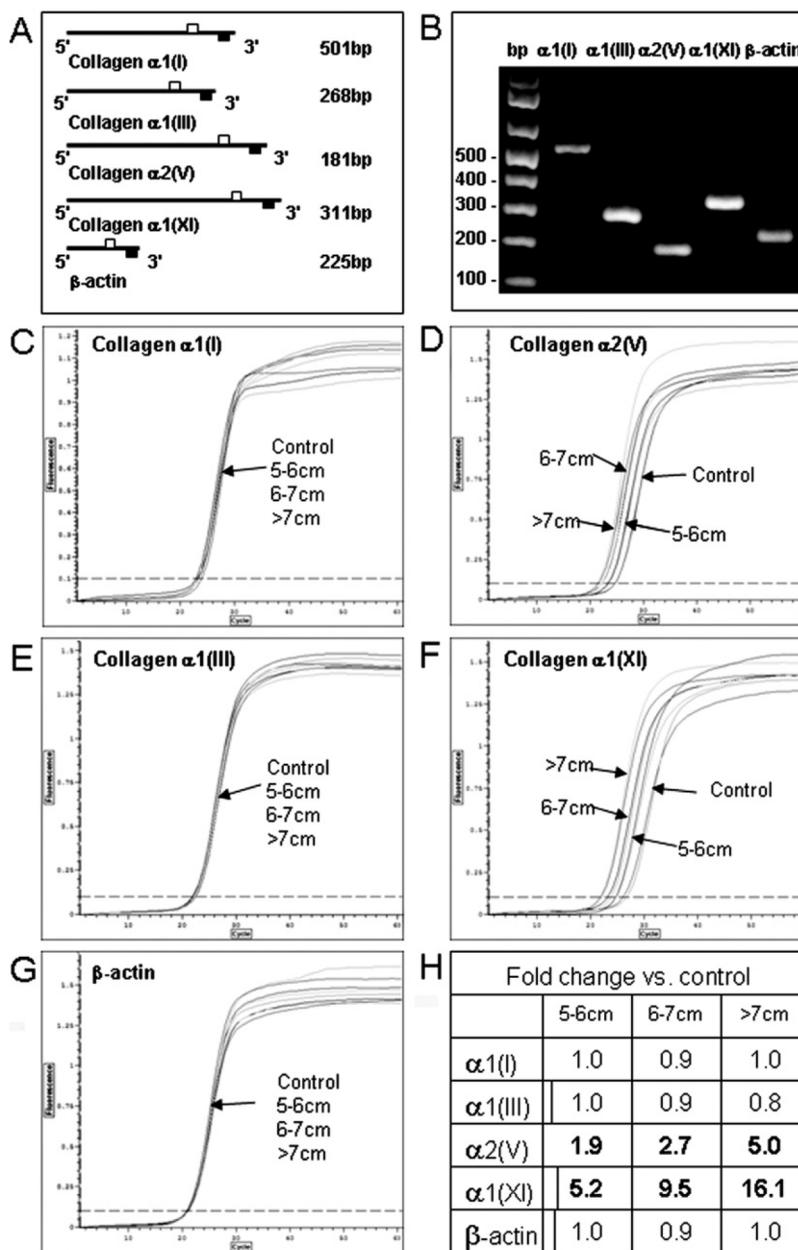


Fig 3. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Panel A shows primer sets used for qRT-PCR and expected product size (open squares = forward primer; closed squares = reverse primer). Panel B shows a representative 1.5% agarose gel of amplified products from each primer set. Panels C to G show real-time quantitative amplification curves for collagen  $\alpha 1(I)$ ,  $\alpha 1(III)$ ,  $\alpha 2(V)$ ,  $\alpha 1(XI)$ , and  $\beta$ -actin. For C–G, x-axis = cycle; y-axis = fluorescence. In C, measurements are 0–60 fluorescence units at increments of 10 along x-axis and 0–1.2 fluorescence units at increments of 0.1 along y-axis; in D–G, measurements are 0–60 fluorescence units at increments of 10 along x-axis and 0–1.5 fluorescence units at increments of 0.25 along y-axis. Ascending thoracic aortic aneurysm size is indicated. Panel H shows the fold changes versus controls. Significant differences versus control at  $p$  less than 0.001 are shown in bold type.

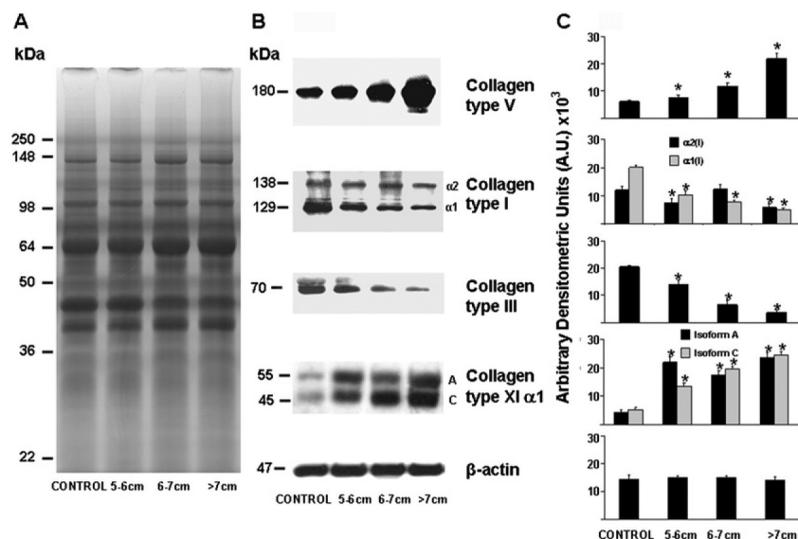


Fig 4. Western blot analysis. A representative 10% sodium-dodecyl-sulfate -polyacrylamide gel stained with Coomassie brilliant blue for each aneurysm size is shown in panel A. Representative Western immunoblots are shown in panel B. Densitometric analysis of Western blots is shown in panel C. Ascending thoracic aortic aneurysm size is indicated. Significant differences at  $p$  less than 0.001 versus control are shown as \*.

*Spearman Rank Correlation Analysis*

The Spearman rank correlation analysis was performed for mRNA and for protein levels in comparison to aneurysmal size (Fig 5). Increased mRNA expression levels for collagen a1(XI) and collagen a2(V) showed linear correlation with the size of the aneurysm ( $p < 0.001$  for both). There was no linear correlation between the expression of collagen a1(I) ( $r = -0.020$ ) or collagen a1(III) ( $r = -0.063$ ) with the size of the aneurysm (Fig 5A). Decreased expression levels of collagen a1(I) and collagen type III protein showed linear correlation with the size of the aneurysm (Fig 5B;  $p < 0.001$  for both). Increased expression levels of collagen a1(XI) and collagen type V protein also showed linear correlation with the size of the aneurysm (Fig 5B;  $p < 0.001$  for both).

**Comment**

Collagen type composition is crucial for the

maintenance of vessel wall integrity and tensile strength<sup>5,7,15,16</sup>. In the present study both transmission electron and light microscopy demonstrated that collagen fibrils in ATAAs were fragmented and disorientated, with a less ordered appearance, as compared with control nonaneurysmal samples. Our results demonstrate that collagen a1(XI) and collagen type V mRNA and protein expression levels are significantly increased within regions of cystic medial degenerative lesions in human ATAAs from patients with tricuspid aortic valves as compared with control aortas, and that there is a linear correlation with the size-diameter of the aneurysm. Our data also show that although collagen types I and III mRNA expression levels are similar in ATAAs as compared with controls there is a significant decrease in their corresponding protein levels, which are also linearly correlated with the size of the aneurysm.

Increased expression of collagen a1(XI) and type V protein may putatively represent a regulatory

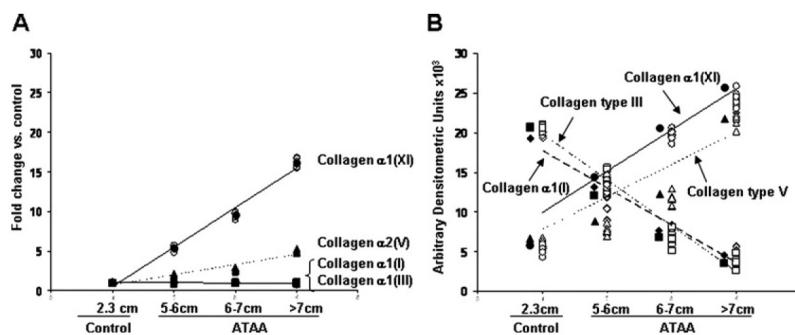


Fig 5. Spearman rank correlations of the messenger ribonucleic acid (A) and protein (B) expression levels of collagens type I, III, V, and a1(XI) with aneurysm size are shown. Control mean diameter was 2.3 cm. (ATAA = ascending thoracic aortic aneurysm.)

mechanism for the lateral growth and diameter of fibrils containing collagen types I and III. Previous studies have shown that collagen  $\alpha 1(\text{XI})$  and type V protein have a large globular amino-terminal domain with similar structure and size<sup>5</sup>. This large globular domain has been suggested to reduce tensile strength through steric hindrance between the large globular amino-terminal domain and the major fibrillar collagens, preventing their assembly into the heterotypic fibrils<sup>7</sup>.

The overexpression of collagen  $\alpha 1(\text{XI})$  and type V would also allow for the formation of heterotrimeric collagen XI/V<sup>17</sup>. These heterotrimeric collagens would inhibit the deposition of collagen types I and III into the fibrils due to the aforementioned steric hindrance. This possible mechanism is supported by basic research studies showing that there is a dose-dependent competition for collagen fibril formation between collagen type I and V as well as collagens type I and  $\alpha 1(\text{XI})$ <sup>7,18</sup>.

Overexpression of collagen  $\alpha 1(\text{XI})$  and type V would therefore lead to thinner collagen fibers and decreased tensile strength in the aortic wall increasing the susceptibility to dilatation.

Our data demonstrate that the increase in collagen  $\alpha 1(\text{XI})$  and type V protein content during ATAA expansion is associated with increased mRNA levels while there is no change in the mRNA levels associated with the decrease in collagen types I and III. This differential regulation has been previously demonstrated in smooth muscle cells in the tunica media of ATAAs<sup>19,20</sup> and in aortic smooth muscle cells in culture<sup>17</sup>, and has been suggested as a possible mechanism modulating ECM remodeling. Recent studies have shown that the amino-terminal propeptide of collagen  $\alpha 1(\text{XI})$  contains a well-characterized heparin binding domain<sup>21,22</sup>. This heparin binding domain has been shown to interact with specific integrin receptors that promote the regulation of expression and activity of matrix metalloproteinases (MMPs)<sup>23</sup>. Increased collagens  $\alpha 1(\text{XI})$  and V mRNA levels could therefore act indirectly to either induce or to further increase MMP synthesis and increase ECM degradation. This cascading effect would further reduce major collagens I and III, which would be unable to be replaced due to static transcription, and increase collagen V and

$\alpha 1(\text{XI})$  content due to increased mRNA expression levels. These events would ultimately lead to a weakening of the aortic wall and increased susceptibility to dilatation and rupture.

Support for this mechanism comes from Ikonomidis and colleagues<sup>24</sup> who have shown that MMP levels and activity are differentially increased in ATAAs leading to ECM and collagen degradation. The authors showed that in patients having tricuspid aortic valves there was an increase in MMP-13 in ATAAs 4.0 to 5.9 cm and an increase in MMP-7 in larger ATAAs. The MMP-13 and MMP-7 are both expressed by aortic wall cells and have been shown to significantly contribute to ECM remodeling through increased collagen and ECM degradation<sup>25</sup>. Whether MMP degradation proceeds and upregulates collagen V and  $\alpha 1(\text{XI})$  mRNA and protein expression or is the result of upregulated collagen V and  $\alpha 1(\text{XI})$  mRNA and protein expression, or acts in a coordinate and additive manner, is beyond the scope of this paper and remains to be determined.

The findings of the present study are in agreement with two recently published studies. Tang and colleagues<sup>16</sup> have also shown that mRNA expression levels of collagen types I and III in ATAAs are unchanged but that there is a 45% decrease in total collagen content as compared with control. Our results also agree with Della Conte and colleagues<sup>25</sup> who have shown a significant reduction in major fibrillar collagens I and III in ATAAs as compared with controls. Our data regarding minor collagens  $\alpha 1(\text{XI})$  and V mRNA and protein expression levels are unique as none of these studies provided experimental data on minor fibrillar collagen expression and protein synthesis.

In conclusion, we present a molecular mechanism for the formation of ATAAs in patients with tricuspid aortic valves based on the overexpression of minor fibrillar collagen  $\alpha 1(\text{XI})$  and V, which may regulate the assembly of the major fibrillar collagens I and III. We also report the involvement of collagen  $\alpha 1(\text{XI})$  in the normal adult human thoracic aorta and its increased expression in ATAAs. Our results demonstrate that increased collagen  $\alpha 1(\text{XI})$  and collagen V mRNA and protein levels are linearly correlated with the size of

the aneurysm and we provide a potential mechanism for the generation and progression of the aneurysmal enlargement.

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# Female gender is independently associated with increased carotid temperatures in patients with coronary artery disease

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## ABSTRACT

**Background:** Limited are the data regarding the sex differences in functional carotid artery characteristics. Microwave Radiometry (MWR) is a new noninvasive method, which measures in vivo instantly the internal temperatures of tissues, reflecting inflammation. The aim of the present study was to investigate whether in patients with coronary artery disease (CAD), gender related differences apply in carotid plaque functional characteristics, as assessed by MWR.

**Methods:** Consecutive patients with significant CAD were included in the study. All patients underwent evaluation of both carotid arteries by 1) ultrasound and 2) MWR. During ultrasound common carotid IMT and plaque thickness were assessed according to Mannheim consensus. During MWR measurements, temperature difference ( $\Delta T$ ) was assigned as maximal temperature along the carotid artery minus minimum.  $\Delta T \geq 0.90$  °C was assigned as high  $\Delta T$ .

**Results:** In total 364 patients with significant CAD were included in the study. Of these 54 were female and 310 were male. Max plaque thickness and ccIMT were similar between males and females ( $2.38 \pm 1.16$  vs.  $2.46 \pm 1.12$  mm,  $p=0.63$  and  $0.944 \pm 0.172$  vs.  $0.942 \pm 0.169$  mm,  $p=0.96$ ). Carotid arteries of females showed higher  $\Delta T$  values ( $1.16 \pm 0.48$  vs.  $0.87 \pm 0.45$  °C,  $p < 0.001$ ). Interestingly, females had more commonly high  $\Delta T$  values bilaterally (35.2% vs 15.5%,  $p = 0.001$ ). In multivariate analysis, female sex was independently associated with bilateral high  $\Delta T$ , when adjusted to potential covariates (OR =2.78, 95% CI= 1.42–5.45,  $p = 0.003$ ).

**Conclusions:** In patients with CAD, sex specific differences apply in functional but not in structural carotid artery characteristics. Whether this discrepancy has prognostic significance, remains to be clarified in future studies.

**Keywords:** Carotid artery, Gender differences, Inflammation, Microwave radiometry

## 1. Introduction

Carotid atherosclerosis represents a major cause of stroke. Recent reports show differences in the incidence, prevalence and severity of ischemic strokes between the two genders [1]. In specific, women suffer from stroke in older age than men, but the total lifelong incidence is higher in females. Interestingly, stroke related mortality and morbidity appears to be higher in women [2]. Moreover, carotid endarterectomy, as the basic therapy for critical carotid stenosis, shows greater long-term benefit in men than women, both for symptomatic and asymptomatic stenosis [3,4].

Despite these major differences, few studies have addressed gender related differences in pathophysiology of carotid atherosclerosis and most of our knowledge regarding this topic is derived from coronary arteries [5–7]. Pathological studies have revealed a significantly more vulnerable carotid plaque phenotype in men compared to women. Indeed, inflammatory cell infiltration and intraplaque hemorrhage are more prominent in male carotid endarterectomy specimens [8–10]. In contrast, women show *in vivo* more intense intraplaque neovascularization, as assessed by contrast enhanced ultrasound [11]. Limited are the data, however, in regard to sex differences in functional characteristics of carotid arteries.

Microwave radiometry (MWR) allows *in vivo* noninvasive measurement of the temperature of carotid atherosclerotic plaques, reflecting their inflammatory status, as it has been shown in recent studies [12–18]. More importantly, MWR measurements have been associated with vulnerable carotid plaque characteristics, including plaque neovascularization [15].

In the present study, we aimed to investigate in patients with significant coronary artery disease (CAD), whether: 1) sex related differences apply in carotid plaque temperatures, as assessed by MWR

and 2) differences are evident in carotid morphological characteristics, as assessed by ultrasound.

## 2. Methods

### 2.1. Study population

Consecutive patients with significant coronary artery disease-CAD ( $\geq 50\%$  stenosis in at least one major epicardial vessel), undergoing coronary angiography due to stable angina or variant acute coronary syndromes, were prospectively enrolled in the study.

During their stay in the hospital, all patients underwent ultrasound evaluation of both carotid arteries followed by MWR measurements performed by specialists blinded to angiographic results. Patients with any cerebrovascular disease, previous stroke or transient ischemic attacks, vasculitis, non-atherosclerotic carotid artery disease, intermittent inflammatory, infectious or neoplastic conditions, or patients that were treated with corticosteroids or/and NSAD (except aspirin) were excluded from the study.

Medical history, conventional risk factors for coronary artery disease and current medical therapy were recorded in all patients. Data from the angiography were used to identify the percentage of arterial stenosis and the number of coronary vessels involved. Written informed consent was obtained from each patient. The study protocol was approved by the hospital's Ethics Committee.

### 2.2. Ultrasound imaging

A high-resolution B-mode ultrasound unit (iE33 xMATRIX, Philips Healthcare, Bothell, WA, USA), with a 7.5 MHz transducer was used to examine both carotid arteries (common, internal, external) throughout their whole length, in transverse and longitudinal sections. Ultrasound

imaging procedures and specific definitions of the examined parameters were previously described [19,20]. In brief, ultrasound measurements were performed over three segments of 20mm in length. Carotid bifurcation was the middle segment and was used as a marker. Carotid plaque thickness (PT) and the common carotid artery intima-media thickness (ccIMT) were measured according to Mannheim consensus [21]. In specific, ccIMT was measured at the last 10 mm of the distal wall of common carotid at region without plaque. The highest value of ccIMT and PT for both carotid arteries was assigned as ccIMTmax and PTmax respectively.

Atherosclerotic plaquemorphology, echogenicity, consistency, surface contour and heterogeneity were also defined. Gray–Weale classification was used for plaque echogenicity evaluation (Types I–V) [22]. Based on this, plaques were described, according to the morphology, as fatty (Type I–II) mixed (Type III–IV) and calcified (Type V), or according to the heterogeneity, as heterogeneous (Type I–II) and homogeneous (Type III–V) [23]. The plaque was also defined as regular if its surface was smooth or irregular if a rupture varied between 0.3 mm and 0.9 mm was observed on the surface of any plaque [24]. All data were collected and interpreted by experienced ultrasonographers. In case of disagreement, data were evaluated by a third one, and the final decision was extracted by the research team.

### 2.3. Microwave radiometry measurements

A microwave computer-based system (RTM 01 RES, Bolton, United Kingdom) that detects temperature from internal tissues at microwave frequencies was used to measure carotid plaque temperature [25,26]. The basic principles, the technical and functional characteristics of MWR device have been previously described [12-17]. In brief, MWR measurements were obtained over the previously defined segments, at least 10 min after the ultrasound examination in order to avoid any influence on temperature from palpation or the ultrasound study.

Carotid plaque temperature was the median value of three repeated measurements after set-

ting vertically the transducer on the specific segment for 10 s. This procedure was repeated over all the previously defined from the ultrasound segments, starting from the distal to the proximal segment. [20,27]. During MWR measurements, temperature difference ( $\Delta T$ ) was defined as maximal temperature along the carotid artery minus minimum.  $\Delta T \geq 0.90$  °C was assigned as high  $\Delta T$  according to previous observations [15].  $\Delta T_{max}$  was assigned as the maximal value of the  $\Delta T$ s of both carotid arteries [19].

### 2.4. Statistical analysis

Carotid artery and patient based analysis were performed to determine the impact of gender on morphological and functional carotid artery characteristics.

Quantitative data are presented as rates or mean values  $\pm$  SD, while qualitative variables as absolute and relative frequencies. Probability values were two-sided from the Student t-test for continuous variables. Non-continuous values were compared by chi square test. All risk factors examined for interactions. The data were thereafter analyzed using both standard logistic and linear regression as well as multiple logistic and linear regression analysis in order to determine those factors which are independently associated with  $\Delta T$ . The variables examined in the prediction models made to reveal any correlation between gender and  $\Delta T$ , were known cardiovascular disease risk factors (smoking, dyslipidemia, arterial hypertension, diabetes mellitus, and family history), demographic characteristics (gender, age), severity of coronary heart disease (number of vessels), plaque thickness and medication. A two-tailed value of  $p < 0.05$  was considered statistically significant throughout. Statistical analyses were performed using commercially available software (SPSS, version 20, SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Baseline demographic and clinical characteristics

A total of 728 arteries from 364 patients with sig-

**Table 1**  
Demographic characteristics of the study population.

N = 364	Male (N = 310)	Female (N = 54)	p
<i>Clinical variables</i>			
Age	63.99 ± 10.77	65.89 ± 10.34	0.23
Dyslipidemia	230 (74.2%)	46 (85.2%)	0.08
Smoking	153 (49.4%)	18 (33.3%)	0.03
Diabetes mellitus	109 (35.2%)	25 (46.3%)	0.12
Hypertension	205 (66.1%)	40 (74.1%)	0.25
CAD family history	134 (43.2%)	31 (57.4%)	0.05
<i>Medication</i>			
Aspirin	213 (68.7%)	39 (72.2%)	0.61
ADP blockers	112 (36.1%)	20 (37%)	0.90
Statin	207 (66.8%)	40 (74.1%)	0.29
ACE inhibitors	89 (28.7%)	10 (18.5%)	0.12
Angiotensin II receptor antagonist	79 (25.5%)	15 (27.8%)	0.72
Nitrates	41 (13.2%)	11 (20.4%)	0.17
B-Blockers	136 (43.9%)	32 (59.3%)	0.04
Ca channel blockers	53 (17.1%)	15 (27.8%)	0.06
<i>CAD severity</i>			
One vessel CAD	118 (38.1%)	20 (37%)	0.11
Two vessels CAD	119 (38.4%)	22 (40.7%)	
Three vessels CAD	73 (23.5%)	12 (22.2%)	

nificant CAD were included in the analysis. Of these patients, 310 were male and 54 were female. Table 1 shows the distribution of the participants among males and females by demographic variables, medication, cardiovascular disease risk factors and severity of CAD. Male sex seems to be more often smokers ( $p=0.03$ ). On the other hand, female sex was associated with positive family history for CAD ( $p=0.05$ ), and intake of b-Blockers medication ( $p=0.04$ ).

No statistically significant association was noted among the two groups for other variables especially those of statins intake and severity of CAD.

### 3.2. Carotid ultrasound analysis

#### 3.2.1. Patient- and vessel-based analysis

Atherosclerotic plaques were detected in both carotid arteries in 198 out of 310 males (63.9%) and in 38 out of 54 females (70.4%) ( $p=0.36$  for the comparison). Patient based analysis revealed no statistically significant difference in carotid ultrasound characteristics between males and females (ccIMTmax:  $0.944 \pm 0.172$  vs.  $0.942 \pm 0.169$  mm,  $p=0.96$ ; PTmax:  $2.38 \pm 1.16$  vs.  $2.46 \pm 1.12$  mm,  $p=0.63$ , Fig. 1).

When a vessel based analysis was performed, 551 out of 728 carotid arteries (75.7%) had atherosclerotic plaques – 466 in male and 85 in female subjects. Table 2 depicts the distribution of ultrasound plaque characteristics by gender. Female sex was statistically significantly associated with irregular plaque surface ( $p < 0.001$ ). Carotid plaque

thickness was similar in males and females ( $1.99 \pm 1.07$  vs  $2.03 \pm 1.03$  mm,  $p=0.66$ , Fig. 2). There was no difference in ccIMT between the two genders ( $0.86 \pm 0.19$  for males vs  $0.83 \pm 0.14$  mm for females,  $p=0.20$ , Fig. 2).

### 3.3. Microwave radiometry analysis (MWR)

#### 3.3.1. Patient- and vessel-based analysis

Female carotid arteries showed higher  $\Delta T_{max}$  values in the patient based analysis (female:  $1.16 \pm 0.48$  vs male:  $0.87 \pm 0.45$  °C,  $p < 0.001$ , Fig. 3). Interestingly, females had more commonly high  $\Delta T$  values ( $\geq 0.9$  °C) bilaterally (female: 35.2% vs male: 15.5%,  $p=0.001$ ) or in at least one carotid artery (female: 75.9% vs male: 38.7%,  $p=0.001$ ). Similar results were recorded when a vessel based analysis was performed. More specifically, higher  $\Delta T$  values were found in female carotid arteries than in male ones ( $0.98 \pm 0.51$  vs  $0.70 \pm 0.43$  °C,  $p < 0.001$  respectively, Fig. 4) as assessed by the MWR measurements. When the comparison was limited in high level of  $\Delta T$ , these values were most commonly found in carotid arteries of female subjects (female: 57.4% vs male: 27.4%,  $p=0.001$ ).

### 3.4. Regression analysis

#### 3.4.1. Linear regression

Linear regression analysis was conducted in order to investigate the relation of gender with  $\Delta T_{max}$  values. Univariate analysis showed a statistically significant linear association of gender (beta = 0.23, 95% CI = 0.16–0.43,  $p < 0.001$ ), diabetes mellitus (beta = 0.17, 95% CI = 0.06–0.26,  $p=0.002$ ), hypertension (beta = 0.16, 95%

**Table 2**  
Distribution of ultrasound plaque characteristics by gender: vessel-based analysis.

Carotid arteries with atherosclerotic plaques	Males (N = 466)	Females (N = 85)	p
Severity of stenosis	27.87 ± 24.76	23.12 ± 23.18	0.12
ccIMT	0.86 ± 0.19	0.83 ± 0.14	0.20
PT	1.99 ± 1.07	2.03 ± 1.03	0.66
<i>Plaque morphology</i>			
Calcified	109 (23.4%)	26 (30.6%)	0.08
Fatty	92 (19.7%)	22 (25.9%)	
Mixed	265 (56.9%)	37 (43.5%)	
<i>Plaque surface</i>			
Regular	378 (81.1%)	54 (63.5%)	<0.001
Irregular	88 (18.9%)	31 (36.5%)	
<i>Plaque heterogeneity</i>			
Homogeneous	361 (77.5%)	59 (69.4%)	0.11
Heterogeneous	105 (22.5%)	26 (30.6%)	

CI = 0.05–0.26,  $p = 0.003$ ) and PTmax (beta = 0.17, 95% CI = 0.03–0.11,  $p = 0.001$ ) with  $\Delta T_{max}$  (Table 3).

In multiple linear regression analysis, after adjustment for possible covariates, the association between gender and  $\Delta T_{max}$  remained significant (beta = 0.20, 95% CI = 0.14–0.40,  $p < 0.001$ ). Diabetes mellitus and PTmax were also statistically significantly associated with  $\Delta T_{max}$  (beta = 0.15, 95% CI = 0.05–0.24,  $p = 0.003$  and beta = 0.16, 95% CI = 0.03–0.11,  $p = 0.002$  respectively), while hypertension did not reach statistical significance (beta = 0.09, 95% CI = –0.009–0.19,  $p = 0.08$ ).

### 3.4.2. Logistic regression

Logistic regression analysis was performed in order to study the contribution of gender in bilateral high  $\Delta T$ . In univariate logistic regression analysis,

gender (OR = 2.96, 95% CI = 1.57–5.61,  $p = 0.001$ ), diabetes mellitus (OR = 2.03, 95% CI = 1.19–3.47,  $p = 0.01$ ), hypertension (OR = 2.07, 95% CI = 1.10–3.91,  $p = 0.03$ ), CAD severity (OR = 1.73, 95% CI = 1.22–2.45,  $p = 0.002$ ) and PTmax (OR = 1.34, 95% CI = 1.08–1.66,  $p = 0.008$ ) were statistically significantly associated with high  $\Delta T$  in both carotid arteries (Table 3). In multivariate logistic regression analysis, female sex was an independent predictor of bilateral high  $\Delta T$ , when adjusted for diabetes mellitus, hypertension, extent of CAD, maximum plaque thickness and statin intake (OR = 2.78, 95% CI = 1.42–5.45,  $p = 0.003$ ). Moreover, diabetes mellitus (OR = 1.99, 95% CI = 1.12–3.53,  $p = 0.008$ ) and severity of CAD (OR = 1.62, 95% CI = 1.11–2.36,  $p = 0.01$ ) were also found to be independent predictors for bilateral high  $\Delta T$  (Table 4).

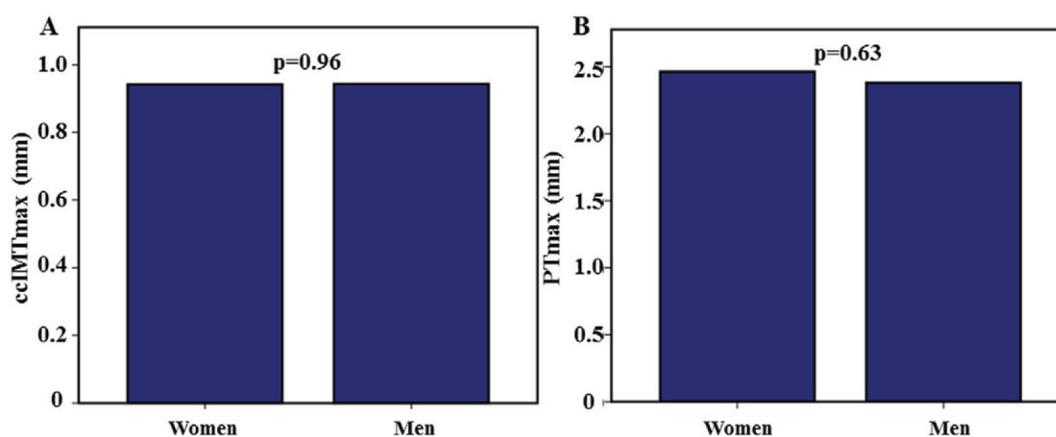


Fig. 1. Comparison of cclMTmax (Panel A) and max Carotid Plaque Thickness (PTmax, Panel B) between men and women. Patient-based analysis.

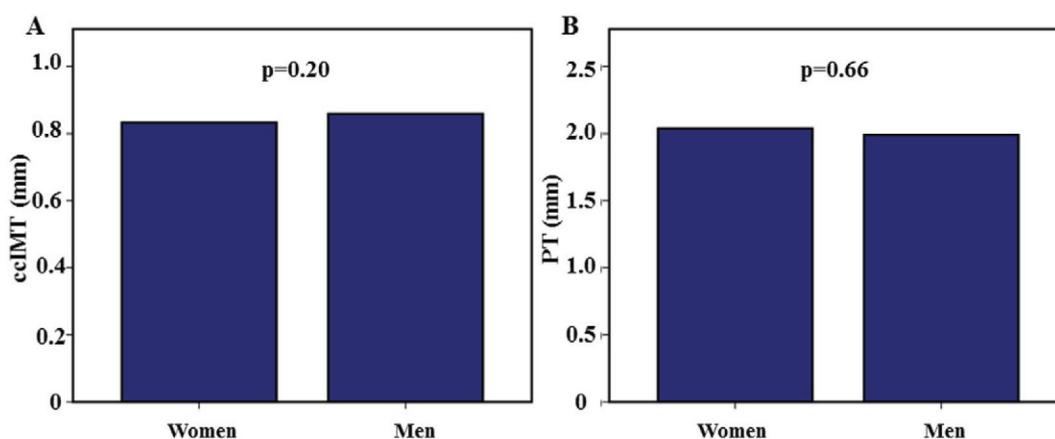


Fig. 2. Comparison of cclMT (Panel A) and Carotid Plaque Thickness (PT, Panel B) between men and women. Vessel-based analysis.

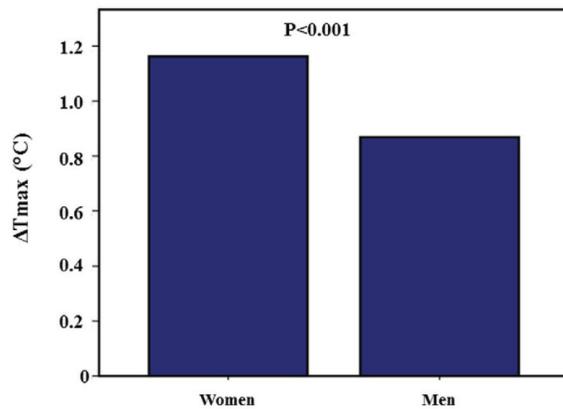


Fig. 3. Comparison of  $\Delta T_{max}$  measurements between males and females. Patient-based analysis.

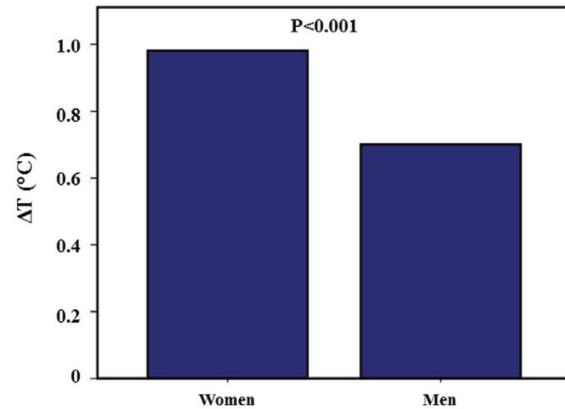


Fig. 4. Comparison of  $\Delta T$  measurements between males and females. Vessel-based analysis.

#### 4. Discussion

In the present study we showed that in patients with CAD: a) there are no significant differences in morphological characteristics of carotid plaques between the two genders; b) women exhibit higher carotid temperatures compared to men; and c) female sex is independently associated with high carotid plaque temperatures, after adjustment for potential cofactors.

According to the results of our study in a high risk population with significant CAD there were no significant differences in ccIMT of carotid arteries between the two sexes in both vessel and patient based analysis. Similar to our findings, in a recent study ccIMT measurements were performed in 1083 patients classified to three risk categories according to the Framingham score. No significant differences were reported in ccIMT between the two genders in all three risk categories [28].

Controversial are the results from imaging studies, regarding the sex-related differences in carotid plaque morphology. In concordance to our findings, in an ultrasound study of 159 asymptomatic patients with at least one cardiovascular risk factor, the incidence of carotid plaques did not differ significantly between the two sexes. More importantly, in the subgroup of patients with carotid atherosclerosis, there was no statistically significant difference in mean and maximum carotid plaque thickness between males and females [11]. In contrast, contrast enhanced ultrasound

revealed higher intraplaque neovascularization in carotid plaques of female patients, implying that in vivo female sex is associated with a vulnerable carotid plaque phenotype.

In our study women had higher carotid artery temperatures, while female sex was an independent predictor of high carotid temperatures bilaterally. Few are the studies evaluating gender-related differences in functional carotid artery characteristics. Most of the information regarding sex-related differences in carotid inflammation is derived from ex-vivo studies, which have presented different results. In specific, intense inflammatory cell infiltration, a large necrotic core and extended intraplaque hemorrhage were more common characteristics in male specimens. In contrast, female carotid plaques were rich in collagen and smooth muscle cells, integrating a more stable phenotype [8-10]. These differences could be attributed to different study populations, patients with significant CAD and intermediate carotid plaques from the one hand and patients with high grade symptomatic or asymptomatic carotid stenosis from the other, respectively. On the other hand, several are the imaging studies showing a male predominance in vulnerable carotid plaque characteristics. More specifically, in the population-based Tromso study, where carotid ultrasound was performed in 3016 asymptomatic men and 3404 asymptomatic women, men had more often softer and fatty plaques in all age groups [29]. Moreover, a recent MRI study of 96 patients with bilateral carotid atherosclerosis undergoing ca-

**Table 3**

Univariate linear and logistic regression derived beta/Odds Ratios (OR) and 95% Confidence Intervals (95% CIs) for  $\Delta T_{max}$  and bilateral high  $\Delta T$  respectively by demographic/anthropometric variables, CAD risk factors and severity and PTmax.

Variables	Univariate linear regression			Univariate logistic regression		
	Beta	95% CI	p	OR	95% CI	p
Gender	0.23	0.16–0.43	<0.001	2.96	1.57–5.61	0.001
Age	0.04	–0.003–0.006	0.44	1.01	0.99–1.04	0.44
Dyslipidemia	0.06	–0.04–0.18	0.22	1.58	0.80–3.10	0.19
Smoking	–0.003	–0.1–0.09	0.95	1.20	0.71–2.05	0.49
Diabetes mellitus	0.17	0.06–0.26	0.002	2.03	1.19–3.47	0.01
Hypertension	0.16	0.05–0.26	0.003	2.07	1.10–3.91	0.03
CAD family history	0.007	–0.09–0.10	0.89	0.78	0.45–1.33	0.36
CAD severity	0.09	–0.006–0.12	0.08	1.73	1.22–2.45	0.002
PTmax	0.17	0.03–0.11	0.001	1.34	1.08–1.66	0.008
Statins	0.06	–0.04–0.16	0.25	1.14	0.64–2.03	0.66

PTmax: maximum bilateral plaque thickness.  
95% CI: 95% Confidence intervals.

rotid endarterectomy revealed higher prevalence of thin/ruptured cap or intraplaque hemorrhage in the contralateral intermediate carotid plaques of men [30]. Sex-related differences seem also to apply in carotid endarterectomy outcomes. Indeed, stroke-protective effect of carotid endarterectomy is higher in men for both symptomatic and asymptomatic carotid stenosis [3,4]. Interestingly, women are characterized by higher risk for operative stroke and death and therefore, female sex is classified as a surgical risk in these patients [31,32].

#### 4.1. Clinical implications

From previous studies strokes have higher incidence, morbidity and mortality in female sex. As the surgical treatment of carotid artery disease is mitigated in women, improved risk stratification models are required, which need to be sex-specific [3,4]. The functional and morphological characteristics of the carotid plaques provide distinct information in males and females. Thus, new markers that could discriminate those women at high risk of stroke are necessary. MWR is safe and radiation free and seems promising as an initial screening tool for detecting high carotid plaque temperatures. The prognostic value of this finding, however, remains to be defined in large prospective studies.

#### 4.2. Study limitations

MWR cannot measure a particular point of the segment under consideration because the sensor of the radiometer receives and measures the temperature of the segment concerned in total. For

**Table 4**

Multiple logistic regression derived Odds Ratios (OR) and 95% Confidence Intervals (95% CIs) for bilateral high  $\Delta T$  by demographic/anthropometric variables, CAD risk factors and severity, PTmax.

Variables	OR	95% CI	p
Gender	2.78	1.42–5.45	0.003
Diabetes mellitus	1.99	1.12–3.53	0.008
Hypertension	1.62	0.83–3.16	0.16
CAD severity	1.62	1.11–2.36	0.01
PTmax	1.26	0.98–1.60	0.07

PTmax: maximum bilateral plaque thickness.  
95% CI: 95% Confidence Intervals.

this reason, the maximum temperature in each measurement is underestimated and hence the calculated  $\Delta T$  is underestimated. Moreover, the depth of maximum penetration varies as it depends on the different dielectric characteristics of the tissues and the wavelength used. With regard to technical biases, we considered it essential to make the measurements in all patients under the same conditions. The potential increased distance of the carotid arteries from the body surface was eliminated by applying slight pressure on the MWR probe. For these reasons, high  $\Delta T$  values found in women can only be attributed to the characteristics of atherosclerotic plaques. Since the study is based on the consecutive recruitment of patients with significant CAD undergoing coronary angiography, the possibility of selection bias is relatively small. Therefore, the resulting underrepresentation of women in the sample, although it should be noted, cannot be considered as a selection bias.

## 5. Conclusions

Female gender is associated with higher carotid artery temperatures, as assessed by MWR, implying an in vivo vulnerable plaque phenotype. Thus, sex-specific differences seem to apply in functional carotid artery characteristics. Whether these differences pose an additional risk for stroke on female gender needs to be investigated in large prospective studies.

#### Conflict of interest

There is no potential conflict of interest.

#### Disclosures

None.

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# Antioxidants in Experimental Ischemian-reperfusion Injury of the Testis: Where are we Heading Towards?

*George Vaos, Nick Zavras*

## **Abstract**

Testicular torsion (TT) is a medical emergency that primarily affects newborns and young adolescents. It causes testicular injury due to the torsion of the spermatic cord and its components, initially in the venous blood flow and finally in the arterial blood flow. Prompt diagnosis and early surgical management are necessary in managing this urgent situation. The process of the pathophysiological events in ischemia-reperfusion is multifactorial and deals with the perception of the oxidative stress responsible for the consequences of ischemia/reperfusion (I/R) stress following TT. Duration and severity of torsion also play a significant role in the oxidative stress. A detrimental result of the defense system of the testes takes place resulting finally in testicular atrophy and impaired function. Antioxidant factors have been experimentally studied in an effort to front this state. They have been classified as endogenous or exogenous antioxidants. Endogenous antioxidants comprise a structure of enzymic enzymatic and non-enzymic enzymatic particles presented within cytoplasm and numerous other subunits in the cells. Exogenous antioxidants include a variety of natural and pharmaceutical agents that may prevent or ameliorate the harmful effects of I/R injury. In this study we review those factors and their ability to enhance the oxidative status of the testis. A feature insight into where we are heading is attempted.

**Key words:** Testis; Torsion; Experimental; Ischemia-reperfusion injury; Antioxidants

**Core tip.** Testicular torsion is an emergency condition, most commonly seen in newborns and adolescents, which can be considered as an ischemia-reperfusion injury. We provide an overview of the molecular pathogenesis of the disease, and the current evidence of antioxidants use in the experimental torsion-detorsion situation. Possible

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adaptation of the experimental factors in the clinical practice is discussed.

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## INTRODUCTION

Testicular torsion (TT), first described by Hunter in 1776<sup>[1]</sup>, is one of the most serious surgical emergencies, deriving from the twisting of the spermatic cord and its contents, and causing decreased blood flow to the affected testis and finally testicular atrophy<sup>[2]</sup>. The testis is exclusively prone to ischemic insults due to anatomical reasons (terminal arteries without anastomoses) and the inflexible properties of the tunica albuginea which restricts satisfactory expansion of the testis<sup>[3]</sup>. Although TT can be detected at any age, it is usually seen during perinatal period and puberty<sup>[4-6]</sup>. Two main types of TT exist: extravaginal and intravaginal<sup>[3]</sup>. Extravaginal TT is usually seen during perinatal period, and is due to the absence of normal fixation between testicular coverings and tunica vaginalis resulting in abnormal motility of the testis within scrotum. Intravaginal TT is most commonly seen in adolescent boys and results from a long mesorchium which allows a greater mobility of the testis within the tunica albuginea<sup>[4]</sup>.

TT has an annual incidence of about 3.8 per 100.000 males less than 18 years<sup>[7]</sup>, and in cases of bilateral torsion, there is evidence that may be inherited<sup>[8]</sup>. If left untreated within 4 to 6 hours, loss of spermatogenic cells will occur<sup>[9]</sup> leading to harmful results such as infertility and subfertility<sup>[10]</sup>. The degree of twisting of the spermatic cord may also play an important role. In animal studies, 720° torsion caused significant reduction blood flow when compared with a twisted spermatic cord of 360° or less<sup>[11]</sup>.

There are two kinds of injuries responsible for testicular necrosis after TT: the first is related to ischemia (I) injury during torsion, and the second to reperfusion (R) injury during detorsion<sup>[12]</sup>. Consequences of the I/R injury are involved in involve testicular cells damage from generation of reactive oxygen species (ROS), proinflam-

matory cytokines and adhesion molecules, lipid peroxidation, apoptosis, anoxia and alteration in microvascular blood flow, which finally lead to testicular atrophy<sup>[13]</sup>. Although the testicular environment is characterized by low oxygen tensions, testes are susceptible to oxidative stress due to the plethora of highly unsaturated fatty acids and the presence of ROS<sup>[14]</sup>.

Antioxidants represent the first line defense of the organism in order to prevent the harmful consequences of I/R injury occurring in the environment of the testicular cell<sup>[15]</sup>. Antioxidants may be classified as endogenous and exogenous<sup>[15]</sup>. Endogenous antioxidants include a variety of enzymic enzymatic and non-enzymic enzymatic molecules that are presented within the cytoplasm. Common existing endogenous antioxidant enzymes include superoxide dismutase (SOD), catalase, and peroxidases<sup>[15,16]</sup>. Exogenous antioxidants include natural derived components such herb productions<sup>[17-25]</sup>, vitamins<sup>[26-31]</sup>, selenium<sup>[32]</sup>, hormones<sup>[33-36]</sup>, hormones receptors<sup>[37,38]</sup>, vascular agents<sup>[39-41]</sup>, phosphodiesterase inhibitors<sup>[42,43]</sup>, anesthetic and non-steroid anti-inflammatory drugs<sup>[44-47]</sup>, mucolytic agents<sup>[48]</sup>, and hyperbaric oxygen<sup>[49]</sup>. All have been used in an effort to prevent the consequences of the oxidative stress in I/R injury.

The aim of this review is to present the pathophysiological changes that take place during I/R injury and to summarize the current literature regarding the role of antioxidants in the prevention of experimental I/R injury. Possible translation from the experimental laboratory studies to clinical practice are described.

## METHODS

We conducted a search focusing on TT and experimental I/R injury in PubMed publishing over the last five years, between 2012 and 2016. The following search terms were used: “testicular torsion”, “experimental ischemia-reperfusion

injury”, “protective agents”. A total number of 22 full papers were extracted.

### A. Pathophysiological alterations during I/R injury

The pathophysiological alterations during I/R injury are multifactorial and difficult to understand. A cascade of events take place during the course of ischemia and further perturbations of biomolecules in cells are seen during the blood re-establishment after reperfusion. The basic mechanisms of I/R are described below.

#### 1) Ischemia injury: the role of $Ca^{2+}$

During ischemia a decrease of cell pH is observed due to accumulation of lactic acid, protons and  $NAD^+$ . To balance these alterations, the cell forces out  $H^+$  via the  $Na^+/H^+$  exchanger system [50]. Thereafter,  $Na^+$  ions are swapped for  $Ca^{2+}$  by the plasmalemmal  $Na^+/Ca^{2+}$  exchanger, which results in increase of  $Ca^{2+}$ , exacerbated furthermore during reperfusion. These huge alterations in  $Ca^{2+}$  stimulate an array of systems, which finally contribute to cell death [50-52]. For instance,  $Ca^{2+}$  entry into the mitochondria via a mitochondrial protein further increases the lethal concentration of  $Ca^{2+}$  [53-55]. In addition, the  $Ca^{2+}$  cytosolic elevation during I/R can trigger the  $Ca^{2+}$ /calmodulin-dependent protein kinases, which further added to cell death and tissue dysfunction [53]. Additionally, the activation of calpains, a family of cysteine proteases by  $Ca^{2+}$  elevation, further degrades a group of intracellular proteins, including cytoskeletal, endoplasmic reticulum, and mitochondrial proteins [56]. Furthermore,  $Ca^{2+}$  forces the creation of calcium pyrophosphate structures and uric acid, a pair that binds to a protein complex called inflammasomes which in turn increase the production of cytokines IL-1 $\beta$ , and TNF, which lead to a cytokine cyclone that irritate further the I/R injury [53].

#### 2) Reperfusion injury: (a) Oxidative stress, and (b) Nitric oxide stress

Studies have shown that during reperfusion, the returned oxygenated blood restores the ATP production but also results in production of ROS, which in turn may modify every biomolecule

found in cells, producing further cell dysfunction (oxygen paradox) [57,58]. Redox molecules derived from nitric oxide (NO), the so called reactive nitrogen species (RNS) interact with ROS and lead to the production of reactive nitric oxide species (RNOS), such as peroxynitrite, responsible for harmful damage of macromolecules, initiation of death of endothelial and parenchymal cells, stimulation and release of pro-inflammatory mediators by various cell groups, and induction of adhesion molecules supporting leukocyte/lymphocyte-endothelial cells interactions, and reduction of protective NO [57-59].

##### (a) Oxidative stress

The classic theory of oxidative stress was that it arises from an imbalance between pro-oxidants versus antioxidants intracellular compounds [39]. Currently, it is believed that oxidative stress is involved in three mechanisms in I/R injury: i) indirect, through non-radical oxidants such as hydrogen peroxide ( $H_2O_2$ ), ii) modulator, via molecular bond, oxidative or nitrosative modification of principle regulatory proteins, and iii) direct damage by oxidant radicals of DNA, proteins, lipids and carbohydrates [53, 60].

Superoxide anion radical ( $O_2^-$ ) is the first product of ROS during I/R injury, and subsequently all the other reactive species are derived from interactions or dismutation with other reactive species [39]. This is supported by experimental studies showing that I/R were considerably attenuated by treatment with SOD or SOD analogues [53, 61, 62].  $O_2^-$  oxidizes various biomolecules and inactivates enzymes such as NADH, creatine kinase, and calcineurin [58]. Sources of  $O_2^-$  are xanthine oxidoreductase, NADPH oxidase, cytochrome P450, and uncoupled nitric oxide species (NOS) [53].

##### (b) Nitric oxide stress

Nitric oxide ( $NO$ ) is elicited during oxidation of arginine to citrulline, through nitrite or nitrate through the action of xanthine oxidoreductase, or by mitochondrial cytochrome c [63, 64].  $NO$  plays a protective role in the vascular system by producing dilation of blood vessels, modulating pla-

telets aggregation and adhesions, and inhibiting leukocyte-endothelial adhesive interactions and angiogenesis [53]. Interactions of NO with O<sub>2</sub> or O<sub>2</sub><sup>-</sup> forming N<sub>2</sub>O<sub>3</sub> or peroxynitrite, are associated with overproduction of NO and O<sub>2</sub><sup>-</sup> resulting in pathophysiological nitrosative and oxidative stress [53].

In summary, the oxidative/nitric oxide stress may have negative impact on the cell function in I/R stress through three ways: i) destruction of cellular macromolecules such as membrane lipids, proteins, and DNA, ii) production of possibly toxic peroxynitrite and other RNOS, and iii) side effects on distinct cellular systems and functions [53].

### **B. Current antioxidant treatment of I/R injury in experimental TT**

Comparable to other tissue-cells which live under aerobic conditions, spermatozoa produce ROS which is a physiological process activity [65]. Moreover, spermatozoa contain an array of ROS scavengers such as SOD, catalase, and substances such as ascorbic acid, taurine, hypotaurine, albumin, and carnitine to balance any ROS high concentration. However, any increased concentration of toxic metabolic products over the ROS scavenging ability, may cause loss of sperm motility and viability [66-68].

A substantial number of experimental studies by using different agents have studied experimental TT focusing on the effect of I/R injury on ipsilateral and contralateral testis, on treatment and prevention of this injury [53]. However, conflicting results are raised due to different animal species, such as rats or pigs, model of I/R injury, age, and technique that has been performed to evaluate the I/R damage [69]. Furthermore, several experimental studies proposed that the contralateral testis is not affected by unilateral torsion [70-72]. Nevertheless, there is evidence that both testes are affected, and contralateral testis is not disturbed by initial removal of the torsed testis and pretreatment with antioxidants [73-75].

There are two therapeutic opportunities to counteract oxidative stress. In the first, the superoxide radical and hydrogen peroxide are eliminated by using specific enzymes such as SOD, catalase, and glutathione peroxidase (GPX) either by admini-

nistration of these enzymes or by increasing them *in vivo* actions. In the second, radical production is prevented by antioxidant scavenging systems [66].

Some authors showed that apigenin may prevent lipid peroxidation and protect the antioxidant system [76, 77]. We also found a decrease in immunoreactivity of TNF and IL-10, suggesting a synergistic action of apigenin with endogenous IL-10. This antioxidant effect may be due to the H<sup>+</sup> donation of the OH<sup>-</sup> aromatic group [6]. Among others, we demonstrated [42] that intraperitoneal injection of erythropoietin and sildenafil protects against I/R injury.

Amlodipine is a calcium channel blocker with antioxidants properties, effectively decreasing experimental vascular ischemia-induced damage in the liver and other tissues [78]. Dogan et al [79] examined the effect of amlodipine in a rat model of TT injury. They found a significant decrease of TNF and transforming growth factor-beta in the treatment group, decreases in free radicals and increases in antioxidants such as SOD and GSH.

*Goji berry* (GB) is a traditional Chinese plant product, from the Solanaceae family with antioxidant effects. In experimental studies, GB has been shown to reduce blood sugar and lipid levels, and exhibits male fertility-enhancing effects, immunomodulating, antitumor, and anti-fatigue properties. GB is composed from six monosaccharides and influences its effects via ion exchange chromatography. In a rat experimental study of TT, administration of GB reduced I/R injury by the antioxidant effects of GB [9].

Mannitol is usually administered before partial nephrectomy to reduce renal damage due to intravascular volume expansion and its free-radical scavenging [80]. Kurt et al [81] in a rat model of TT, demonstrated that the treatment with mannitol group had less seminiferous tubules disruptions when compared to the TT group without mannitol treatment.

Hesperidin, is another antioxidant compound belonging to flavones with significant antioxidant effects in many tissues [82,83]. Hesperidin was given intraperitoneally by Celik et al [12] in an experimental group of rats underwent TT and the sample was compared to control group. They found a re-

duced effect on histological examinations of the hesperidin group when compared to control, while MDA levels were increased, and SOD, catalase and GSH levels were decreased as compared to the control group, concluding that hesperidin has positive results in cases of TT.

Polyphenolic catechins are components of green tea and comprise (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin gallate, and (-)-epigallocatechin gallate (EGCG) [84]. Sugiyama et al [85] studied an experimental rat model by producing 4 hours' ischemia and giving orally a single dose of (-)-EGCG 1 hour before reperfusion. Histologic examination 4 weeks after reperfusion found that EGCG protected against testicular damage from I/R injury and inhibited a further decrease in the activity of SOD.

Dexketoprofen, is a racemic mixture from the arylpropionic acid family of NSAIDs. Yildirim et al [86] studied the intraperitoneal effect of dexketoprofen in a rat model of I/R injury. Malondialdehyde (MDA) levels were investigated in tissue and serum of torsioned testicles in the dexketoprofen group and control group. They found a statistically lower serum MDA levels in the dexketoprofen group compared to control group, and decreased, but not statistically significant, pathological changes in the spermatogenic cells of the control group.

Tyrphostin AG 556 is a tyrosine kinase inhibitor and belongs to the tyrphostin group which has been assessed in animal models of spinal cord and coronary I/R injury [87,88]. Karaguzel et al [89] investigated the effect of Tyrphostin AG 556 by giving it intraperitoneally and measured the following biochemical parameters: MDA, ischemia modified albumin, signal peptide-CUB (complement C1r/C1s, Uegf, and Bmp1), epidermal growth factor like domain-containing protein1, oxidative stress index, total oxidant status, and total antioxidant status. They concluded that tyrphostin AG 556 has a protective effect on I/R injury

The protective effect of udenafil citrate, piracetam and dexmedetomidine in different doses was evaluated by Tuglu [90] and found that all these agents have antioxidant effects on I/R injury.

Grape seed proanthocyanidin extract has been reported to display better antioxidant activity than other antioxidants such as vitamin C, vitamin E, and gallic acid [91]. Bayalti et al [92] examined the protective effect of grape seed proanthocyanidin after TT performed for 2 hours and administered it daily for a week prior to torsion/detorsion. They reported that grape seed proanthocyanidine prohibited the rise of MDA, apoptosis and endothelial nitric oxide synthase (eNOS) expression and enhanced testicular morphology.

Carnosine, is a dipeptide found in high amounts in mammalian tissues [93]. Abbasoğlu et al [94] demonstrated that carnosine treatment has a protective effect on pro-oxidant and antioxidant status in rat testes with I/R injury.

Ozone has been studied as a potential therapeutic agent for the treatment of various physiopathologic conditions expressing high levels of ROS [95,96]. Ekici et al [97] assessed the potential effects of ozone in testicular function and morphology in a rat experimental study, in a mixture of ozone/oxygen and compared the results with those of melatonin. They found similar results in the amelioration of I/R injury between melatonin and ozone, but in different pathways.

Ethyl pyruvate, a ROS scavenger, has been found to ameliorate in different conditions such as sepsis, acute pancreatitis, burn, radiation injury and hemorrhagic shock [98, 99]. Turkmen et al [100] reported that ethyl pyruvate has a positive effect on torsion-detorsion associated I/R injury in an experimental rat model.

Carvedilol is a third generation vasodilator agent which has been used in the treatment of hypertension, congestive heart failure and ischemic heart disease [101, 102]. Parlaktas et al [103] investigated the antioxidant effects of carvedilol against I/R injury, and found a decrease in MDA and protein carbonyl and an increase in the level of antioxidant enzymes SOD, and GPX, but not histopathological changes against the control group. They concluded, that carvedilol may have a potential therapeutic value and improve fertility in the clinical practice in patients with TT.

Jiang et al [104] investigated the effect of intraperitoneally injected hydrogen rich saline solution

on the protection against testicular damage induced by I/R injury in rats. They found a significant decrease of MDA and a significant improvement of SOD activity in the group of rats which received hydrogen rich saline solution. Therefore, the concluded that hydrogen rich saline solution may have a protective and therapeutic action against testicular damage.

Inhaled hydrogen gas has been shown to produce a therapeutic activity in a middle cerebral artery occlusion in a rat model and reduce infarct volumes of brain, liver, and myocardium [105, 106]. Lee et al [107] studied the possible therapeutic properties of inhaled 2% hydrogen in pubertal rat model underwent testicular I/R injury. The results of histopathological and biochemical studies suggested that inhalation of hydrogen gas has anti-apoptotic and anti-oxidant properties in cases of TT.

Alpha-lipoic acid is an eight-carbon endogenous cofactor which works against oxygen radicals [108]. It is established that  $\alpha$ -lipoic acid catches hydroxyl and nitric oxide radicals, peroxy-nitrite anions and hydrogen peroxide. Moreover,  $\alpha$ -lipoic acid may act indirectly by enhancing the level of other natural antioxidants such as glutathione, ascorbic acid and tocopherol [109-112]. Ozbal et al [108] investigated the role of  $\alpha$ -lipoic acid in testicular I/R injury in rats and concluded that it is a potential beneficial agent in preserving testicular function.

Genistein is an isoflavone extracted by soy [113] which displays anti-oxidant and anti-inflammatory properties [114]. Furthermore, genistein promotes steroidogenesis by restriction progesterone synthesis and decreases secretion of cortisol and corticosterone in mature female pigs [115]. In addition, it has a protective role against gamma irradiation-induced testicular dysfunction [116]. Recently, Al-Maghrebi et al [117] reported that genistein protects the extracellular matrix of the testis which is responsible for the structural integrity of the testicular components, and prevents spermatogenesis's suppression, mitigating oxidative stress and apoptosis in experimental testicular I/R injury.

Nuclear factor kappa B plays a crucial role in

immune response, cellular proliferation, inflammatory, and apoptosis [118]. Pyrrolidine dithiocarbamate (PDTC) is a stable low-molecular thiol compound which acts by neutralizing ROS. Kemahli et al [119] studied the antioxidant effect of PDTC in a TT model and found that administration of PDTC exaggerates the antioxidant system by lowering MDA levels, increasing SOD activity and improving Johnson scores of biopsy specimen.

Urocortin, is a 40-amino acid peptide found in different organs, such as digestive tract, cardiovascular and reproductive system [120]. For instance, urocortin has been shown that protect cardiovascular system against I/R injury [121]. Samii et al [122] investigated the role of urocortin in testicular apoptosis in an experimental I/R rat model and found a cytoprotective role in germ cells through the activation of anti-apoptotic proteins.

Melatonin is an endogenous compound secreted by the pineal gland and influences reproduction via its activity on the hypothalamus [123]. Kurcer et al [124] reported that melatonin protects testicular tissue against oxidation and alleviates histopathologic changes after experimental testicular I/R injury. Metformin belongs to the biguanide family and has the capacity to reduce ROS [125]. Asghari et al [126] investigated a combined use of melatonin and metformin in a rat model and found that may protect the testes from I/R injury by restoring SOD activity, and MDA and myeloperoxidase levels.

Very recently Erol et al [127] investigated the effect of a antioxidant factors combination, constituting either by l-carnitine, fructose, citric acid, ascorbic acid, cyanocobalamin, selenium, coenzyme Q10, zinc and folic acid or fructose, cellulose microcrystalline, pygeum shell, L-arginine, L-carnitine, zinc, vitamin E, folic acid, vitamin B6, sodium selenite, and hydroxypropyl methyl cellulose. They found that combined antioxidants were more effective than one protective antioxidant by reducing apoptosis and preventing I/R injury.

### C. Antioxidants and I/R injury in clinical practice

The large body of experimental studies demonstrated undoubtedly that oxidative stress is a dominant factor in the creation of testis impairment after I/R injury. Furthermore, all these antioxidant compounds have been sought to be clearly capable to protect testicular function from oxidative stress. However the relationship between experimental results and clinical practice has not come together until now. A feature mandatory pursuit is to advance understanding of the basic mechanism of oxidative stress in the male reproductive tract and to develop optimizing antioxidant factors in order to treat the pathological consequences from imbalance in the oxidation state of testicular tissue. These mandatory demands are beyond laboratory ways that outline the present approach to counterbalance the deleterious effects of TT.

### CONCLUSION

Currently, a large number of studies investigate the role of I/R injury in experimental animal models and many antioxidants and free radical scavengers have been studied to indicate their possible application in human beings. However, the molecular mechanism by which these agents may control the harmful effect of TT has to be clarified. Moreover, experimentally checked drugs or compounds still anticipate clinical utilization. Additional experimental and future clinical studies have to be performed to further assess the effects on antioxidant therapy.

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Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards?  
Vaos G et al. Antioxidants in experimental testicular ischemia-reperfusion injury*

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# The neuroprotective agent Rasagiline mesylate attenuates cardiac remodeling after experimental myocardial infarction

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## Abstract

**Aim:** Rasagiline mesylate (N-propargyl-1 (R)-aminoindan) (RG) is a selective, potent irreversible inhibitor of monoamine oxidase-B with cardioprotective and anti-apoptotic properties. We investigated whether it could be cardioprotective in a rat model undergoing experimental myocardial infarction (MI) by permanent ligation of the left anterior descending coronary artery.

**Methods and results:** RG was administered, intraperitoneally, for 28 days (2 mg/kg) starting 24 h after MI induction. Echocardiography analysis revealed a significant reduction in left ventricular end-systolic and diastolic dimensions and preserved fractional shortening in RG-treated compared with normal saline group at 28 days post-MI ( $31.6 \pm 2.3$  vs.  $19.6 \pm 1.8$ ,  $P < 0.0001$ ), respectively. Treatment with RG prevented tissue fibrosis as indicated by interstitial collagen estimation by immunofluorescence staining and hydroxyproline content and attenuated the number of apoptotic myocytes in the border zone (65%) as indicated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Caspase 3 relative protein levels were significantly decreased in the non-infarcted myocardium. Markedly decreased malondialdehyde levels in the border zone indicate a reduction in tissue oxidative stress.

**Conclusions:** Our study demonstrates a positive effect of RG in the post-MI period with a significant attenuation in cardiac remodelling.

**Keywords:** Rasagiline mesylate; Myocardial infarction; Cardiac remodelling; Fibrosis; Apoptosis

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## Introduction

Myocardial infarction (MI) remains one of the most dramatic presentations of coronary artery disease with left ventricular remodeling (LVR) being a significant factor of post-MI prognosis.[1] LVR is a process of gradual cardiac enlargement, dysfunction, and typical molecular changes such as increased cell death, collagen accumulation, and oxidative stress. Cell death is the ‘primum movens’ of the process.[2] New insights in the pathobiology of myocardial ischemic injury suggest that myocyte loss during the acute stage involves both apoptotic and non-apoptotic cell death, thus enabling the development of new pharmacological agents.[3] Monoamine oxidase (MAO) inhibitors have been shown to be effective against myocardial ischemia/reperfusion injury.[4] In the present study, we investigated Rasagiline mesylate (RG) effects in LVR after a permanent ligation MI model. This experimental model permits the long-term study of the LVR as previously described.[5, 6] RG is a potent, selective, irreversible monoamine oxidase-B (MAO-B) inhibitor, developed to prolong the action of dopamine in the brain[7] and is an FDA-approved drug, used to treat Parkinson’s disease. It has neuroprotective and anti-apoptotic properties in a variety of *in vitro* and *in vivo* animal models relevant to Parkinson’s disease.[8-11] RG can rescue degenerating dopamine neurons through inhibiting death signal transduction initiated by the mitochondria permeability transition pore.[12] Kleiner *et al.*[13] reported the potential cardioprotective property of the S-isomer of RG, TVP1022, a non-MAO B inhibitor, in neonatal rat ventricular myocyte cultures, with attenuation of doxorubicin cardiotoxicity, manifested by inhibition of cleaved caspase 3 levels increase and reversal of the decline of Bcl-2/Bax ratio. More recent studies demonstrated that TVP1022 attenuated cardiac remodelling and kidney dysfunction in an experimental volume overload-induced congestive heart failure model[14] and preserved mitochondrial integrity via activation of the PKC/GSK-3 $\beta$  pathway in a rat model of ischemia/reperfusion injury, when given before induction of ischemia.[15] Regarding the cardiovascular ef-

fects of RG, it has no sympathomimetic activity[16] nor causes significant changes in cardiac hemodynamics.[17]

In view of the major role of apoptosis and oxidative stress in the pathogenesis of cardiac LVR, we investigated the cardioprotective and anti-apoptotic properties of RG in a rat model of permanent MI and long-term LVR.

## Methods

### Experimental model

Experiments were conducted in 6 month male Wistar rats (350–400 g) maintained in the animal facility of BRFAA. All animals were housed on a 12 h light–dark cycle in a room at a constant temperature ( $22 \pm 1^\circ\text{C}$ ), humidity control, and with *ad libitum* access to tap water and standard rodent diet. The investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985) and to the National legal framework (P.D. 56/2013) in harmonization to the *European Directive 63/2010*. [18]

The study included three groups ( $n = 10$  rats per group). Sham: Thoracotomy without MI induction or any treatment, RG: MI and RG, 2.0 mg/kg/day, N/S: MI and normal saline (N/S) 0.9%/day. RG or N/S was administered by intraperitoneal injections,[19, 20] for 28 days, beginning 24 h post-MI.

### Transthoracic echocardiography

The rats were anesthetized with 1.0% isoflurane by mask and situated in the supine position on a warming pad. The chest was shaved and electrocardiogram limb electrodes were placed. Cardiac function ( $n = 10$  rats per group) was assessed by two-dimensional targeted M-mode echocardiography imaging from the left parasternal short axis view at the level of greatest left ventricular (LV) dimension (Vivid 7, GE, 13 MHz linear transducer), as previously described,[21-24] at the following time intervals: baseline (pre-MI induction), 7, 14 and 28 days post-MI induction. Images were analysed offline

using the Echopac PC SW 3.1.3/software (GE). The LV end-diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) were measured. The percentage of LV fractional shortening (FS),  $FS (\%) = [(LVEDD - LVESD) / LVEDD] \times 100$  was calculated.

#### **Ligation of the left anterior descending coronary artery**

MI was induced surgically by a permanent ligation of the left anterior descending (LAD) coronary artery. Surgery was performed under deep isoflurane anesthesia (5% in 0.8 l/min O<sub>2</sub> for induction anesthesia and 3% for intubation and maintenance of anesthesia) determined by total absence of reaction to pain under spontaneous respiration; all efforts were made to minimize suffering of the animals. Left thoracotomy was performed at the fourth intercostal space to expose the heart and LAD coronary artery. A 7-0 polypropylene suture (Prolene, Ethicon, Germany) was then used to ligate permanently the LAD coronary artery, and the incision site was closed using standard surgical techniques with absorbable suture 4/0 (Vicryl, Ethicon, Germany).[25] Electrocardiography was used to demonstrate ST-segment elevation and thereby confirm the success of surgery. The sham group underwent the same surgical procedure without LAD coronary artery occlusion. At the endpoint of the experiment (28th day), the hearts were excised, and the area extending 1.0–2.0 mm from the infarct scar was considered to represent the border zone (BZ), while the rest of the LV was considered to represent the non-infarcted remote myocardium (Remote Region, RR).[26]

#### **Determination of myocardial infarct area (infarct area/area at risk%, I/AAR%)**

At the endpoint of the experiment, the hearts ( $n = 5$  rats per group) were excised and stained with Evans Blue, through the aorta, in order to reveal the normally perfused part of the myocardium. Subsequently, 1% triphenyltetrazolium chloride (TTC, in PBS, pH = 7.4) was injected, and the heart was incubated at 37°C for 20 min, in order to determine the ischemic and the inf-

arcted area. After staining, the heart was stored in –80°C and then sliced into 5 mm sections. Evans blue stained (blue staining, non-ischemic area), TTC stained (red staining, ischemic area), and non-TTC stained (white, infarct area) area were analysed. The ischemic region (area at risk) was determined as the percentage of red plus white in relation to the total area (red plus white plus blue). Infarct size was determined as the percentage of white compared with the total area of white plus red as previously described.[27] The non-ischemic, ischemic, and infarct regions were quantified by ImageJ software. Calculations were averaged over all sections from each heart.

#### **Immunofluorescent staining**

Frozen tissue sections (10 µm thick) from the three experimental groups 28 days post-MI were fixed with acetone/methanol at ?20°C for 20 min and then used for immunolabeling. The anti-desmin monoclonal antibody (1:50 dilution, D33, DAKO Carpinteria, CA) and the anti-collagen- $\alpha$ I polyclonal antibody (1:300 dilution, LF-67, kindly provided by Dr. Larry Fisher, NIH, USA). The appropriate secondary antibodies (conjugated with AlexaFluor-594 and AlexaFluor-488) from Molecular Probes (Leiden, Netherlands), used in 1:1200 dilutions. All the antibodies were incubated in 2% BSA in PBS with 0.1% Tween-20 for 3 h at room temperature. Sections were mounted with fluorescent mounting medium from DAKO (Carpinteria, CA). For confocal imaging, a Leica TCS SP5, DMI6000, microscope (inverted, with the acquisition software LAS-AF, at 23–24°C; Leica Microsystems, Wetzlar, Germany) was used. For the collagen analysis, three sections per animal for the BZ and five sections per animal for the RR were analysed. Each section was 0.5 mm apart and stained with the anti-collagen- $\alpha$ I polyclonal antibody as described above. The extent of collagen content was graded from 0 to 4, according to the amount of red pixels as a percentage of total pixels in the given section (*Figure 2A–C*). Grade 0, 1, 2, 3, and 4 correspond to 0–5%, 5–10%, 10–20%, 20–40% and more than 40% red pixels respectively, as previously described.[21]

### **Fibrosis assay-hydroxyproline assay**

Quantification of myocardial hydroxyproline (HOP) concentrations, an indicator of collagen content, was performed as previously described.[28] Briefly, the tissue was minced, its mass determined, and hydrolyzed overnight in 2 mL of 6 M hydrochloric acid at 110°C. Subsequently, 10 µL hydrolysate was mixed with 150 µL isopropanol, then 75 µL of 1.4% chloramine-T (Sigma, St. Louis, MO) in citrate buffer and oxidized at room temperature for 10 min. One millilitre of Ehrlich's reagent (1.5 g of 4-(dimethylamino) benzaldehyde, 5 mL ethanol, 338 µL sulfuric acid, 15 mL isopropanol) was added and incubated for 30 min at 55°C followed by extinction measurement at 558 nm. From the initial overnight hydrolysate samples, 5 µL was diluted 10 times with 10 mM Tris-HCl, pH = 8.8, and protein concentration was estimated by the Bradford assay (Sigma). Therefore, results were reported as relative HOP absorption values at 558 nm normalized to protein concentration as estimated by Bradford extinction measurement at 595 nm. Measurements of each group were performed in triplicate, and standard deviation was less than ±10%.

### **Malondialdehyde assay**

Lipid peroxide formation was determined by the presence of thiobarbituric acid reactive substances which can be measured colorimetrically, as previously described[29] in RG, N/S, and Sham group ( $n = 5$  rats, per group). Malondialdehyde (MDA), an end product of lipid peroxidation, can be found in most biological samples, is considered as a marker of lipid peroxidation and provides an estimation of oxidative stress.[29, 30] Results are expressed as nanomole of MDA per milligram of protein.

### **Terminal deoxynucleotidyl transferase dUTP nick-end labeling assay**

Apoptotic cells were identified by immunofluorescent staining, with terminal deoxynucleotidyl transferase and terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, on frozen cardiac tissue sections, as previ-

ously described.[21] Briefly, four sections for each heart region (BZ or RR) were analysed by two independent, blinded observers. Each section was 150 to 200 µm apart from the previous one, so a total thickness of 0.6 to 0.8 mm of tissue was analysed. The total number of TUNEL positive nuclei in the given section was counted. The negative control was a serial section in which the terminal transferase enzyme was omitted. The positive control was a DNase-treated section.

### **Western blot analysis**

Whole tissue protein extracts (RR, BZ, Sham,  $n = 5$  rats per group) were homogenized in extraction buffer containing 10 mM Tris (pH 6.8), 2 mmol/L EDTA, 0.2% SDS, 0.2% DOC, 1 mmol/L  $\text{Na}_3\text{VO}_4$ , 2 mM NaF, 2 mmol/L DTT, 0.5 mmol/L PMSF, and protease inhibitors (Protease Inhibitor Cocktail, Sigma-Aldrich). The homogenates were sonicated and centrifuged for 10 min at 10 000 rpm at 4°C. Protein concentration was determined by the Bradford assay. Total protein lysates (50 µg) were resolved in 10% sodium dodecyl sulphate (SDS)- polyacrylamide gels and transferred to polyvinylidene difluoride (PVDF) membranes (Porablot PVDF membranes, Macherey-Nagel). Membranes were incubated with antibodies directed against: Bcl-2 (1:400 dilution, sc-492, Santa Cruz Biotechnology), Bax (1:400 dilution, sc-7480, Santa Cruz Biotechnology), cleaved Caspase-3 (1:500 dilution, Asp175, Cell Signaling Technology), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:3000 dilution, AM4300, Applied Biosystems). Band visualization was performed using the enhanced chemiluminescence detection system (ECL, Amersham Biosciences, PA, USA), and quantification was accomplished using the computerized imaging program Quantity One Basic Software (Biorad Laboratories). The values were normalized to GAPDH intensity levels.

### **Real-time RT-PCR (qRT-PCR)**

Total RNA was extracted (RR, BZ, Sham,  $n = 5$  rats per group) using the TRIzol reagent according to the manufacturer's protocol (Life Technologies-Invitrogen). One microgram of total

RNA was used to perform reverse transcription and cDNA was generated using the Moloney Murine Leukemia Virus Reverse Transcriptase. Primers used for the PCR produced by Integrated DNA Technologies (Leuven, Belgium) and were for TGF- $\beta$ 1: Sense 5' GGGCTTTCGCTTCAGTGCT 3', Antisense 5' TCGGTTTCATGTCATGGATGGT 3', Collagen I: Sense 5' TGGTCCTCTGGCATTGC 3', Antisense 5' CACTGCCAGGGTTACCATCA 3', TIMP-2: Sense 5' GGAGGAAAGAAGGAATAT CTAATTGCAG 3', Antisense 5' CCAGGGCACAAT AAAGTCACAGA 3', and GAPDH: Sense 5' CAACTCCCTCAAGATTGTCAGCAA 3', Antisense 5' GGCATGGACTGTGGTCATGA 3'. qRT-PCR was performed using the LightCycler 480 (Roche Mannheim, Germany). Briefly, each 20  $\mu$ L reaction contained 2  $\mu$ L cDNA (20 ng of total RNA), each primer at 200 nM and 10  $\mu$ L of KAPA SYBR FAST qPCR master mix (KAPA BIO, Boston MA, USA). After an initial denaturation step at 95°C for 10 min, the PCR conditions were: 95°C X 30 s, 60°C X 40 s, 72°C X 40 s, 40 cycles. All samples

were run in duplicate, and the mean value was used for all further calculations. The  $2^{-\Delta\Delta CT}$  method analysis of relative gene expression using qRT-PCR and the  $2(-\Delta\Delta C(T))$  method were used to calculate the relative changes in gene expression. All data were normalized by GAPDH levels and expressed as % relative to controls, as previously described.[31]

### Statistical analysis

Statistical comparisons were performed using analysis of variance (ANOVA) with Bonferroni/Dunn post-hoc test or the unpaired Student's t-test where appropriate. Data are presented as mean  $\pm$  SE and were analysed by using Statview 5.0 (Abacus Concepts, SAS Institute, Cary, USA). A  $P < 0.05$  value was considered significant. Echocardiography data are presented in Table 1. In addition, analysis of variance with Bonferroni/Dunn post-hoc test repeated values analysis (echocardiography data) was used to compare the effects over time within the groups, and the p values are presented in Supporting Information, *Table S1*.

**Table 1** LV function echocardiography analysis

	Pre-MI	7 d	14 d	28 d
<b>Sham (n = 10)</b>				
Heart rate	330.66 $\pm$ 5.72	329.44 $\pm$ 7.09	341.44 $\pm$ 8.39	338.18 $\pm$ 4.43
LVEDD, mm	7.74 $\pm$ 0.19	7.97 $\pm$ 0.17	7.97 $\pm$ 0.16	7.77 $\pm$ 0.15
LVESD, mm	4.52 $\pm$ 0.14	4.74 $\pm$ 0.09	4.62 $\pm$ 0.11	4.53 $\pm$ 0.11
IVSd, mm	1.74 $\pm$ 0.02	1.81 $\pm$ 0.01	1.77 $\pm$ 0.01	1.77 $\pm$ 0.01
LVPWTd, mm	1.74 $\pm$ 0.02	1.81 $\pm$ 0.01	1.77 $\pm$ 0.01	1.77 $\pm$ 0.01
IVSs, mm	2.78 $\pm$ 0.02	2.67 $\pm$ 0.05	2.82 $\pm$ 0.01	2.81 $\pm$ 0.01
LVPWs, mm	2.78 $\pm$ 0.02	2.67 $\pm$ 0.05	2.82 $\pm$ 0.05	2.80 $\pm$ 0.04
LVFS, %	41.75 $\pm$ 0.53	40.51 $\pm$ 0.60	41.98 $\pm$ 0.46	41.68 $\pm$ 0.65
LVEF, %	80.20 $\pm$ 0.53	78.89 $\pm$ 0.67	80.44 $\pm$ 0.46	80.11 $\pm$ 0.65
LVr/h	2.22 $\pm$ 0.06	2.26 $\pm$ 0.03	2.25 $\pm$ 0.05	2.19 $\pm$ 0.04
<b>RG (n = 10)</b>				
Heart rate	331.16 $\pm$ 10.23	294.10 $\pm$ 3.74***	296.50 $\pm$ 6.06	302.00 $\pm$ 4.98
LVEDD, mm	7.66 $\pm$ 0.14	8.59 $\pm$ 0.16*	8.72 $\pm$ 0.22*	8.90 $\pm$ 0.24***
LVESD, mm	4.36 $\pm$ 0.77	6.18 $\pm$ 0.18****	6.01 $\pm$ 0.33**	6.14 $\pm$ 0.37***
IVSd, mm	1.77 $\pm$ 0.02	1.53 $\pm$ 0.03****	1.47 $\pm$ 0.07***	1.48 $\pm$ 0.07***
LVPWTd, mm	1.77 $\pm$ 0.02	1.75 $\pm$ 0.02**	1.51 $\pm$ 0.04****	1.51 $\pm$ 0.05***
IVSs, mm	2.79 $\pm$ 0.04	2.06 $\pm$ 0.07****	2.19 $\pm$ 0.15**	2.27 $\pm$ 0.15***
LVPWs, mm	2.79 $\pm$ 0.04	2.32 $\pm$ 0.07***	2.27 $\pm$ 0.30**	2.22 $\pm$ 0.47***
LVFS, %	43.09 $\pm$ 0.41	28.06 $\pm$ 1.53****	31.39 $\pm$ 2.14***	31.55 $\pm$ 2.27***
LVEF, %	81.55 $\pm$ 0.39	62.31 $\pm$ 2.39****	66.07 $\pm$ 3.57***	66.96 $\pm$ 3.49***
LVr/h	2.17 $\pm$ 0.42	2.29 $\pm$ 0.07	2.93 $\pm$ 0.16**	3.01 $\pm$ 0.21**
<b>N/S (n = 10)</b>				
Heart rate	328.63 $\pm$ 6.57	329.37 $\pm$ 6.20†††	342.90 $\pm$ 8.84	351.43 $\pm$ 4.97
LVEDD, mm	7.66 $\pm$ 0.16	8.96 $\pm$ 0.24***	9.17 $\pm$ 0.22***	9.33 $\pm$ 0.22****
LVESD, mm	4.46 $\pm$ 0.11	6.78 $\pm$ 0.26****†	7.16 $\pm$ 0.33****††	7.52 $\pm$ 0.30****††
IVSd, mm	1.79 $\pm$ 0.02	1.37 $\pm$ 0.06****††	1.31 $\pm$ 0.06****†	1.24 $\pm$ 0.05****†††
LVPWTd, mm	1.79 $\pm$ 0.02	1.69 $\pm$ 0.01****†	1.37 $\pm$ 0.04****††	1.30 $\pm$ 0.04****†††
IVSs, mm	2.83 $\pm$ 0.04	1.78 $\pm$ 0.11****†	1.83 $\pm$ 0.15****†	1.66 $\pm$ 0.13****†††
LVPWs, mm	2.83 $\pm$ 0.04	2.31 $\pm$ 0.04***	1.97 $\pm$ 0.32****†	1.78 $\pm$ 0.38****†††
LVFS, %	41.81 $\pm$ 0.45	24.38 $\pm$ 1.77****†	22.29 $\pm$ 2.01****†††	19.58 $\pm$ 1.82****††††
LVEF, %	80.27 $\pm$ 0.46	56.20 $\pm$ 3.02****	52.24 $\pm$ 3.51****†††	47.30 $\pm$ 3.36****††††
LVr/h	2.14 $\pm$ 0.045	2.52 $\pm$ 0.09*†	3.38 $\pm$ 0.16****†	3.63 $\pm$ 0.17****††

LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; IVSs, intraventricular septum systole; IVSd, intraventricular septum diastole; LVPWTs, left ventricular posterior wall thickness systole; LVPWTd, left ventricular posterior wall thickness diastole; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVr/h, LV radius to PWTd ratio; d, days post-MI. Values in mean  $\pm$  SE (SEM), \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$  vs. Sham, † $P < 0.05$ , †† $P < 0.01$ , ††† $P < 0.001$ , †††† $P < 0.0001$  vs. RG.

## Results

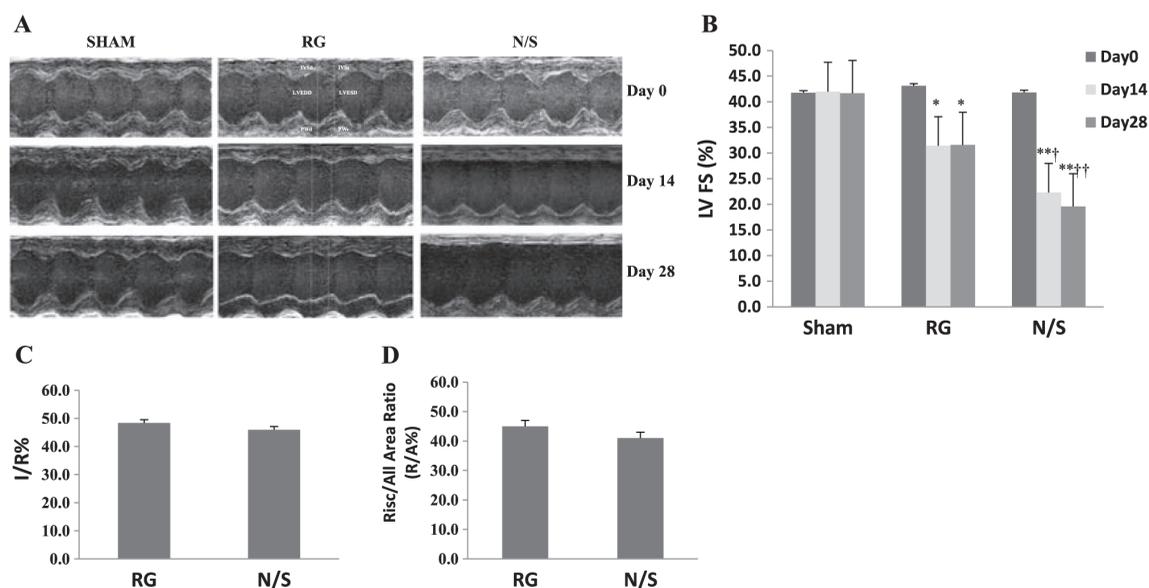
### RG improves cardiac function without altering infarct size

To determine whether RG could improve cardiac function, in a 28 days (post-MI) treatment model, echocardiography analysis was performed (Table 1 and Supporting Information, Table S1). Baseline (pre-MI induction) measurements were similar in all groups. Figure 1A displays representative 2D targeted M-mode images. LVFS (%) was decreased both in RG and N/S-treated rats compared with Sham group at 7, 14, and 28 days post-MI induction (Figure 1B and Table 1). However, RG treatment diminished the increase in LV end-systolic diameter and consequently preserved the FS reduction compared with N/S-treated group at 14 days ( $31.4 \pm 2.1$  vs.  $22.3 \pm 2.0$ ,  $P < 0.0001$ ) and 28 days ( $31.6 \pm 2.3$  vs.  $19.6 \pm 1.8$ ,  $P < 0.0001$ ), respectively (Table 1). In addition, no significant difference was seen in the reduction of infarct/risk area ratio (%) between RG and N/S-treated rats. Quantification diagrams (Figure 1C and D) show infarct/risk area ratio (%) and infarct/all area ratio (%) between groups, respectively. The last is used as internal control of the method.

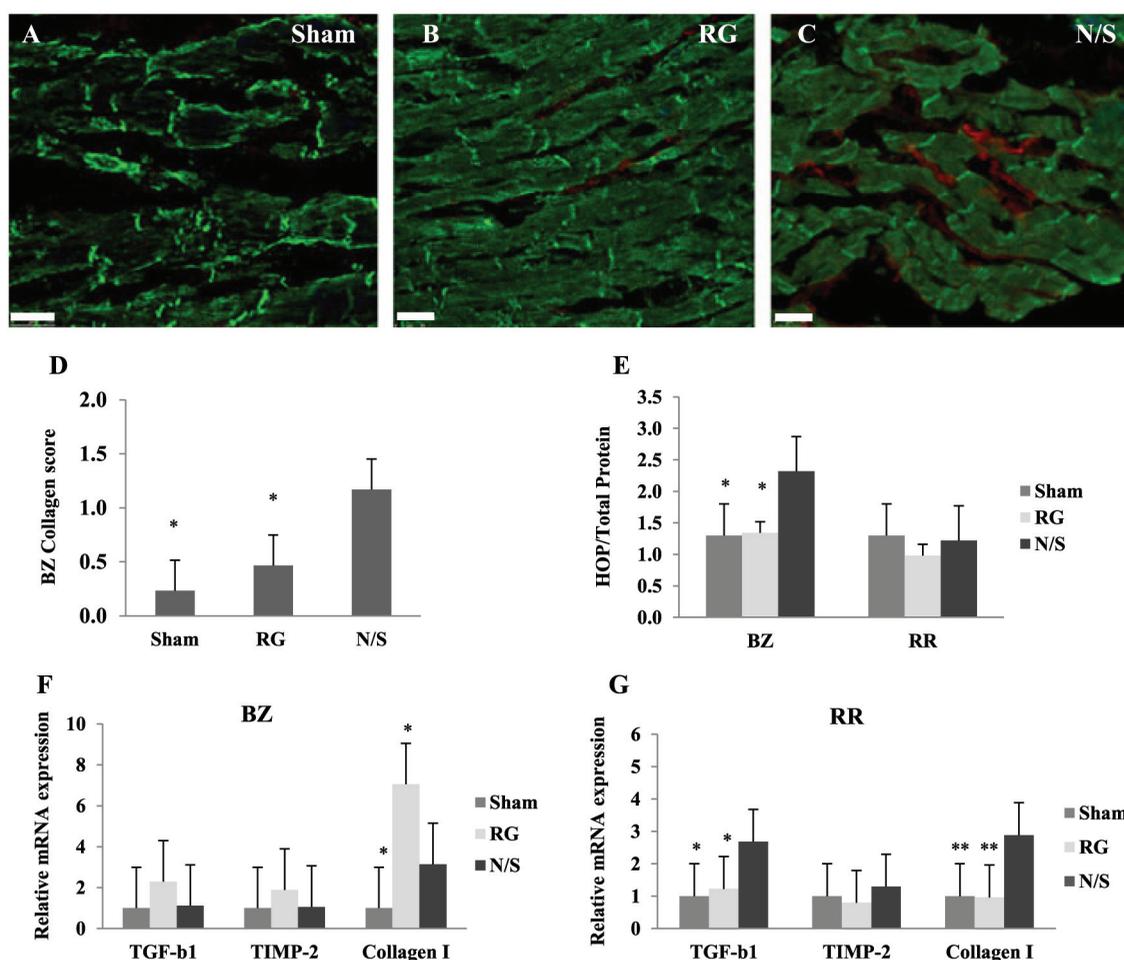
### RG attenuates fibrosis

Post-MI treatment with RG, for 28 days, clearly reduced (60.3%) interstitial fibrosis in the BZ ( $0.46 \pm 0.27$ , Figure 2B) compared with N/S-treated group ( $1.16 \pm 0.16$ ) (Figure 2C) as evaluated by immunofluorescence staining of frozen cardiac tissue sections for collagen- $\alpha$ I, while, interstitial fibrosis on RR cardiac tissue sections did not reveal any difference between groups (data not shown). Desmin staining also indicated less cardiomyocyte damage in RG-treated group (Figure 2B). Furthermore, fibrosis assay analysis by myocardial HOP assay (Figure 2E) revealed that 28 days post-MI, RG treatment decreased myocardial fibrosis in the BZ compared with N/S-treated rats ( $1.34 \pm 0.34$  vs.  $2.32 \pm 0.29$ ,  $P < 0.05$ ). There was no statistical significant difference for the RR ( $0.98 \pm 0.28$  vs.  $1.22 \pm 0.15$ ) between these two groups (Figure 2E).

The mRNA expression levels of the collagen type I in the BZ were increased in RG compared with N/S-treated group ( $7.06 \pm 1.58$  vs.  $3.15 \pm 0.57$ ,  $P < 0.05$ ), (Figure 2F). There was no difference for TIMP-2 and TGF- $\beta$ 1 mRNA ex-



**Figure 1.** Rasagiline mesylate (RG) improves cardiac dysfunction at 14 and 28 days post-MI induction, without altering infarct size. (A) Representative 2D targeted M-mode images from the short axis view. (B) RG diminished the decrease in FS compared with N/S-treated group at 14 and 28 days ( $P < 0.0001$ ). (C) Quantification diagram of infarct/risk area ratio (I/R %) and (D) Risk/all area ratio (%) as internal control of the method. \* $P < 0.001$ , \*\* $P < 0.0001$  vs. Sham and † $P < 0.001$ , †† $P < 0.0001$  vs. RG.



**Figure 2.** Interstitial fibrosis was evaluated by immunofluorescence staining of BZ tissue sections (green = desmin, red = collagen- $\alpha$ I, bar = 25  $\mu$ m). (A) Sham group. (B) RG showed decreased interstitial fibrosis compared with N/S group (C). (D) Quantification diagram of collagen score between groups ( $P < 0.05$  vs. N/S). (E) Fibrosis assay analysis showed that in the BZ, RG treatment decreased myocardial hydroxyproline concentration compared with N/S group ( $P < 0.05$ ,  $n = 5$ ). (F) Quantification diagrams showing variations in mRNA relative expression of TGF- $\beta$ 1, TIMP-2, and collagen type I genes in the BZ and (G) RR between groups ( $n = 5$ ). Values are mean  $\pm$  SE, \* $P < 0.05$ , \*\* $P < 0.01$  vs. N/S.

pression levels in the BZ for the above two groups (Figure 2F). In the RR, collagen type I ( $0.96 \pm 0.17$  vs.  $2.89 \pm 0.65$ ,  $P < 0.001$ ) and TGF- $\beta$ 1 ( $1.22 \pm 0.28$  vs.  $2.68 \pm 0.81$ ,  $P < 0.05$ ) mRNA expression levels were decreased in RG compared with N/S-treated rats (Figure 2G). MMP-2 mRNA expression levels were beyond the detection limit of the method in all samples analysed (data not shown).

#### RG attenuates apoptosis and cell death

To determine whether RG may attenuate the apoptotic cascade, we investigated by western blot

analysis the protein levels of the pro apoptotic proteins Caspase 3 and Bax and the anti apoptotic protein Bcl-2. As shown in Figure 3A, the relative protein expression of cleaved caspase 3 was significantly attenuated by RG in the RR compared with N/S-treated group ( $0.72 \pm 0.06$  vs.  $1.37 \pm 0.11$ ,  $P < 0.001$ ). There was no statistical significant difference either for caspase 3 in the BZ or Bcl-2 and Bax protein levels in the RR or BZ (Figure 3A and B). The protein levels were normalized to GAPDH levels as indicated by representative Western immunoblots in Figure 3C. In order to further investigate the potential anti-apoptotic effect of RG

treatment, apoptotic myocytes were calculated by TUNEL assay and connexin-43 staining of cardiomyocytes. RG treatment attenuated by 65% the number of apoptotic myocytes in the BZ compared with N/S group ( $0.53 \pm 0.19$  vs.  $1.46 \pm 0.30$ , *Figure 3D*). Representative TUNEL assay immunofluorescence staining of the BZ is depicted in *Figure 3E–G*.

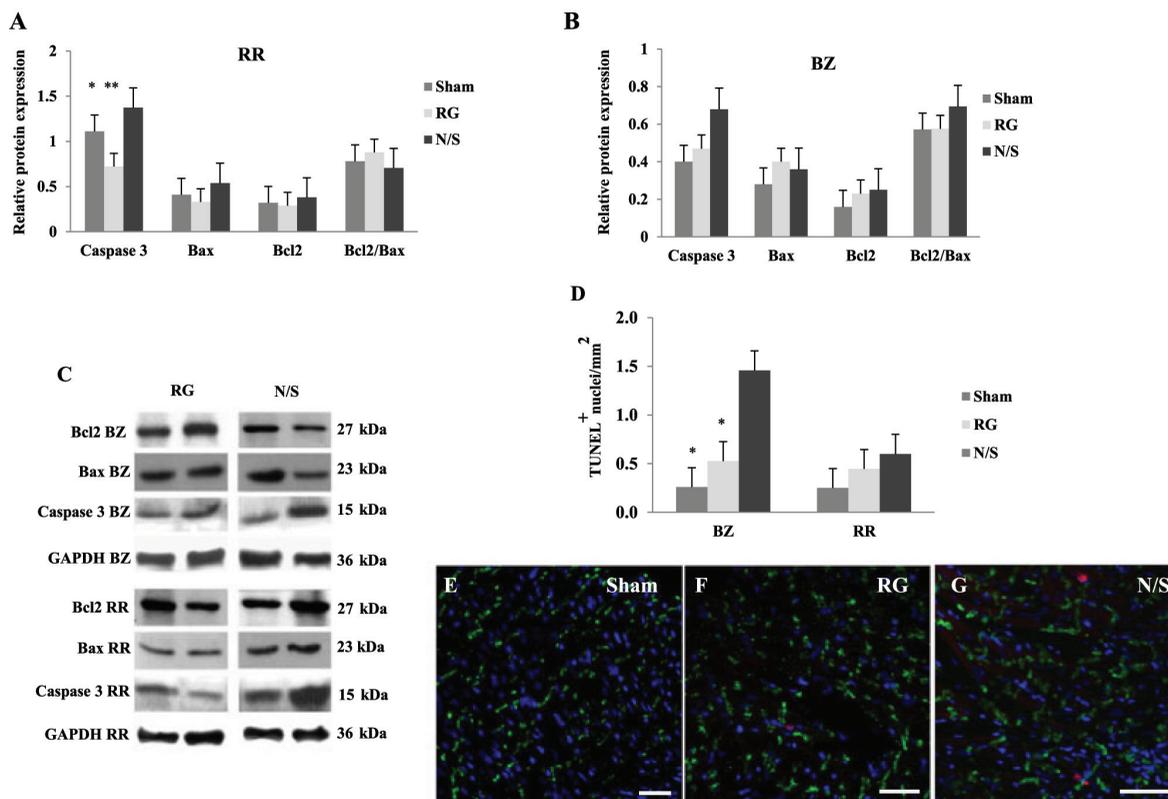
### RG attenuates the increase in tissue oxidative stress

MDA levels were decreased in the BZ of RG compared with N/S-treated group ( $0.29 \pm 0.02$  vs.  $0.53 \pm 0.05$ ,  $P < 0.001$ , *Figure 4A*). However, almost similar MDA levels were calculated in the RR in both groups ( $0.50 \pm 0.08$  vs.  $0.45 \pm 0.08$ , respectively). MDA levels for sham-operated rats were  $0.42 \pm 0.01$  for the BZ and  $0.57 \pm 0.01$  for

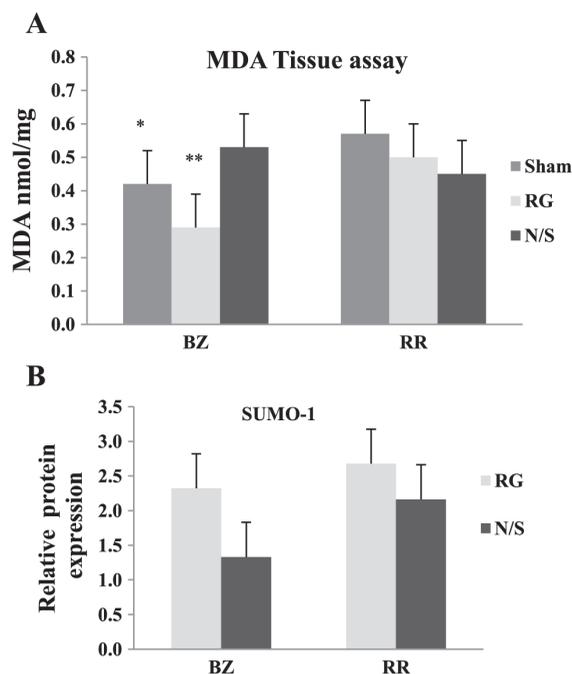
the RR, respectively. In addition, there was a trend for increased small ubiquitin-related modifier 1 (SUMO-1) protein levels in both the BZ ( $2.32 \pm 1.8$  vs.  $1.33 \pm 0.88$ ) and RR ( $2.67 \pm 2.4$  vs.  $2.16 \pm 1.84$ ) of RG compared with N/S-treated group, but without statistical significance (*Figure 4B*).

### Discussion

In the present study, we investigated the cardioprotective action of RG, a MAO-B inhibitor[16] with no adverse cardiovascular effects,[17] in a rat MI model of permanent ligation. Our study revealed a significant attenuation in post-MI LVR, characterized by reduced LV dilation preserving FS at 7, 14, and 28 days post-MI in RG-treated rats, accompanied by less BZ fibrosis and cardiomyocyte apoptosis, indicating a potential



**Figure 3.** The relative protein expression levels of Caspase 3, Bax, and Bcl2 were estimated by Western blot in RR (A) and BZ (B). (C) Representative western blot images are depicted. Cleaved Caspase 3 protein levels were diminished in the RR of the RG compared with N/S group ( $P < 0.0001$ ,  $n = 5$ ). (D) TUNEL quantification showed a significant reduction of apoptotic myocytes by 65% in the BZ of RG compared with N/S group ( $P < 0.05$ ,  $n = 5$ ). Values in mean  $\pm$  SE,  $*P < 0.05$ ,  $**P < 0.0001$  vs. N/S. Representative images of BZ tissue sections from sham (E), RG (F), and N/S (G) group were stained for TUNEL nuclei (red), connexin-43 (green), and DAPI (blue). Bar 50  $\mu$ m.



**Figure 4.** (A) MDA levels were estimated in tissue extracts from BZ and RR. RG diminished MDA levels in BZ compared with N/S group ( $P < 0.001$ ,  $n = 4$ ). (B) Western blot analysis showed variations in small ubiquitin-related modifier-1 relative protein expression levels from RG and N/S group in the BZ and RR ( $n = 4$ ). Values in mean  $\pm$  SE, \* $P < 0.05$ , \*\* $P < 0.001$  vs. N/S.

therapeutic impact of RG.

Several studies have demonstrated that both RG and its S-isomer TVP1022 have cardioprotective effects.[14, 32] Most experimental studies provide TVP1022 before MI induction presenting beneficial effects in post-MI period under different experimental conditions.[13-15] Furthermore, the administration of TVP1022, at the time of coronary artery occlusion, significantly improved cardiac function and reduced myocardial fibrosis given at an ischemia/reperfusion animal model, studied 8 weeks post-MI.[32] We decided to use RG starting one day after MI induction because many drugs are given after primary percutaneous coronary intervention for ST-segment elevation MI (STEMI) and/or thrombolysis.

In agreement with its cardioprotective efficacy, treatment with RG prevented LV interstitial collagen deposition at a protein level (as indicated by immunofluorescence staining and HOP assay) and less cardiomyocyte degeneration was made

evident by desmin staining[21] in the BZ. We also found that collagen type I mRNA levels were significantly increased in the BZ of the RG group. Changes in either synthesis or degradation may lead to heart failure. Preventing the breakdown of the extracellular collagen could arrest infarct expansion and eventually ventricular dilation.[33, 34] Thus, we could hypothesize that RG treatment did not permit collagen mRNA to evolve into collagen protein formation (fibrosis), possibly by keeping fibroblasts in a viable state.

This observation also concurs with the significantly decreased relative mRNA levels of TGF- $\beta$  and collagen type I in the RR of RG-treated rats. The cytokine TGF- $\beta$  increases early in the infarct zone stimulating fibroblast proliferation. Moreover, tissue repair is initiated by the formation of a fibrin-fibronectin matrix, which precedes collagen synthesis. The treatment with RG revealed a preservation of the above mechanism 28 days post-MI in the RR, possibly by rescuing the injured myocytes and activating myocardial repair pathways. No significant difference was seen in the reduction of infarct/risk area ratio between RG and N/S-treated rats, and that could be attributed to the 24 h delay of RG treatment.

Furthermore, RG possesses anti-apoptotic properties either by the preservation of mitochondrial membrane potential[15] or by attenuating the expression of caspase 3.[14] Several studies also show that myocardial apoptosis in experimental MI models is elevated both in the BZ and RR as early as 24 h after MI in the infarct area and BZ[35, 36] and up to 4 weeks post-MI in the RR.[37, 38] In order to define the anti apoptotic effects of RG in this stable MI model, we performed TUNEL analysis which confirmed that RG attenuated the number of dead myocytes in BZ. To further support our data, we also explored caspase 3, an increasingly recognized modulator of cardiomyocyte apoptosis,[38] and Bcl-2/Bax ratio protein expression profile.

According to our findings, RG treatment demonstrated a reduction of activated Caspase 3 in the RR. It has been shown that in contrast to the BZ, the amount of apoptosis in the RR is correlated with an increase in the ventricular diameter

4 weeks after infarction.[37] More specifically, RG significantly preserved LVEDD and LVESD increased almost from 7 days post-MI in our study. This observation provides a possible association towards apoptosis in the RR which has previously been associated with post-infarction LVR, cardiac dilation, and increased cardiac fibrosis after MI, respectively.[37] In addition, we also observed a shift of the Bcl2/Bax ratio toward the regulator protein Bcl2 in the RR (although not statistically significant). This finding suggests that at ischemic injury the increased expression of proapoptotic protein Bax and decreased expression of antiapoptotic protein Bcl-2 induces procaspase-3 cleavage;[30] we believe that the RG administration either earlier or a higher dose would be more effective at a molecular level.

Another important mechanism which plays a key role in cardiomyocyte apoptosis is oxidative stress. MDA is one of the most widely used markers to assess this process.[31, 39] MDA levels were markedly decreased in the BZ of the RG group 28 days post-MI. This finding is very interesting because monoamine oxidases have been characterized as a source of oxidants such as  $H_2O_2$  and aldehyde intermediates in the myocardium.[4] It has also been shown that MAO regulates the lipid peroxidation and other changes leading to cell death through reactive oxygen species.[40] Inhibition of MAO-B results in reduced formation of  $H_2O_2$  and aldehydes, two molecules that are known to stimulate mitochondrial and myocardial damage.[41] Furthermore, in context with oxidative stress, we also explored SUMO-1 which has been found to be highly relevant in the response to cellular stress and rescues SERCA2a ATPase (cardiac isoform of sarcoplasmic reticulum calcium ATPase) activity in heart failure.[42, 43] In the present study, we observed a trend towards elevation in SUMO-1 relative protein levels both in the BZ and RR of RG-treated group. Consequently, a potential increase of SUMO-1 may contribute to the reduction of LV dilation after MI induction and related to the cardioprotective activity of RG.

We consider as limitations of the study the lack of echocardiography and hemodynamic data in the

acute setting. Furthermore, we did not perform an electrophysiology study for heart rate evaluation. The heart rate appeared to be significantly lower within the RG group compared with baseline measurement (pre-MI induction) and to the other two groups at day 7 post-MI, although within the normal limits, respectively. Regarding the excessive catecholaminergic increase in the early stages of heart failure and that the increase in heart rate is detrimental for cardiomyocytes in the long term, we believe that further investigation is required.

Taking into account that a failing heart is characterized by complex tissue remodeling involving increased cardiomyocyte death, impairment of sarcomere function and metabolic activity, together with increased inflammation and interstitial fibrosis.[3] Several studies have revealed that MAO inhibition is beneficial in cardiovascular pathologies. MAOs are able to trigger different signaling pathways leading to proliferation, apoptosis, or cell death, respectively.[4] The potential of their inhibition in the heart during chronic neuro-hormonal or hemodynamic stress can be directly associated with MAO-derived  $H_2O_2$  and oxidative stress[40, 41] or apoptosis reduction as well as mitochondrial viability either through Bcl2 and protein kinase C activation or Bax and caspase-3 down-regulation.[8, 10, 12, 16] According to our findings we believe that RG preserved myocardial performance through several signaling pathways targeting oxidative stress, cardiomyocyte apoptosis, and favourable matrix remodeling.

In conclusion, our study revealed the potential effect of RG treatment in the post-MI period concerning the reduction in the progressive LV dilation, apoptosis, and oxidative stress. Additional studies are required to verify the protective effects of RG in LVR and to define MAO-B as a pharmacological therapeutic target.

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**Conflict of interest** None declared.

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**Supporting Information** Supporting Information may be found in the online version of this article

**Table S1.** ANOVA/ Bonferroni/ Dunn post hoc test repeated measures analysis within groups.

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# Effect of Luteal-Phase Support on Endometrial L-Selectin Ligand Expression after Recombinant Follicle-Stimulating Hormone and Ganirelix Acetate for *in Vitro* Fertilization

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## ABSTRACT

**Context:** The impact of different types of luteal phase support on endometrial receptivity after ovarian stimulation has not been investigated.

**Objective:** Our objective was to evaluate the impact of different luteal-phase support protocols on sex steroid levels and on endometrial expression of L-selectin ligand after ovarian hyperstimulation with a GnRH antagonist protocol.

**Patients and Design:** Seventeen oocyte donors who underwent ovarian stimulation with a recombinant FSH/ganirelix acetate protocol were randomized into three groups: group I had no luteal-phase support; group II had luteal support with micronized progesterone; and group III had luteal support with progesterone plus 17 $\beta$ -estradiol. All donors had endometrial biopsies on the day of retrieval, and then 3, 5, and 10 d after retrieval. In addition, they had serum estradiol and progesterone measurements on d 3, 5, and 10.

**Main Outcome Measures:** Endometrial L-selectin ligand expression was detected by immunohistochemical staining in the luminal and glandular epithelium. A histo-

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logical score was used for the quantification of the immunostaining. Sex steroid levels were measured during the luteal phase.

**Results:** By d 10 after retrieval, there was a significant decrease in mean progesterone levels in group I compared with the other two groups that may reflect the expected demise of the corpus luteum. There was also a significant increase in the presence of L-selectin ligands in the luminal epithelium in group III.

**Conclusions:** During controlled ovarian stimulation with a GnRH antagonist protocol, luteal-phase support with micronized progesterone and  $17\beta$ -estradiol seem to increase endometrial L-selectin ligand expression in the luminal endothelium. (*J Clin Endocrinol Metab* 91: 4043–4049, 2006)

THE HUMAN EMBRYO reaches the endometrial cavity 2–3 d after fertilization and implants several days later. Successful implantation requires a series of highly coordinated interactions between uterine and embryonic factors (1) that result in the attachment of the embryo to the endometrium: penetration through the epithelial layer, degradation of the underlying basement membrane, and invasion of the uterine stroma (2, 3). The so-called implantation window defines the period of maximal endometrial receptivity. Historically, the assessment of endometrial receptivity has been based on histological dating as described by Noyes et al. (4). Recently, however, it has been shown that this approach may be inaccurate (5).

Before and during implantation, extensive cross-signaling occurs between the embryo and the endometrium. This involves a finely tuned spatial and temporal production and secretion of specific hormones, monokines, cytokines, and growth factor-binding proteins as well as adhesion molecules, some of which have been used as markers of endometrial receptivity (2, 6–8).

Recently, mechanisms involving L-selectin and L-selectin ligand interaction have been described in the process of human implantation (9). Selectins constitute a group of cell adhesion molecules that mediate transient cell to cell interactions necessary for the recirculation of lymphocytes from the blood to the lymphoid organs (homing) and back to the blood through postcapillary venules located in the cortex of the lymph nodes (10). These venules are characterized by the height of their endothelium, and they are now commonly called high endothelial venules (HEV). The molecule responsible of the

adhesion of lymphocytes to the HEV is a type I membrane protein identified as L-selectin (CD62L) (11) that interacts with HEV-located L-selectin ligands. Identification of HEV-based L-selectin ligands has been achieved with a monoclonal antibody MECA-79, which has been shown to block lymphocyte attachment to HEV in the Stamper-Woodruff in vitro adherence assay and inhibit short-term lymphocyte homing (12). MECA-79 effectively blocks the tethering and rolling of lymphocytes along HEV, thus preventing the initiation of the recruitment cascade (13). MECA-79 and L-selectin-IgG chimeras immunoprecipitate the same complex of proteins from mouse lymph nodes and human tonsils, possibly because of the resemblance of its sulfated carbohydrate epitope with the L-selectin recognition determinant sialyl Lewis X (6-sulfo sLex) (14).

In the study by Genbacev et al. (9), endometrial biopsies obtained from oocyte donors revealed a strong staining of the luminal epithelium for L-selectin ligand during the luteal phase. Subsequent immunoblot analysis with MECA-79 confirmed an up-regulation of L-selectin ligands as the window of implantation opened (d 3 and 6 after retrieval compared with d 0 and 2). A similar pattern was observed in endometrial samples obtained from women during their natural cycle (15). Staining of embryos at different stages of development with a specific L-selectin antibody was weak, when the zona pellucida was intact, whereas there was a strong trophoblast staining for L-selectin after hatching. Epithelial binding of cytotrophoblasts onto the receptive luteal phase endometrium was effectively inhibited by adding an

antibody to L-selectin or by preincubation with MECA-79 (9). These findings support a pivotal role for the L-selectin system in the process of implantation.

In the present study, we evaluate the impact of different types of luteal-phase support after ovarian stimulation with a GnRH antagonist protocol on the endometrial receptivity by using the expression of L-selectin ligands as a surrogate marker. The availability of oocyte donors offers a good model for the evaluation of the endometrium because their hormonal milieu after ovarian stimulation approximates closely that of infertile women undergoing controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).

## Subjects and Methods

The Institutional Review Board of the Johns Hopkins University approved this study.

### *Oocyte donors*

Women from 21–29 yr of age were eligible as oocyte donors. The selection process included an extensive questionnaire and psychological evaluation of the potential donors followed by a detailed physical examination and consultation about the process of oocyte donation by one of the physicians in the group. The risks of the procedure were discussed in detail, and written informed consents were obtained. All donors were screened for sexually transmitted diseases as well as for genetic conditions such as cystic fibrosis in accordance with the recommendations of the American Society for Reproductive Medicine (16). Women with a body mass index exceeding 28 kg/m<sup>2</sup>, history of pelvic inflammatory disease, sexually transmitted diseases, reproductive tract pathology, or other systemic diseases were excluded. At the time of their initial visit, they received a detailed explanation of the study protocol with particular emphasis on the risks associated with the endometrial biopsy and the use of steroids during their luteal phase. A written informed consent was obtained at that time. From August 1, 2003, to October 30, 2005, 20 healthy oocyte donors were initially recruited, 17 of which completed the study.

### *Stimulation protocol*

Oocyte donors were stimulated with a GnRH antagonist protocol. Briefly, all donors had a baseline measurement of FSH and estradiol (E2) serum concentrations on the second day of their menstrual cycles after the discontinuation of oral contraceptive pills. In addition, a transvaginal sonogram was performed to rule out early follicular development and any anatomic anomalies. Providing that serum FSH was less than 10 mIU/ml and E2 was less than 60 pg/ml, ovarian stimulation was initiated with 225 IU recombinant FSH (Follitropin Alfa, Gonal-F; Serono Laboratories, Norwell, MA). A daily evening dose of ganirelix acetate (Antagon; Organon, West Orange, CA), 0.25 mg sc, was started either 6 d after the initiation of gonadotropins or at the time of identification of a leading follicle with mean diameter more than 13 mm and continued through the day of human chorionic gonadotropin (hCG). Thereafter, the dose of gonadotropins was adjusted in a step-down fashion according to follicular development by serial transvaginal ultrasound and serum E2 response. When at least three follicles reached a mean diameter of 18 mm, ovulation was triggered with a single im dose of 10,000 IU hCG (Profasi; Serono) or 20 U of a GnRH agonist administered in two doses 24 h apart. Transvaginal oocyte retrieval was performed under iv sedation 34–36 h after hCG or the initial dose of GnRH agonist.

### *Randomization*

Using a computer-generated model, study participants were randomized at the time of the retrieval into three groups: group I did not receive any luteal-phase support; group II received micronized progesterone in the form of vaginal suppositories, 200 mg every 6 h starting from the day after retrieval; and group III received a daily oral dose of 2 mg 17 $\beta$ -estradiol in addition to the micronized progesterone. Endometrial biopsies were performed with the use of a Pipelle catheter (Unimar, Wilton, CT) on the day of oocyte retrieval (d 14 of the ideal cycle) and then 3, 5, and 10 d later corresponding to ideal cycle d 17, 19, and 24. At least three endometrial biopsies were obtained from each donor and stored in liquid nitrogen. The specimens were

then fixed in 10% formalin and subsequently embedded in paraffin for tissue microarray sectioning. Serum levels of E2 and progesterone were measured on the day of retrieval and 3, 5, and 10 d after retrieval.

#### **Tissue microarrays (TMA)**

In this study, TMA were assembled from 61 paraffin-embedded endometrial samples. Three representative punches (each at 1.5 mm in diameter) were obtained from each specimen. The arrays encompass 183 tissue cores derived from 17 donors. All tissue cores were sectioned at 5  $\mu$ m thickness and affixed to the TMA slides.

#### **Immunohistochemistry**

The expression of L-selectin ligands was examined by immunolocalization using an antibody (MECA-79) that binds to sulfated oligosaccharide epitopes of L-selectin ligands (14, 17). Briefly, the sections were dewaxed through descending grades of ethanol to distilled water and pretreated with Citra Buffer (Vector H3300; Vector Laboratories, Burlingame, CA) in a steamer (Black&Decker HA900, Hampstead, MD) at 90 C for 20 min. The tissue sections were then labeled with a rat antihuman L-selectin ligand monoclonal antibody (MECA-79; BD PharMingen Inc., San Diego, CA) at a concentration of 3.3  $\mu$ g/ml with dilution of 1:30 in PBS. The sections were then incubated with a biotin-conjugated secondary antibody (goat antimouse Ig), which cross-reacts with the rat primary antibody at a dilution of 1:800 with PBS. Positive immunostaining was detected through interaction of avidin-biotin peroxidase (ABC) complex using a Ventana DAB Detection Kit (Ventana- Biotek Solutions Inc., Tucson, AZ). Isotype-specific irrelevant monoclonal antibody, generated against the human microphthalmia transcription factor (MiTF), was used as a primary antibody for the negative controls (18). Slides were subsequently counterstained with hematoxylin.

The intensity of staining in glandular and luminal epithelium of the tissue sections was assessed using the histological score (HSCORE) as described by others (19, 20). The HSCORE was calculated using the following equation:  $HSCORE = \Sigma Pi$

$(i + 1)$ , where  $i$  is the intensity of staining (1 = weak, 2 = moderate, and 3 = strong) and  $Pi$  is the percentage of stained epithelial cells for each intensity (0–100%). The TMA tissue sections were scored by two independent investigators in a blinded fashion without the knowledge of sample identifiers, using a light microscope (Olympus, CH-2; Hitech Instruments, Inc., Edgemont, PA), and the average HSCORE was documented. This semiquantitative analysis has been shown to have a low intra- and interobserver variation (20).

#### **Serum hormone assays**

Blood samples were collected between 0700 and 0800 h. E2, FSH, LH, and progesterone were quantitatively measured with a solid-phase, two-site chemiluminescent enzyme immunometric assay with the Immulite Automated Analyzer (Diagnostic Products Corp., Los Angeles, CA). The intraassay statistics were calculated for samples from the results of 20 replicates in a single run. Interassay statistics were calculated for samples assayed in 20 different runs. Intra- and interassay coefficients of variation were 6.3–15.0 and 6.4–16.0%, respectively, for serum E2; 5.4–7.7 and 6.5–8.1%, respectively, for serum FSH; and 5.0–16.0 and 5.8–16.0%, respectively, for serum progesterone. The detection limit of the assay was approximately 0.2 ng/ml. All specimens obtained were coded with a combination of letters and numbers that was used to identify the group, the individual donor within the group, and the order of the endometrial biopsy of the specific donor. The evaluation of the endometrial samples was performed by individuals who were blinded to the type of luteal-phase support and the sample order.

#### **Statistical analysis**

Statistical analysis was performed with a commercial statistical package SPSS version 10.0 (SPSS, Chicago, IL). One-way ANOVA was used for comparison of means between groups for normally distributed variables and Kruskal-Wallis when the assumption of normality was not applicable. A  $P$  value of  $<0.05$  was considered significant.

## Results

Of the 20 donors initially recruited, one donor could not tolerate the endometrial biopsy in the office, one did not comply with the medication, and another was cancelled because of poor compliance during the stimulation period. Seventeen donors completed the study. Demographic and stimulation characteristics of the participating donors are shown in Table 1.

Overall, there was no difference in stimulation characteristics between the three groups as well as in the stimulation outcome. Donors in group I had a smaller number of oocytes retrieved, but most likely this represented a random finding that did not reach statistical difference.

Serum progesterone levels were well above the ovulatory range of 10 ng/ml on the day of retrieval as expected in all groups regardless of the type of support (Table 2). In groups II and III, progesterone levels remained elevated for up to 10 d after retrieval, whereas in group I, there was a precipitous drop by d 10. As a result, there was a significant decrease in the mean progesterone level in group I compared with the other two groups ( $P = 0.021$ ). In contrast, E2 levels remained elevated in all groups up to d 5 after retrieval, and there was a gradual drop by d 10 regardless of the type of supplementation (Table 2).

Staining of the specimens with MECA-79 is shown in Fig. 1. Negative control slides stained using MiTF as a primary antibody did not show any detectable staining.

HSCORE for the luminal as well as for the glandular epithelium on postretrieval d 3 and 5 were similar between the three groups (Table 3). By d 10, there was a decrease in the staining on

both the glandular epithelium and luminal epithelium of groups I and II as well as in the glandular epithelium of group III. In contrast, however, there was no decrease in the staining of the luminal epithelium in group III. On d 10, the intensity of staining of the luminal epithelium in group III was significantly stronger than the other two groups ( $P = 0.040$ ).

## Discussion

This is a pilot study designed to evaluate the impact of luteal-phase support on the endometrium using a surrogate marker of endometrial receptivity. In an earlier study, we have shown that the expression of L-selectin ligand in the natural cycle is up-regulated during the window of implantation (15). Our findings indicate that the expression of L-selectin ligand in the luteal-phase endometrium around the time of implantation (postretrieval d 5) is not affected by the type of luteal-phase support. Interestingly, there was a marked decrease in the presence of L-selectin ligand in the luminal epithelium of subjects receiving no luteal-phase support or micronized progesterone only.

Edwards et al. (21) were the first to postulate that inadequacy of the luteal phase after ovarian stimulation may be one of the main reasons for failure in IVF cycles. Subsequently, hormonal support of the luteal phase in patients undergoing COH became a common practice. Use of GnRH agonists in ovarian stimulation protocols to suppress premature LH surges increased the number of mature oocytes and embryos available for transfer and subsequently improved pregnancy rates (22, 23).

GnRH agonist use, however, has been asso-

**TABLE 1.** Demographic and stimulation characteristics of the donors

	Group I	Group II	Group III	P value
No. of cases	5	6	6	
Age (yr)	25.3 ± 2.7	24.0 ± 0.8	23.0 ± 0.8	0.535
Body mass index (kg/m <sup>2</sup> )	22.6 ± 1.2	20.5 ± 0.7	20.9 ± 1.2	0.412
d 2 (Basal levels)				
FSH (mIU/ml)	4.5 ± 0.8	5.6 ± 0.7	4.0 ± 1.0	0.407
LH (mIU/ml)	4.6 ± 2.2	4.6 ± 1.0	5.5 ± 2.1	0.920
E2 (pg/ml)	32.5 ± 9.2	37.2 ± 8.6	29.8 ± 9.8	0.839
No. of ampoules used	38.8 ± 7.6	32.2 ± 1.2	35.3 ± 2.6	0.563
Days of stimulation	10.4 ± 1.2	9.3 ± 0.3	10.2 ± 0.7	0.588
No. of oocytes	13.6 ± 4.3	21.3 ± 4.4	19.2 ± 2.1	0.367
No. of fertilized oocytes	9.4 ± 2.5	13.7 ± 4.0	14.7 ± 2.7	0.514
Peak E2 level (pg/ml)	1827.0 ± 332.3	2644.7 ± 408.5	2547.5 ± 482.4	0.378
Day-of-retrieval E2 (pg/ml)	1199.5 ± 441.5	1158.8 ± 219.8	1118.0 ± 220.5	0.980

Results are shown as mean ± SE. No significant differences between the groups were found in any of the factors that could affect outcome. The statistical method used was one-way ANOVA.

**TABLE 2.** Steroid levels during the luteal phase of the three groups

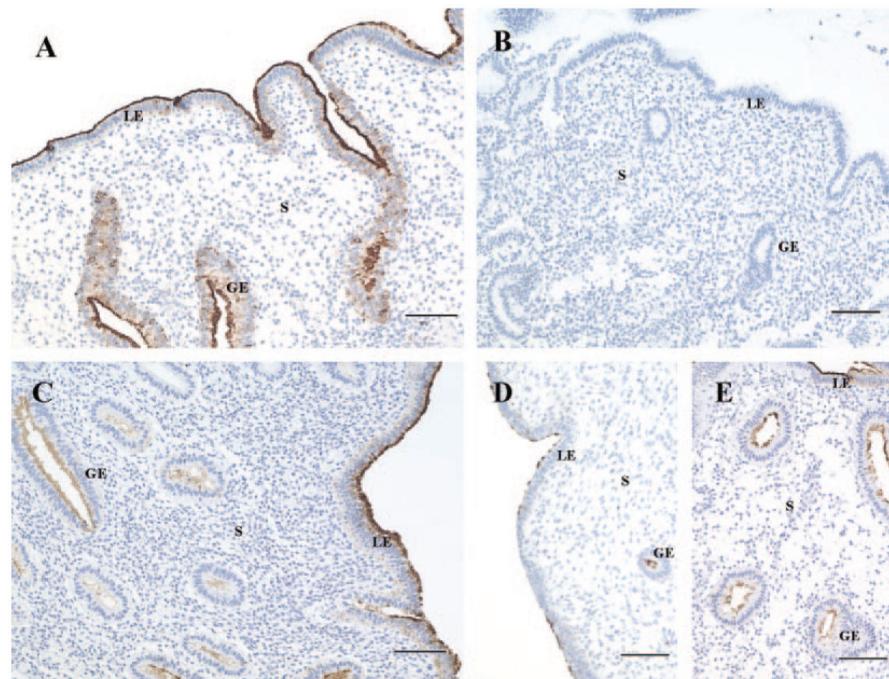
	Group I	Group II	Group III	P value
No. of cases	5	6	6	
Day of retrieval				
E2 (pg/ml)	1199.5 ± 441.5	1158.8 ± 219.8	1118.0 ± 220.5	0.980
P4 (ng/ml)	21.0 ± 14.4	18.0 ± 1.5	16.3 ± 3.6	0.833
d 3 after retrieval				
E2 (pg/ml)	879.8 ± 470.6	609.4 ± 167.1	944.2 ± 212.4	0.660
P4 (ng/ml)	36.6 ± 11.6	29.1 ± 4.9	36.1 ± 3.5	0.781
d 5 after retrieval				
E2 (pg/ml)	1264.5 ± 760.2	599.4 ± 319.0	938.2 ± 417.2	0.657
P4 (ng/ml)	26.2 ± 9.4	22.1 ± 6.3	31.4 ± 5.3	0.639
d 10 after retrieval				
E2 (pg/ml)	196.5 ± 96.3	84.8 ± 64.1	232.8 ± 64.5	0.386
P4 (ng/ml)	3.4 ± 1.7	20.4 ± 5.0	13.0 ± 2.9	0.021*

Results are shown as mean ± SE. There was a significant decrease in serum progesterone (P4) levels by d 10 in the group that had no luteal support (\*,  $P = 0.021$ ). The statistical method used was one-way ANOVA.

ciated with several undesired effects. Premature luteolysis and inadequate endometrial priming because of oversuppression of pituitary function are some of the unwanted consequences (24). A rapid increase in progesterone and E2 levels has been described during the early luteal phase of stimulation protocols using GnRH agonists. This is followed by premature luteolysis during the mid-luteal phase (25). Luteal-phase support with progesterone or hCG has been found to improve pregnancy rates when human menopausal gonadotropins stimulation and IVF (26).

A newer group of agents derived from additional substitutions on the original GnRH mo-

lecule has become clinically available (27, 28). These agents (GnRH antagonists) bind to GnRH receptors and, by competitive blockage, cause an immediate inhibition of gonadotropin release without the initial stimulatory response (29). Initial studies with GnRH antagonists showed suppression of serum LH levels within hours of administration followed by a rapid recovery of the pituitary function within 24 h after discontinuation (30, 31). Preliminary experience with ovarian stimulation protocols showed that these agents effectively prevent premature luteinization without compromising implantation and pregnancy rates (32, 33). Interestingly, in all the initial studies involving GnRH



**FIG. 1.** Immunostaining of endometrial sections with MECA-79. A, Strong positive immunostaining in both luminal epithelium and glandular epithelium cells but not in stroma cells; B, use of MiTF as primary antibody revealed no detectable staining (negative control); C, strong luminal staining; D, weak luminal staining; E, weak glandular staining. GE, Glandular epithelium; LE, luminal epithelium; S, stroma. Magnification,  $\times 40$ . Scale bar, 50  $\mu$ m

antagonists, luteal-phase support was routinely either in the form of progesterone or hCG, despite limited information about the quality of the luteal phase. The necessity of luteal-phase support after GnRH antagonist has been addressed in a recent prospective randomized study designed to evaluate luteal-phase characteristics in women who had final induction of oocyte maturation with recombinant hCG, recombinant LH, or Triptorelin in two respected centers. The study was interrupted prematurely because of an unacceptably low pregnancy and implantation rate in the group that had no luteal-phase support (34).

Thus far, studies comparing different luteal support protocols in women undergoing ovarian stimulation used implantation and pregnancy rates as endpoints (35-37). As expected, several confounding factors (such as oocyte quality and transfer technique as well as other preimplantation events) that could not be controlled for could have affected implantation and pregnancy rates independently of the endometrial quality. There is limited knowledge regarding the characteristics of the endometrium in COH protocols involving GnRH antagonists. This study was designed to investigate possible alterations in the luteal-phase endometrium by using a surrogate marker of endometrial receptivity that has been found to play an important role in human implantation. To allow for a high-throughput tissue analysis, we have used a tissue chip approach (38) on paraffin-embedded samples instead of the traditional methods of immunostaining that are time consuming and rapidly exhausting of precious tissue resources. L-selectin ligands were identified at the time of retrieval as

well as 3 and 5 d after retrieval in all groups regardless of the type or lack of luteal-phase support. On d 10, however, there was a significant decrease in the presence of L-selectin ligands in all groups except in group III, which had received a combination of E2 and micronized progesterone. Administration of micronized progesterone alone did not seem to have any additional effect on the presence of L-selectin ligands compared with the group that had no support at all. The clinical relevance of these findings is not clearly understood. According to Beckers et al. (34), progesterone supplementation is necessary after ovarian stimulation with an antagonist protocol. From our data, there was no difference in the presence of L-selectin ligand around the time of implantation (d 5) between the group that received micronized progesterone and the one that had no support at all. In addition, at the same time, the mean serum levels of progesterone were similar in all groups (26.2 vs. 22.1 vs. 31.4 ng/ml,  $P = 0.639$ ). It seems, therefore, unlikely that a potential beneficial effect of progesterone is exerted around that time.

Only on d 10 were progesterone levels in the nonsupplemented group severely decreased compared with the other two groups ( $P = 0.021$ ), and at the same time there was a complete absence of L-selectin ligand staining in some of the samples. These findings indicate that maintenance of progesterone levels may be important for the events that follow the initial attachment of the embryo. Interestingly, on d 10 after retrieval, we observed a significant increase in the presence of L-selectin ligands only in the group that had received a combination of E2 and progesterone (group III).

**TABLE 3.** Staining of the endometrium with MECA-79

	Group I	Group II	Group III	<i>P</i> value
No. of cases	5	6	6	
No. of biopsies	19	20	22	
HSCORE, median (interquartile range)				
Day of retrieval				
Luminal	3.2 (2.6–3.8)	2.2 (1.2–3.5)	1.8 (0.7–3.1)	0.329
Glandular	0.7 (0.0–1.7)	1.0 (0.0–2.5)	0.5 (0.0–1.1)	0.997
d 3 after retrieval				
Luminal	2.4 (1.6–3.0)	2.0 (0.8–3.3)	1.8 (0.8–2.7)	0.642
Glandular	0.7 (0.0–1.7)	0.9 (0.2–1.5)	1.7 (0.1–3.6)	0.756
d 5 after retrieval				
Luminal	2.3 (1.3–4.0)	2.2 (0.3–3.5)	2.2 (0.7–4.0)	0.971
Glandular	1.0 (0.0–1.5)	1.5 (0.9–1.5)	1.4 (0.8–2.3)	0.795
d 10 after retrieval				
Luminal	0.2 (0.0–1.3)	0.4 (0.3–0.5)	1.6 (0.6–2.8)	0.040
Glandular	0.2 (0.0–0.7)	0.6 (0.0–1.3)	0.6 (0.0–1.5)	0.839

There was a significant increase in L-selectin ligand expression by postretrieval d 10 in group III ( $P = 0.040$ ). The statistical method used was Kruskal-Wallis.

The fact that the combination of estrogen and progesterone was associated with persistence of L-selectin ligands on d 10 is interesting and should be evaluated further. The clinical significance of this finding and whether this may impact the events of early implantation is unclear. One could speculate that the addition of E2 may act either directly on the endometrium through estrogen receptors or indirectly by influencing the induction of endometrial progesterone receptors and augmenting the action of progesterone. Whether this contributes to an improvement in the endometrial receptivity and subsequent implantation and pregnancy rates is unclear. In stimulation protocols with GnRH agonists, there are data to support an improvement in implantation and pregnancy rates in the groups that had received a combination of estrogens and progesterone for luteal-phase support (39), but this is not a common practice by all.

In a previous publication (15) looking at L-selectin ligand expression in the natural cycle, we were able to show that there was a significant increase in both luminal and glandular endometrium during the early, mid, and late luteal phase compared with the follicular phase. In contrast, there was no difference in the expression of L-selectin ligand in either the glandular or the luminal endometrium throughout the luteal phase. In a subsequent publication (40) comparing the endometrium of donors supplemented with progesterone only, we have demonstrated a significant decrease in L-selectin expression during the mid to late luteal phase compared with unstimulated controls. Our findings in the current report support the notion that the combination of E2 and progesterone for luteal-phase support after ovarian stimulation with GnRH antagonists compares favorably to the unstimulated cycle in terms of L-selectin ligand expression. Evidence indicates that the attachment of an embryo to the endometrium depends upon the binding of L-selectins expressed by the trophoblast to L-selectin ligands expressed in the endometrium (9). The intensity of immunostaining for MECA-79 was increased in the luminal epithelium compared with the glandular epithelium in natural cycles (15). These results may be explained by the fact that the luminal epithelium serves as the initial

contact point between the blastocyst and the endometrium, whereas glandular epithelium may be involved during placentation.

To the best of our knowledge, this is the first prospective randomized study to provide interesting information regarding the preparation of the endometrium in assisted reproduction cycles. There are certain limitations that need to be presented. The small number of oocyte donors could potentially limit the power of the study. Furthermore, the administration of a GnRH agonist in place of hCG for final oocyte maturation in cases at risk for ovarian hyperstimulation syndrome may impact the results. In addition, regarding the morphological evaluation of the endometrial samples, one has to take into account that we have used a semiquantitative method to evaluate the intensity, which can allow a certain degree of subjectivity. Finally, the compliance of the participants could represent yet another limiting factor because there were occasions in which some donors could not tolerate all four endometrial biopsies.

In summary, there is evidence that some type of lutealphase support is necessary in ovarian stimulation protocols that include GnRH antagonists. Whether progesterone alone is adequate or a combination of progesterone and E2 is preferable is unclear. It seems that a combination of the two agents is associated with increased expression of L-selectin ligands. Larger prospective studies in the future may improve our understanding of endometrial physiology and provide more information about the best possible method for endometrial preparation after assisted reproductive technologies.

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# Effects of intensive care unit nursing shortage on cardiac surgery in New York State

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The focus of this study was to determine if the practice of cardiac surgery is affected by the shortage of critical care nurses. We conducted a survey encompassing 25 institutions in the state of New York, representing 10,827 patients. In addition to determining the statewide effect of the nursing shortage, the questionnaire was designed to yield answers to the coping mechanisms of individual institutions.

In July 1988, the American Association of Critical Care Nurses<sup>1</sup> published a summary analysis of the supply and requirements for critical care nurses in order to practice critical care. The following data from that report serve as introduction and illustration of the nationwide problem: a) In 1988, the combined part-time and full-time percentage of vacancies in critical care nursing was 13.8% (rates >10% represent a severe nursing shortage)<sup>2</sup>. b) In 1986, critical care beds represented 10.8% of inpatient beds, an increase from the 7.4% reported in 1979. c) The number of critical care beds in the United States increased by >20,000 from 1979 to 1986. d) Critical care units report an average bed increase of nearly 30%. e) The occupancy rate in critical care units averaged 84%, which was greater than the average for total hospital occupancy, which was 70%.

## Materials and Methods

A questionnaire was designed with 18 independent questions. Nine questions required a number as an answer. Three questions allowed the respondent a selection from which one answer could be chosen, while six answers had to be answered with yes or no. The questionnaire was sent to ICU directors, nursing directors, or hospital administrators of all institutions in the state of New York that performed open-heart surgery during 1988. The questions related to postoperative cardiac surgical nursing, with special focus on the cardiovascular ICU and its organization and integration into a hospital between January 1, 1988 and December 31, 1988. The names of all institutions, as well as data concerning cardiac surgery in the state, were obtained from the New York State Department of Health. No questions regarding step-down units or floor nursing were asked.

Data are presented as mean  $\pm$  SD.

## Results

Twenty-nine questionnaires were mailed. The response rate was 100%. Of the 29 institutions that

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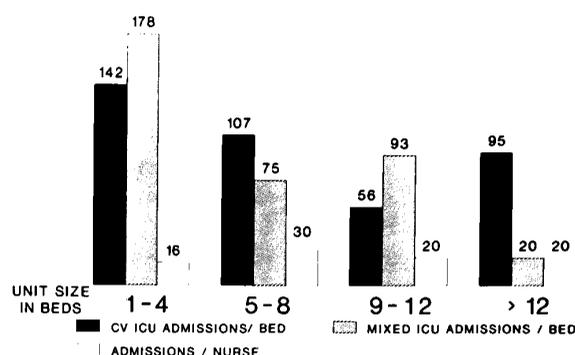
responded, two started their programs after the beginning of the study period, and therefore were excluded. Two institutions, one in New York City and one in the New York metropolitan area, felt the subject of nursing staffing to be too sensitive to release their data. The 25 remaining institution responses were used for analysis.

These 25 institutions offered a combined total of 216 ICU beds designated for cardiac surgical patients, with an average of  $8.9 \pm 4.4$  (SD) beds per hospital. A total of 10,827 patients were cared for by 881 nurses in the 25 hospitals. Of those nurses, 85.9% were full-time RNs and 14.1% part-time RNs. Four units reported the use of nurses hired from a nursing agency. The average ICU stay was  $2.0 \pm 0.7$  days per patient. In eight institutions, the patients were cared for in a mixed surgical ICU or recovery room.

Fourteen institutions had cardiothoracic ICUs. Among the surveyed institutions, 36% (9/25) had to eliminate use of cardiac surgical ICU beds because of understaffing. In 44% (11/25), the limited nurse staffing of the ICU affected the operating room schedule, which resulted in operating room cancellations of elective cardiac surgery in 40% (10/25) of the hospitals. An arbitrary separation by size (>4 or <4 beds in a unit) did not result in any significant difference in admissions per bed in large vs. small units. Moreover, the number of admissions per nurse was not size-dependent (Fig. 1). Twelve university hospitals were identified. The patient:nurse ratio in university hospitals vs. other major hospitals did not differ significantly (21:1 for university and 20:1 for nonuniversity hospitals). The number of full-time staffed nursing positions was unchanged from January to December, yet  $9.7 \pm 5.6$  nurses per ICU left the institution and  $6.9 \pm 7.8$  nurses per ICU from within the same institution and  $10.2 \pm 7.5$  nurses from the outside were recruited. Most of these newly recruited nurses worked part-time. The nursing turnover rate was comparable for university hospitals when compared with other major hospitals.

## Discussion

We are not aware of any studies examining the impact of the critical care nursing shortage on the practice of cardiac surgery. With nearly half (44%) of the institutions in New York State reporting inability to provide safe and adequate (i.e., inadequate nurse staffing) ICU care as the reason for alterations of the operating schedule in cardiac surgery, there can be little doubt that this problem is important.



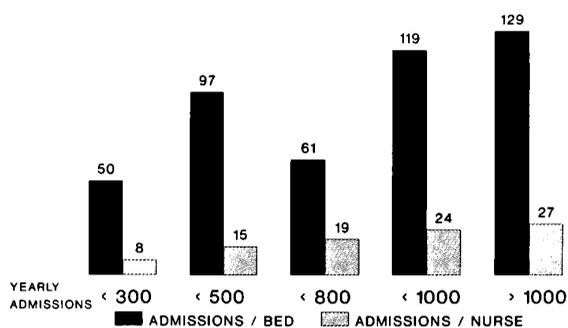
**Figure 1.** Cardiac surgical ICU admissions during 1988 by ICU size. CV ICU, cardiac surgical patients exclusively; MIXED ICU, general and cardiac surgical patients.

It is not clear as to the implications of these findings. Is the public willing to accept waiting lists, as occurs in countries with socialized medicine? Does this shortage foster a trend, whereby increased monitoring and automated interventions would allow an increase in the nurse/patient ratio? The uniformity with which the entire state is affected is a surprise. Most likely, this uniformity is a reflection of the severity of the problem and also may be a reflection of the competition between institutions in attracting critical care staff, which makes for a relatively equal competitive salary structure throughout the state. Institutional differences in the total number of patients cared for were not due to more efficient ICUs (Fig. 2). Rather, the tendency for large hospitals to have more step-down beds seems to be the determining factor. Hospitals that can move their cardiac surgical patients from the ICU to step down beds tend to be more efficient in utilization of their ICU beds than hospitals where there is no alter-

native but the ICU until the patient is ready for a regular floor bed.

Newly recruited nurses tend to work part-time. It is a challenge to keep this increasing pool of part time staff abreast of the newest technology and familiar with the highly specialized type of ICU care. In the short term, the trend of more part-time staffing of units will most likely increase because the competition between institutions for skilled ICU nurses will lead to increased migration of nurses.

This study was not designed to address the question of whether the shortage of critical care nurses with the sequelae discussed before has an impact on patient outcome in cardiac surgery. It is conjecture to speculate if part of the already observed increase in mortality from cardiac operations in New York State compared with earlier years is due to the nursing shortage<sup>5</sup>.



**Figure 2.** Cardiac surgical ICU admissions for 1988. Comparison of number of admissions per ICU bed and nurse. The categories are based on the total number of admissions per ICU.

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