5TH INTERNATIONAL CONGRESS

AORTIC SURGERY AND ANESTHESIA

"HOW TO DO IT"

Editors
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FOREWARD

In the last two years the Euro Zone has been hit by a very profound economic crisis that has also touched many aspects of medical care and education. Nevertheless, despite many difficulties we have managed to organize the 5th International Congress Aortic Surgery and Anesthesia "How to do it" and it is, therefore, with immense pleasure that we welcome the participants, wishing them a very stimulating and educative conference.

This year we have the pleasure and honour to announce a truly international faculty of over 300 experts in their fields; they will offer very intense, dynamic sessions of rapidly paced presentations. The meeting will also feature distinguished keynote lecturers who will share their outstanding experiences.

The main features of this edition include:
- Multidisciplinary up-to-date topics
- Keynote Lectures by acknowledged opinion leaders
- Rapidly paced presentations
- World-class speakers
- Intense panel discussions
- No parallel sessions
- Hands-on workshops
- No language barriers
- Industry updates
- Cardiovascular Nursing Symposium

We would also like to express our deep gratitude to the Colleagues who contributed to this book with their manuscripts.

Once again, the warmest welcome to all the participants.

Roberto Chiesa
Germano Melissano
Alberto Zangrillo

The 5th International Congress

Aortic Surgery and Anesthesia "How to do it"

is organised under the auspices of

SICVE
Società Italiana di Chirurgia Vascolare ed Endovascolare

SCU

The European Society for Cardiovascular Surgery

Società Italiana di Chirurgia Cardiaca
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Istituto Superiore di Sanità

Sistema Sanitario Regione Lombardia

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Endovascular approach for Leriche's syndrome
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Comment: Tommaso Donati

Laparoscopic sutureless aorto-bifemoral revascularization
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THURSDAY, DECEMBER 13TH

AFTERNOON

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FRIDAY, DECEMBER 14TH

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FRIDAY, DECEMBER 14TH

MORNING

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Chairmen: Timothy A.M. Chuter, Francesco Musumeci, Vincenzo Rampoldi

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Trans-cardiac and other unusual routes to the ascending aorta
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(Age, creatinine, ejection fraction and the law of parsimony)
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Chairmen: Mauro Ferrari, K. Craig Kent, William Quinones-Baldrich

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Branched arch devices
Speaker: Stéphan Haulon
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Comment: Joseph S. Coselli

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Chairmen: Francesco Speziale, Peter R. Taylor, Piero Zannini

Predictive factors for stroke after TEVAR
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Comment: Antonio M. Jannello

Stroke following open ascending aorta and arch repair
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Comment: Vincenzo Rampoldi

Endovascular repair of ruptured thoracic aortic aneurysms: predictors of procedure-related stroke
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Comment: Pierfranco Salcuni

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Comment: Giampiero Esposito

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Chairmen: Angelo Argenteri, Bart L. Loeys, Francesco Mascoli

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Creation of regional centers for Marfan patients
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Bart L. Loeys
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16:00 - 16:50

President: Flavio Peinetti
Chairmen: Arnaldo Ippoliti, Martín Landaluce Chaves, Enzo Liguori

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Piero Anversa
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Chairmen: Nicholas J. Cheshire, Carlo Staudacher, Marian Zembala

Results of the French Trial on the endovascular repair of thoraco-abdominal aneurysm
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Comment: Francesco Stillo

Funnel technique for EVAR "A Way Out" for abdominal aortic aneurysms with ectatic proximal necks
Speaker: Salvatore Ronsivalle
Comment: Armando Natale

Laparoscopic treatment of the "Arcuate Ligament Syndrome"
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Comment: Yves S. Alimi

Aortic disease in patients with kidney transplantation
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Comment: Marian Zembala

Lung issues during thoracic and thoraco-abdominal aortic open procedures
Speaker: Giampiero Negri
Comment: Joseph J. Ricotta II

ERAS in aortic surgery
Speaker: Domenico Baccellieri
Comment: Marco Braga

Pulmonary artery catheter-directed rapid right ventricular pacing to facilitate precise deployment of thoracic endografts
Speaker: Joseph J. Ricotta II
Comment: Patrizio Mazzone

Technique, outcome, indications and complications associated with the snorkel technique for juxtarenal aneurysms
Speaker: Ronald L. Dalman
Comment: Hung-Pin Liu

CHIMPS (chimney, snorkels, sandwich, etc): is there a case to use them as first choice?
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Comment: Marcelo Ferreira

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Chairmen: Luigi Martinelli, Federico Pappalardo, Alexander Stepanenko

Left lateral thoracotomy for LVAD implantation: when?
Speaker: Alexander Stepanenko
Comment: Luigi Martinelli

Jarvik 2000
Speaker: Massimo Massetti
Comment: Alexander Stepanenko

HeartWare HVAD
Speaker: Alexander Stepanenko
Comment: Michele De Bonis

Pulsatility in patients with LVADs
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Comment: Giulio Melisurgo

Retrograde flow and aortic root stasis: tricks and pitfalls of modern LVAD technologies
Speaker: Friedrich Kaufmann
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President: Giovanni Simonetti
Chairmen: Piergiorgio Cao, Gian Paolo Cornalba, Alessandro Del Maschio

CT protocols with lower radiation and contrast media
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Comment: Maurizio Cariati

4D imaging for the thoraco-abdominal aorta
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Comment: Frans L. Moll

Angiographic "tips and tricks" during aortic procedures
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Comment: Eric Verhoeven

Innovative technologies for patient safety in aortic surgery: surgical robotics and automation
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Comment: Nicholas J. Cheshire

Transthoracic real-time 3D echocardiography: clinical role, value and limitations
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Comment: Norio Hongo

Fusion imaging for "Zero-Contrast" aortic procedures
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Comment: Francesco De Cobelli

New frontiers in imaging of aortic inflammation
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Medical digital photography: a precious asset
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Comment: Antonio G. Rampoldi

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President: Domenico Tealdi
Chairmen: Joseph S. Coselli, Michael Jacobs, Germano Melissano

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Comment: Giovanni Coppi

"Off the shelf" branched grafts for TAAA: how many patients can be treated, will it affect the outcome?
Speaker: Timothy A.M. Chuter
Comment: Roberto Pacchioni

Branched grafts for TAAA will it ever become simple and affordable?
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Comment: Timothy Resch

Contemporary improvements to TAAA open surgery
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Comment: Bart E. Muhs

Technical considerations of open TAAA repair in a transition country
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Comment: Giovanni Pratesi

Surgical management of TAAA in patients with connective tissue disorders
Speaker: James H. Black III
Comment: Yamume Tshomba

How to transfer open surgical outcomes to the rest of the world
Speaker: Joseph S. Coselli
Comment: John H.N. Wolfe

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Timothy A.M. Chuter
History of endovascular aortic procedures

SESSION 14
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President: Yves S. Alimi
Chairmen: Roberto Chiesa, Olivier A. Goëau-Brissonière, Francesco Spinelli

Persistent type 2 endoleak one year after EVAR: a negative prognostic factor
Speaker: Antoine Millon
Comment: Giuseppe Panuccio

Late surgical conversion after EVAR
Speaker: Fabien Koskas
Comment: Gabriele Maritati

Open surgery for infra-renal aortic aneurysm in patients under 80: the reasons of this first-line choice
Speaker: Patrick Moreau
Comment: Germano Melissano

European experience of the fenestrated EVAR Anaconda
Speaker: Dominique Midy
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Emergent endovascular treatment of thoracic aortic lesion
Speaker: Yves S. Alimi
Comment: Vincenzo Monaca

Long-term complications of endovascular treatment for descending thoracic aorta disease
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Technical aspects of aortic arch debranching
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Comment: Massimo Lenti

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11:20 - 12:30

President: Attilio Odero
Chairmen: Stephen Cheng, Franco Grego, Randall B. Griepp

Spinal cord vascular anatomy, what do we know and what we still don't
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Comment: Burkhart Zipfel

Preoperative spinal cord imaging
Speaker: Michael Jacobs
Comment: Frank J. Criado

Open surgical strategies for SCI prevention
Speaker: Joseph S. Coselli
Comment: Pierluigi Giorgetti

Spinal cord ischemia after endovascular repair of thoraco-abdominal aortic aneurysms
Speaker: Piergiorgio Cao
Comment: William Quinones-Baldrich

Spinal cord monitoring during TEVAR
Speaker: Nicholas J. Cheshire
Comment: Norio Hongo

Predictors of SCI after TEVAR
Speaker: Michel S. Makaroun
Comment: Fabio Verzini

Cerebro spinal fluid automated monitoring and drainage
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Early imaging of spinal cord ischemic injuries: correlation with clinical outcomes
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Randall B. Griepp
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Late results of the INSTEAD trial
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Comment: Hiroshi Otake

Late results of the ADSORB trial
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Comment: Laurent Chiche

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EVAR: WHY DO I USE THIS DEVICE?

15:50 - 16:50

President: Michel S. Makaroun
Chairmen: Franco Nessi, Piergiorgio G. Settembrini

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Speaker: Gioachino Coppi

Cook: the Zenith AAA Low Profile (LP) Stent-Graft
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Cordis: the Incraft AAA Stent-Graft
Speaker: Carlo Pratesi

Endologix: the Nellix AAA Sac-anchoring Endoprosthesis
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Gore: the Excluder AAA Stent-Graft with C3 Delivery System
Speaker: Dittmar Böckler

Jotec: the E-vita AAA Stent-Graft System
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Medtronic: the AAA Endurant Stent-Graft
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Trivascular: the Ovation AAA Stent-Graft
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Vascutek: the Anaconda AAA Stent-Graft with BluGlide introducer sheath
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Speaker: Burkhart Zipfel

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18:10 - 19:05

President: Maurizio Puttini
Chairmen: Domenico Palombo, Pietro Rispoli, Maurizio Taurino

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Speaker: Dieter Mayer
Comment: Antonio Sarcina

Treatment of ruptured AAA after endovascular abdominal aortic repair
Speaker: Gioachino Coppi
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Midterm results of EVAR for ruptured AAA
Speaker: Adamastor H. Pereira
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Open versus endovascular repair of ruptured thoracic aortic aneurysms
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Thoracic aortic pulsatility decreases during hypovolemic shock: implications for stent-graft sizing
Speaker: Bart E. Muhs
Comment: Giancarlo Mansueto

SESSION 20
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19:05 - 20:00

President: Roberto Chiesa
Chairmen: Stefano Camparini, Nabil Chakfé, Karaoglan Liberato de Moura

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Speaker: Dieter Mayer
Comment: Giovanni Lorenzi

Endovascular repair of ruptured AAA does not confer survival benefits over open repair
Speaker: Michel S. Makaroun
Comment: Gianmarco de Donato

Blunt abdominal aortic disruption
Speaker: Francesco Speziale
Comment: Marcelo Liberato de Moura

Endovascular and open repair for blunt aortic injury in Brazil
Speaker: Ricardo Aun
Comment: Giovanni Nano

Endovascular treatment of traumatic aortic lesions
Speaker: Mauro Gargiulo
Comment: Dittmar Böckler

Chairmen

ROBERTO CHIESA
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Pietro Spagnolo Division of Nuclear Medicine	**Carlo Staudacher** General Surgery Department
Yamume Tshomba Division of Vascular Surgery	**Piero Zannini** Division of Thoracic Surgery

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Giuseppe Biondi Zoccai Sapienza – Università di Roma Latina	**Stefano Bonardelli** Università degli Studi di Brescia Brescia
Giancarlo Bracale Università degli Studi di Napoli Federico II Napoli	**Stefano Camparini** Azienda Ospedaliera "G. Brotzu" Cagliari
Piergiorgio Cao Azienda Ospedaliera San Camillo-Forlanini Roma	**Alessandro Cappelli** Azienda Ospedaliera Universitaria Senese Siena
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Gian Paolo Cornalba Azienda Ospedaliera San Paolo Milano	**Gianmarco de Donato** Azienda Ospedaliera Universitaria Senese Siena
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Fabio Verzini Ospedale Santa Maria della Misericordia Perugia	

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Fabien Koskas Hôpital Pitié Salpêtrière Paris – France	**Martín Landaluce Chaves** Complejo Hospitaliero Universitario Albacete Albacete – Spain
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Burkhart Zipfel Deutsches Herzzentrum Berlin Berlin – Germany	

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John A. Elefteriades Yale University School of Medicine New Haven – Connecticut – USA	**Simone Fajer** Meir Medical Center Kfar Saba – Israel
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Po-Jen Ko Chang Gung Memorial Hospital Linkou Linkou – Taipei – Taiwan	**K. Craig Kent** University of Wisconsin-Madison Madison – Wisconsin – USA
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Lucien Castellani Tours – France	**Massimo Clementi** Milano – Italy
Valerio Di Carlo Milano – Italy	**† Sergio Ferrero** Ceriale – SV – Italy
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Edouard Kieffer Paris – France	**Benedetto Marino** Roma – Italy
Dieter Raithel Nürnberg – Germany	**Antonio Robecchi** Torino – Italy
Ugo Ruberti Milano – Italy	

Please note that the Congress Programme and the Faculty list are subject to last minute changes.

THE TIMELINE OF VASCULAR SURGERY TEACHING AT SAN RAFFAELE

by Andrea Kahlberg, MD and Luca Bertoglio, MD

Both formal and informal teaching has always been considered a priority in the department of Vascular Surgery at San Raffaele Scientific Institute. Medical education was carried out simultaneously with clinical and surgical activities since the early 1990s and has involved both university and post-graduate students.

Training in vascular surgery has been expressed over the years through group lessons, individual tutoring, publication of textbooks and, in the past eight years, also through the four previous editions of the International Congress Aortic Surgery "How to do it" congress. The emphasis given by Professor Chiesa and his collaborators not only to the formal aspects of teaching but also to the most innovative practical activities has created a school of vascular surgery to highest levels in Italy.

Technical courses

In order to focus on the more practical and technical aspects of the discipline, the **Course on Techniques in Vascular Surgery**, directed by Professor Roberto Chiesa and Germano Melissano, was first organized in November 1995 by the Division of Vascular Surgery of San Raffaele Scientific Institute in Milan in collaboration with the Department of Vascular Surgery of the University of Siena chaired by Professor Carlo Setacci. Over a 10-year period, the **15 editions** of this unique course offered for the first time in Italy a very **practical teaching methodology**, that integrated the training of students and residents in Vascular Surgery, and supported general surgeons interested in vascular techniques. Course subjects included vascular techniques, vascular anastomosis, infra-inguinal revascularization, abdominal aortic reconstruction, carotid surgery, and techniques in vascular

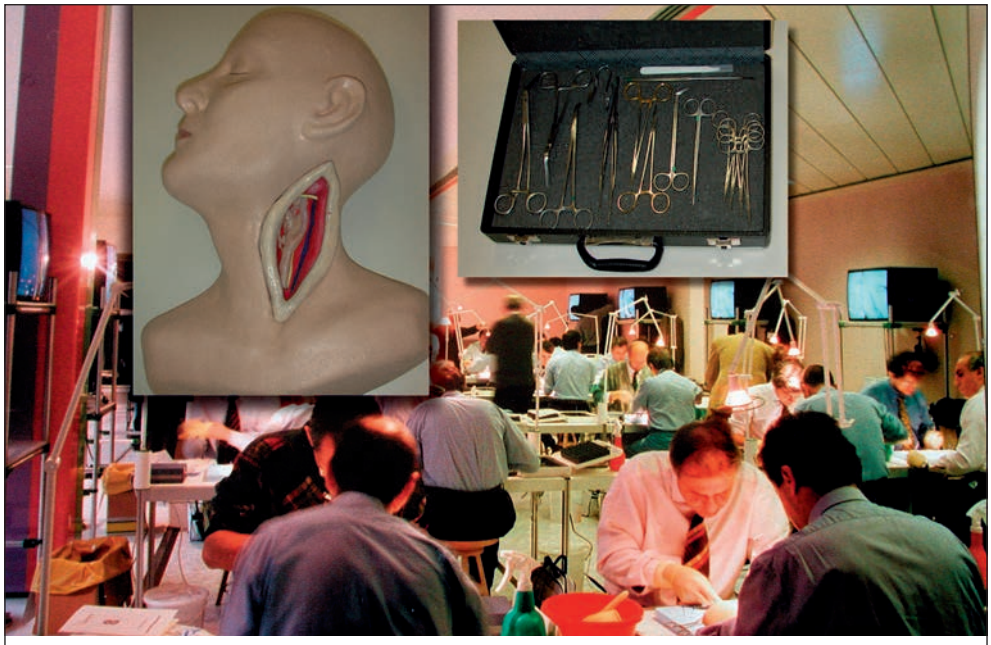


Figure 1: The 1997 edition of the Course on Techniques in Vascular Surgery, focused on carotid surgery. Participants practiced their skills on cadaveric vessels inserted on specifically prepared neck plastic models.

ultrasonography. **Round tables** on different controversial issues were also offered during the events. Every course was limited to 40 participants so as to favor personalized teaching and to encourage close contact between participants and teachers. The practical exercises were carried out on **anatomic models** specifically prepared with the use of materials that closely mimic the various anatomical details in order to check the accuracy of the particular technical aspects.

Each of the participants had a **video-monitor,** in order to follow directly the surgical gestures of the teacher and reproduce them in real-time models, while other *tutors* closely follow the exercises performed by students in order to check the work and correct any errors. The Technical Course was also organized in 1999 at Sao Rafael Hospital – Salvador – Bahia, (Brazil), entitled "Curso de Técnica em cirurgia vascular: Endoarterectomia Carotidea", in collaboration with the Vascular Surgery Unit of Sao Rafael Hospital, directed by Dr. Karaoglan Liberato de Moura.

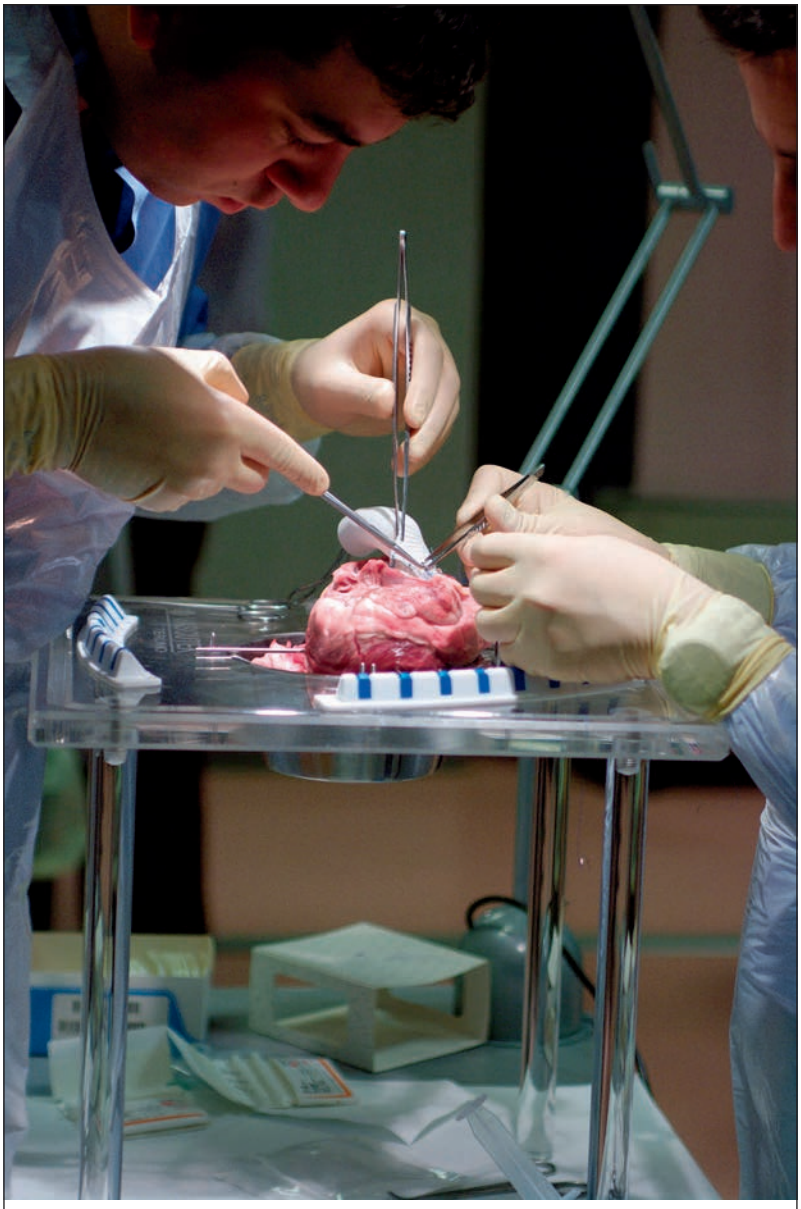


Figure 2: (2008) The hands-on training practical workshop performed during the 3rd "How to do it" congress using real bovine hearts and organs.

Figure 3: (1995) The two young convenors of the course on techniques in Vascular Surgery, Prof. Roberto Chiesa and Dr. Germano Melissano, demostrating to a participant how to perform an aortic anastomosis on a cadaveric model. The exercise was diplayed directly on different monitors on the auditorium.

Figure 4: (1995) Prof. Roberto Chiesa showing different surgical techniques to course participants.

Figure 5. (2005) Professors Carlo Setacci and Roberto Chiesa attending the 15th edition of the Course on Techniques in Vascular Surgery at San Raffaele Scientific Institute.

One-Day symposia

Thanks to the valuable collaboration and to the long-time friendship with **Professor Joseph S. Coselli** from Texas Heart Institute, St. Luke's Episcopal Hospital, Houston (TX, USA),

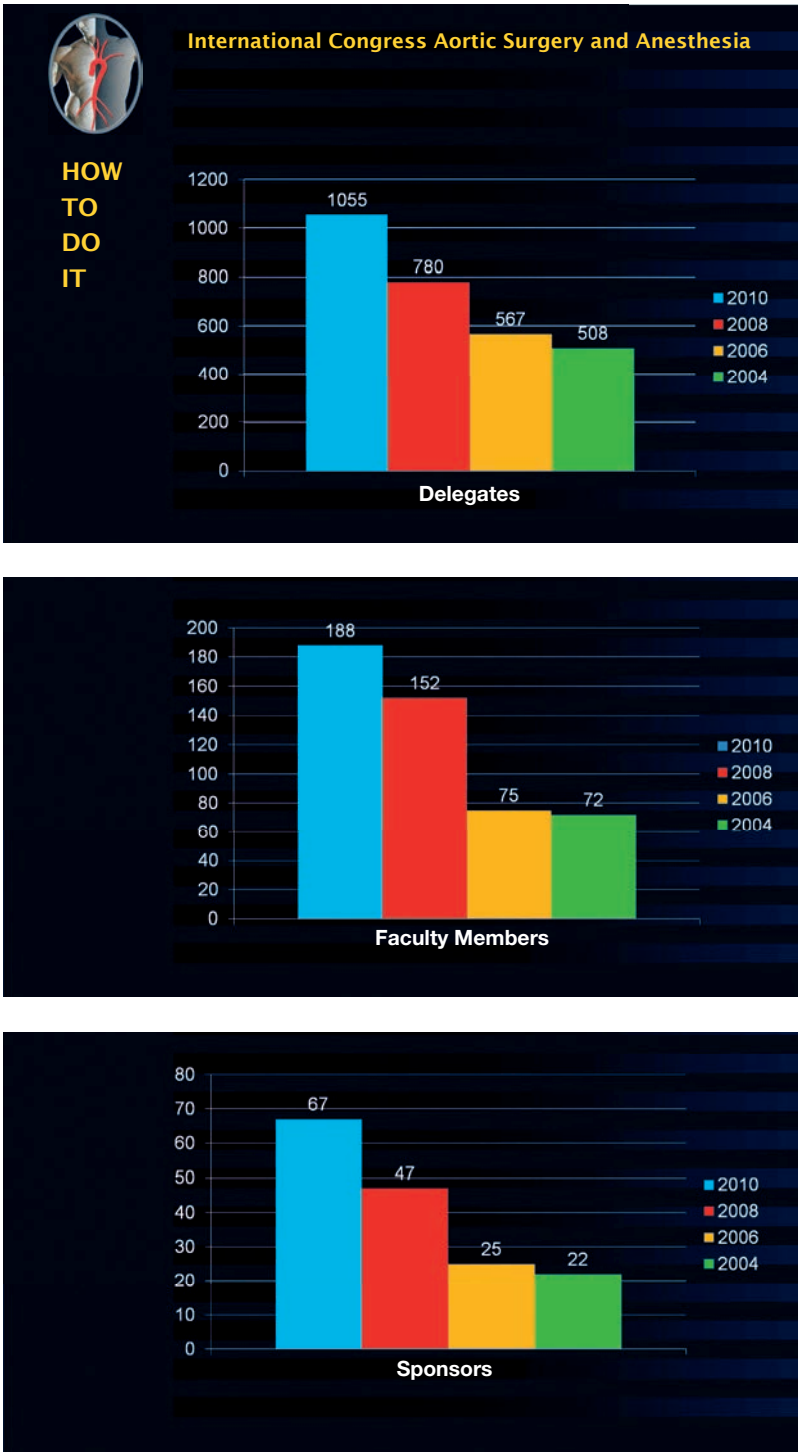
Figure 6. (2001) A young Prof. Joseph S. Coselli and Prof. Roberto Chiesa shared their experiences on thoraco-abdominal aortic surgery during one of the San Raffaele "one-day symposia"

and with **Professor Hans Borst** from the Hannover Medical School, Hannover (Germany), the Division of Vascular Surgery of San Raffaele Scientific Institute organized a series of "one-day" symposia from 1994 to 2001 with the aim to offer a comprehensive **update on surgical strategies for thoracic and thoraco-abdominal aortic disease**. Five symposia were hosted by Professor Chiesa in 1994, 1996, 1997, 1999 and 2001 with the participation of Professor Coselli performing live surgical cases, focused on the advances in the surgical treatment of thoraco-abdominal aortic aneurysms, on paranastomotic aneurysms, and on the surgical techniques for aortic arch disease. A symposium focused on the managenemt of thoracic aortic dissections was hosted by Professor Chiesa with the participation of and lecture by Professor Borst in 1998. Together with the scientific programme and lectures, a series of cases of thoracic aortic surgery were performed live and discussed during the day-long symposium.

"How to do it" International congress

Figure 7. (2010) The auditorium desk of the 4th International congress Aortic Surgery and Anesthesia "How to do it".

In 2004 Professor Roberto Chiesa and Germano Melissano organized the 1st International Congress **Aortic Surgery and Anesthesia "How to do it"**. The congress, now at its fifth edition, has evolved over the years, also including the anesthetic management of aortic operations and related cardiac surgery



Tab. 1 Growing trend of participation during the previous four editions of the "How to do it" congress.

Figure 8. (2004) Prof. Chiesa at the entrance of the first "How to do it" congress venue, next to Schumacher's F2004 Ferrari racing car, the winning car of the Formula One Championship of the same year.

Figure 9. (2010) Exhibition of racing motorbike during the 4th "How to do it" congress.

Figure 10. (2010) Prof. Chiesa chairing the 4th edition of the "How to do it" congress.

Figure 11. (2010) The main auditorium of the 4th "How to do it" congress, with the extensive participation of more than 1000 delegates from all over the world.

Figure 12. (2010) Bird's-eye view of the main auditorium of the 4th "How to do it" congress during one of the scientific sessions.

Figure 13. (2006) A GT3 racing Porsche car on exhibition during the 2nd "How to do it" congress.

Figure 14. (2008) Exhibition of Maserati and Ferrari cars during the 3rd "How to do it" congress.

Figure 15. (2008) The Italian Prime Minister, Silvio Berlusconi, and Prof. Roberto Chiesa attending the official dinner of the 3rd "How to do it" congress at Four Seasons Hotel Milano.

Figure 16. (2008) Professors Alberto Zangrillo and Roberto Chiesa at the official dinner of the 3rd "How to do it" congress.

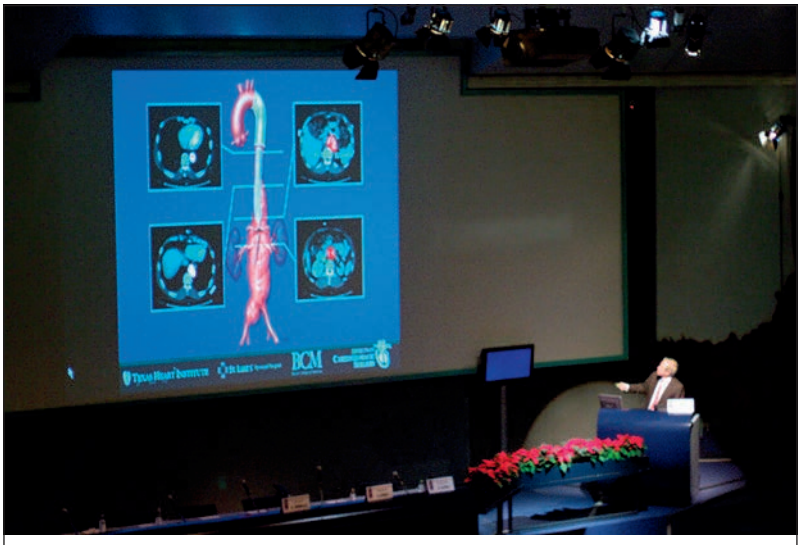


Figure 17. (2008) Professor Joseph S. Coselli giving an honorary lecture on thoraco-abdominal aortic surgery at the 3rd "How to do it" congress.

Figure 18. (2010) Professor Massimo Clementi, Dean of the Faculty of Medicine of "Vita-Salute" University, introducing the 4th edition of the "How to do it" congress.

Figure 19. (2010) Professors Roberto Chiesa and Ottavio Alfieri, chairing the 4th edition of the "How to do it" congress.

topics under the chairmanship of Professor Alberto Zangrillo and Professor Ottavio Alfieri, respectively. Due to its international faculty, which includes **top-rated experts in cardiovascular field** from Europe, the United States, Latin America and Asia, and to the highest scientific level of presentations and discussions, this conference has become an event of greatest importance in the field of vascular surgery, cardiac surgery and cardiovascular anesthesiology. **Over 1000 delegates in each edition** considered this event as the opportunity to meet outstanding experts and together to promote global exchange of recent achievements in open and endovascular aortic procedures and relevant anesthetic management.

Education in vascular nursing

Figure 20. (2010) Professor Chiesa introducing the 4th Nursing Symposium during the "How to do it" congress.

In the wake of the continuing successful experience in vascular teaching to medical students and doctors, since 1992 the educational program of the Division of Vascular Surgery at San Raffaele Scientific Institute included a series of educational activities for nurses interested in vascular surgery nursing skills. **Three educational textbooks on nursing care in vascular surgery** were edited in the last 20 years by Professor Roberto

Chiesa and Germano Melissano, and are still considered reference texts for nursing degree in vascular surgery. Moreover, during each of the past four editions of the "How to do it" congress, a parallel **nursing symposium** was hosted to improve knowledge in perioperative care of vascular patients, define nursing guidelines, and compare different nursing approaches in cardiac surgery, vascular surgery, and intensive care. Debated topics included fast track surgery protocols, the evolution of nursing care in the endovascular era, technical aspects of operating room nursing during aortic interventions, innovations in vascular wound care, and rehabilitation protocols.

Figure 21. The three textbooks on nursing care edited by the Department of Vascular Surgery at San Raffaele Scientific Institute.

Educational textbooks

The organization of Vascular Surgery Techniques Courses coincided with the publication of **four volumes**, edited by Professor Roberto Chiesa and Germano Melissano, conceived as comprehensive textbooks on most important **vascular surgical techniques**, focusing on basic techniques and infra-inguinal revascularization, carotid surgery, abdominal and thoraco-abdominal aortic surgery. These books were also considered as a preparatory theoretical guide to interactive technical courses, in order to facilitate the process of combining book-based and practical teaching, especially in post-graduate vascular education.

On the occasion of the International "How to do it" congresses in 2004, 2006, 2008 and 2010, **four volumes**

Figure 22. The four textbooks on vascular surgical techniques, that were also freely distributed during the editions of the Course on Techniques in Vascular Surgery at San Raffaele Scientific Institute.

Figure 23. An illustrated volume including unpublished scientific papers signed by the "How to do it" congress faculty was freely distribuited during all the editions of the meeting.

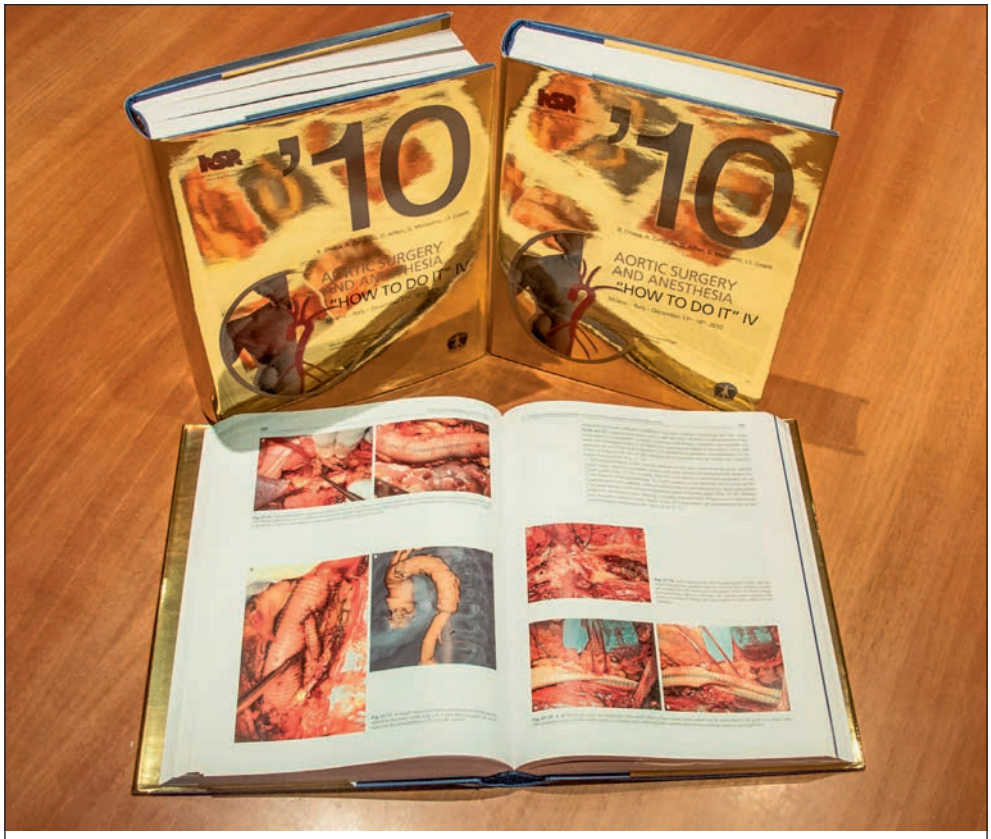


Figure 24. During the 4th edition of the "How to do it" congress a comprehensive textbook edited by Springer was distributed to participants (http://www.springer.com/medicine/surgery/book/978-88-470-1856-3).

including unpublished scientific papers related to aortic surgery and signed by top-rated world specialists in cardiovascular surgery and anesthesia were published, in order to give participants a valuable reference instrument to help in the decision of the best therapeutic approaches to aortic problems. The last editorial project entitled "**Thoraco-Abdominal Aorta: Surgical and Anesthetic Management**" and edited in 2010 by the prestigious publishing house Springer, has matured with the ambitious and impressive goal to communicate a wealth of knowledge accumulated over many years of clinical and scientific commitment. These books are well-known in the scientific community as reference-texts on aortic surgery and anesthesia, thanks to the authoritative contributions of major international vascular schools, and to the unique richness of the illustrations.

Medical education at "Vita-Salute" University

Figure 25. Residents in Vascular Surgery during the Academic Year 2011-2012 at the "Vita-Salute" University School of Medicine

Teaching medical students was considered a priority since the very foundation of the Vascular Surgery Unit at San Raffaele Hospital in 1992, firstly in collaboration with the "Università degli Studi di Milano" School of Medicine, and then (from 1996) with the **"Vita-Salute" University School of Medicine**, combined with the San Raffaele Scientific Institute. As Roberto Chiesa became Associate Professor in Vascular Surgery in 2001 and Full Professor in Vascular Surgery in 2006, his didactic work included the Vascular Surgery Educational Program in the **Integrated Course of Surgery** (Faculty of Medicine) giving theoretical and practical lessons to **over 1000 students**, incorporating formal teaching activities carried out with the help of audio-visual aids (slides, transparencies, films, tutoring, visits to the ward and operating theaters). He also held a number of collateral **optional courses** within the Faculty of Medicine, focusing on "Insights into vascular surgery", "Surgical anatomy of the arteries", "Angiology as clinical support to the vascular surgery", "Endovascular surgery as a minimally invasive approach in the future of vascular surgery","Vascular surgery in emergencies",

Figure 26. Practical surgery teaching in one of the Vascular operating theaters at San Raffaele Scientific Institute

and "Advanced diagnostic imaging of vascular disease". These courses, in addition to traditional lectures, offered the students the possibility of practicing with the help of **simulation mannequins, anatomic pieces**, and other useful equipment. In addition, Prof. Chiesa directed the vascular surgery teaching programme included in the integrated course of "Elements of Surgery and Nursing Techniques applied to Surgery" (Bachelor of Science in Nursing).

From 2001 Professor Roberto Chiesa has also been the Director of **Vascular Surgery Residency Programme** at the "Vita-Salute" University. He was also Director of the **Cardiology Residency Programme** at the same University between 2008 and 2010. He directed and coordinated **weekly seminars** on most discussed vascular surgery and cardiovascular, inviting highly-rated experts in that specific fields coming from Italy and Europe, in order to promote a continuing update on most debated topics and regular discussion between residents and preeminent vascular surgeons, cardiac surgeons, radiologists, cardiologists, and anesthesiologists.

Postgraduate education programme

Figure 27. The practical book created during the hands-on courses "Planning and Sizing of the Aortic Disease with Osirix".

Based on a 20 years of successful experience in the organization of theoretical and practical courses, the same teaching methods were also applied effectively to postgraduate university courses. From 2006, the postgraduate education programme of the Vascular Surgery Department includes a **Second Level Master's Degree in Aortic Surgery**, directed by Professor Roberto Chiesa. The course for Master's Degree is designed to provide participants with an updated and adequate theoretical and practical training in major areas of aortic surgery, both open and endovascular. Besides theoretical lessons, participants are fully involved in the clinical and scientific activities of the Department, including daily practice in the ward, in the laboratory for non-invasive vascular imaging, and in the operating theater. Final evaluation includes the preparation of an experimental thesis.

Moreover, in order to offer the colleagues a valid opportunity to improve their knowledge, in 2009 the Vascular Department

Figure 28. The journal "Abstracta", containing an extensive review of most relevant published articles in other journals, was published from 1993 to 1996 by the Department of Vascular Surgery at San Raffaele Scientific Institute.

started to organize the **hands-on courses "Planning and Sizing of the Aortic Disease with Osirix"**. With the advent of endovascular techniques, accurate preoperative imaging evaluation ("planning and sizing") has become mandatory, especially in case of thoracic and thoraco-abdominal aortic stent-grafting. The recent development and improvement of Osirix, a highly functional open source software designed for the navigation and manipulation of medical images, has now radically changed the approach to preoperative "planning and sizing" of the aortic disease, enabling simple and straightforward initial computed tomography data acquisition, sensitive information retrieval and correct planning of endovascular procedures.

Finally, the Department of Vascular Surgery has hosted a number of postgraduate medical doctors from the United States, Brazil, Ecuador, Mexico, United Kingdom, France, Germany, Austria, Romania, Croatia, Russia, Turkey, Egypt, Congo, South Africa, China, and Japan for 2-month to 1-year internships in vascular surgery, in order to improve their surgical skills and scientific curriculum.

Scientific update journals

On the basis of its vast experience in vascular research, resulting in more than 250 scientific publications on peer-reviewed

Figure 29. All the editions of Vascular Update journal, from 1996 to present, completely edited by the Department of Vascular Surgery at San Raffaele Scientific Institute.

international journals, from 1993 the Division of Vascular Surgery at San Raffaele Hospital coordinated the publication of **high-diffusion journals providing periodic updates on the international literature** in Vascular and Endovascular Surgery. Under the scientific coordination of Professor Roberto Chiesa, the journals "**Abstracta**" (1993 to 1996) and "**Vascular Update**" (1996 to present) were published quarterly. These journals contain an extensive review of the most relevant recently published articles abstracted from authoritative international scientific cardiovascular journals (Journal of Vascular Surgery, European Journal of Vascular and Endovascular Surgery, Circulation, Stroke, Journal of Endovascular Therapy, Seminars in Vascular Surgery, Annals of Vascular Surgery, The Journal of Cardiovascular Surgery, Annals of Surgery, Annals of Thoracic Surgery atc.).

Scientific societies

Over the last 20 years, Professor Roberto Chiesa and Germano Melissano have been part of the international scientific community, being active members of the most important world Societies in cardiovascular fields, such as the Society for Vascular Surgery (SVS), European Society of Vascular and Endovascular Surgery (ESVS), Italian Society of Vascular and Endovascular Surgery (SICVE), Italian Society of Surgery (SIC), Société de

Chirugie Vasculaire de Langue Française (SCV), and the European Society for Cardiovascular and Endovascular Surgery (ESCVS).

Professor Chiesa was also a member of the SICVE Board of Directors for the biennia 1998-2000 and 2002-2004. As a valuable SCV member since 2006, he is the President-elect of the Society for the year 2013, and will chair the Annual Society Meeting in June 2013 in Nice (France).

Figure 30. The forthcoming Annual Meeting of the Société de Chirugie Vasculaire de Langue Française (SCV) will be held in Nice in June 2013, under the Chairmanship of Professor Roberto Chiesa.

Keynote

1: Thursday, December 13th

Frank J. Veith, MD:
"Despite the level 1 evidence, EVAR is the best treatment for AAAs in fit and unfit patients with suitable anatomy"

Professor of Surgery at New York University Medical Center and the Cleveland Clinic

Former Chief of Vascular Surgery and Chairman of Surgery at Montefiore Medical Center and Albert Einstein College of Medicine

William J. Von Liebig Chair in Vascular Surgery

Past President of the Society for Vascular Surgery

Chairman of the American Board of Vascular Surgery

Founder and Chairman of the "VEITHsymposium"

The First U.S. Surgeon to perform an Endovascular Aneurysm Repair

Despite the level 1 evidence, evar is the best treatment for AAAs in fit and unfit patients with suitable anatomy

Frank J. Veith, MD, Benjamin W. Starnes, MD, Christopher J. Kwolak, MD,

Juan C. Parodi, MD

From the Divisions of Vascular Surgery, New York University Medical Center, New York NY, the Cleveland Clinic, Cleveland OH, The University of Washington, Seattle WA, The Massachusetts General Hospital and Harvard Medical School, Boston MA and The Universidad de Buenos Aires, Buenos Aires Argentina

Introduction

This chapter will make a judgment whether or not level 1 evidence justifies the conclusion that endovascular repair of abdominal aortic aneurysms (EVAR) is the best treatment for abdominal aortic aneurysms (AAAs) in fit and unfit patients with anatomy suitable for EVAR. In order to do this, we must first evaluate the value and limitations of Level 1 evidence. Then we must examine the Level 1 evidence that compares EVAR with open repair (OR) in patients who are fit for OR, have anatomy suitable for EVAR and require treatment for an abdominal aortic aneurysm (AAA) over 5.5 cm in diameter. We next must evaluate the level 1 evidence comparing EVAR with conservative or observational treatment in patients who have anatomy suitable for EVAR, are unfit for OR and have an AAA over 5.5 cm in diameter. And finally we must examine the level 1 evidence comparing EVAR and OR for the treatment of ruptured AAAs. This chapter will analyze critically the relevant level 1 data bearing on the superiority of EVAR in these various settings. We can then reach appropriate conclusions whether or not EVAR is the best treatment for these patients in each setting.

Value and limitations of level 1 evidence

Level 1 evidence consists of good randomized controlled trials (RCTs). Such RCTs, especially when published in leading peer reviewed journals, are considered the best possible basis for

determining good medical practice. Indeed many consider them the Holy Grail of medical evidence. However, such trials have several limitations. (1,2) These include flaws and weaknesses in the design and the timeliness of RCTs. Progress in a treatment method or control arm may invalidate a trial. So too can defects in patient selection, randomization, applicability, end-points, the nature of the population being studied and the competence of physicians doing the trial. Idiosyncratic flaws can also invalidate a RCT.

Another problem with RCTs is the possibility that author error or bias will render the conclusions of the article reporting the trial misleading. This can occur even when the report is published in a leading journal like Lancet or the New England journal of Medicine. This plus further misinterpretation or "spinning" of the trial results or conclusions by others can make the effect of the trial misleading with an unintended detrimental result on medical practice. The problem can be further compounded when Guidelines are based on such errors or bias-based conclusions. (1,2)

All physicians should recognize these value-limiting processes so that RCTs can be evaluated adequately and fairly. In that way these trials and level 1 evidence can be used optimally along with good physician judgment and other data to improve the care delivered to individual patients and to the patient population at large.

Level 1 evidence comparing evar with or in fit aaa patients

Three RCTs compared the results of EVAR with those of OR in patients suitable for either procedure. These were the EVAR 1 trial conducted in the UK (3,4,5); the DREAM trial conducted in the Netherlands (6,7); and the OVER trial conducted in Veterans Administration hospitals in the US. (8) All 3 trials observed a significantly lower 30-day mortality after EVAR. However, two of the trials, EVAR 1 and the DREAM trial, observed a "catch-up phenomenon" wherein the late mortality after 2 years became equal in patients undergoing EVAR and those undergoing OR. Largely on the basis of this equivalent late mortality, EVAR was deemed no better than OR and in some ways worse.

Because the EVAR 1 trial was the largest and most important

trial, we will analyze this trial and its reporting separately. The long-term results of this trial were published in the New England Journal of Medicine in 2010 (4). The authors observed that while EVAR had a 2.4 times lower perioperative mortality than open repair (OR), *"no differences were seen in total mortality or aneurysm-related mortality in the long term."* The authors also observed that *"endovascular repair was associated with increased rates of graft-related complications and re-interventions and was more costly*. The conclusions reached were that EVAR was neither superior to, nor the equivalent of OR. In the EVAR 1 Trial, EVAR reportedly had no better long-term survival, but did have more complications and increased costs (4).

However, we believe that there are many limitations to EVAR 1 and its author' interpretations of this trial. To be specific the trial's own data indicate that EVAR is actually superior to OR for the following reasons.

First, the EVAR 1 trial enrolled patients between 1999 and 2004 from thirty-seven hospitals in the United Kingdom. Twelve hundred fifty-two patients with aortic aneurysms over 5.5 cm in diameter and deemed suitable for either treatment were randomly assigned to undergo either open or endovascular repair. There were 626 patients in each group. Outcome measures included overall and aneurysm related mortality, graft-related complications, re-interventions, and resource usage through 2009. (3,4) Although 30-day mortality rates were 4.3% for OR, versus 1.8% for EVAR, all-cause mortality in the two groups converged to become equal at two years and aneurysm-related mortality converged at six years (Figure1). This "catch-up phenomenon" in mortality, with the two types of mortality curves then remaining equivalent out to 8 years, was the reason that EVAR was deemed by the investigators not to be superior to OR. However, the area between the all-cause mortality lines for the two groups during the first 2 years represents increased survival for the EVAR treated patients. Although this area seems small, this increased time of survival is considerable and meaningful in AAA patients. What could be more important to elderly AAA patients than many months or years of additional survival in good health? By this criteria alone, the EVAR 1 trial data documents the superiority of EVAR over OR.

Second, EVAR 1 reflected EVAR results based on old technology,

relatively inexperienced EVAR operators and outdated secondary treatment. EVAR 1 results are now more than 12 years old, and newer devices and better skills are generally available. Criteria for re-interventions are understood and applied better. EVAR operators have more experience performing the procedures and correcting potential complications. Earlier devices which had an increased incidence of migration and late failure are now rarely utilized. The delay in treatment of patients with endograft complications which eventually lead to rupture would be less likely in today's practice.

Evidence of this progress is provided in one of the EVAR articles which acknowledges that many failures such as graft disconnections and migrations were detected before aneurysm rupture, but were often not treated.(5) In fact 17 out of 22 patients who experienced late rupture had recognized graft complications that were not corrected. In 15 of these patients, aneurysm expansion was noted and not treated. Many of these ruptures might have been averted by an appropriate and timely re-intervention. The area between the curves for the two treatments, indicative of increased patient survival from EVAR, would thereby have been substantially increased.

This superiority of current EVAR results is further documented by recent reports of only 1 rupture in 974 cases of EVAR with Zenith or Excluder grafts compared to 25 ruptures occurring in 626 EVAR treated patients in EVAR 1 over comparable follow-up periods. (5,9,10)

Third, complications were not well defined in EVAR 1 and not applicable to current practice. In EVAR 1 all endoleaks were considered complications. This is misleading. Type 2 endoleaks are often benign and resolve on their own. Intervention is now required only for patients with persistent endoleaks and aneurysm sac growth. In the EVAR 1 trial, there were a total of 288 "complications" in the EVAR group versus 72 in the open group. Of these 288, 156 were Type 2 endoleaks, sharply lessening the difference in complications between the EVAR and OR groups. This difference was further reduced because in EVAR 1 the incidence of OR complications were substantially underestimated since readmission data were not collected on re-interventions for abdominal wall hernias, bowel

obstruction or late wound complications resulting from OR. The underreporting, in EVAR 1, of complications and reinterventions after OR is emphasized by the more complete data from the OVER trial. In that trial, hernia repair was required within 2 years after 4.9% of ORs, and there was no difference between the EVAR and OR groups in major morbidity or secondary interventions.(8)

Fourth, in EVAR 1 the cost comparison between EVAR and OR was unfair. Population-based studies now show that patients undergoing open aneurysm repair are twelve times as likely to undergo laparotomy and lysis of adhesions for small bowel obstruction.(11) In EVAR 1, the costs of laparotomy-related complications such as ventral hernia repair and bowel obstruction were not included in the cost analysis for the OR treated patients. It is, thus, misleading to state that EVAR was costlier than OR. Moreover, current follow-up of EVAR patients would require fewer expensive CT scans than were performed in EVAR 1, further decreasing EVAR costs and invalidating the claim that EVAR is more expensive than OR.

Based on these four considerations, it appears that the EVAR 1 conclusions that EVAR has no better long-term outcomes, but a higher incidence of complications requiring more reinterventions and is more costly than OR are misleading. These conclusions are no longer applicable to patients currently treated by EVAR. Although the level 1 evidence from all the EVAR RCTs can be construed to make a case that OR is better than EVAR for patients fit physiologically and anatomically to receive either treatment, we believe that this is an incorrect conclusion about EVAR today. All the current evidence, including a reinterpretation of some of the EVAR 1 RCT data showing that EVAR prolongs life longer than OR, indicates that EVAR is a better treatment for infrarenal aortic aneurysms in anatomically suitable, fit patients.

To conclude otherwise highlights the danger of applying level 1 data blindly and excessively. If one considers the flaws and weaknesses of the available level 1 data and reanalyzes those data and other information as we have done, the correct conclusion is inescapable: EVAR is the best treatment for AAAs in fit patients with suitable anatomy.

LEVEL 1 EVIDENCE COMPARING EVAR WITH CONSERVATIVE TREATMENT IN AAA PATIENTS UNFIT FOR OPEN REPAIR

Since its introduction in 1991, EVAR was deemed to have its greatest value as a treatment for large threatening AAAs in patients who were poor candidates for OR.(12,13) However, there has only been one RCT to test this hypothesis by comparing in a randomized study EVAR with conservative or observational treatment in high risk patients with AAAs >5.5 cm and anatomy suitable for EVAR. This trial is EVAR 2 which was performed in the UK beginning in 1999 on patients who were judged by their responsible surgeon as being medically or physically unfit to undergo OR.(14) It provided the only level 1 evidence available about treatment efficacy in these high risk patients.

The EVAR 2 trial results showed that the survival curves in these high risk patients were no better in the group randomized to EVAR than they were in the control patients who in essence underwent no treatment for their AAA. Only about one-third of the patients in both groups survived >4years. In addition, the patients randomized to EVAR had a greater need for post treatment surveillance and reinterventions and cost more to treat. Based on these level 1 findings in EVAR 2, it was concluded that patients unfit for open repair should not undergo EVAR.

Despite this level 1 based recommendation, many disagreed in a series of articles describing lower 30-day mortality rates after EVAR in similar high risk patient groups. It should also be noted that, although overall patient survival in EVAR 2 was not improved by EVAR, late AAA rupture was less frequent in the EVAR treated patients.(15)

Because of the controversy surrounding it and because EVAR 2 may have reached conclusions that are no longer generally applicable, it is appropriate to examine this trial in greater detail to see if it had flaws and to reassess the validity of its conclusions. Probably the most striking flaw is the fact that there was a long delay (averaging 57 days) between randomization to EVAR and actual performance of the procedure. During this delay, 9 of the 20 deaths within the patients randomized to EVAR occurred from AAA rupture. If earlier EVAR would have prevented some of these ruptures, patient survival in the EVAR group would have been substantially better.

A second major flaw in EVAR 2 was the 7.3% 30-day mortality

after EVAR, a figure higher than in other reported series of EVAR treated patients having comparable risk profiles. Perhaps the poor survival in the patients undergoing EVAR in EVAR 2 was due to the performance of the procedures early in the EVAR experience (1999-2004). Survival after EVAR in these high risk patients might well have been far better today with improved operator experience, better endografts and more enlightened secondary treatment of complications.

For all these reasons and even though EVAR 2 constituted level 1 evidence, the results of this trial and its conclusions are not generalizable or applicable currently. We believe more reasonable conclusions regarding the treatment of AAA patients unfit for OR would be as follows: Conservative or non-interventional treatment is acceptable in the worst risk patients with AAAs 5.5-6.0 cm or those high risk patients with anatomy unsuitable for EVAR. However, EVAR is indicated and justified in many patients who are unfit for OR and who have AAAs larger than 6 cm in diameter.

Level 1 Evidence Comparing Evar And Open Repair For Ruptured AAAs

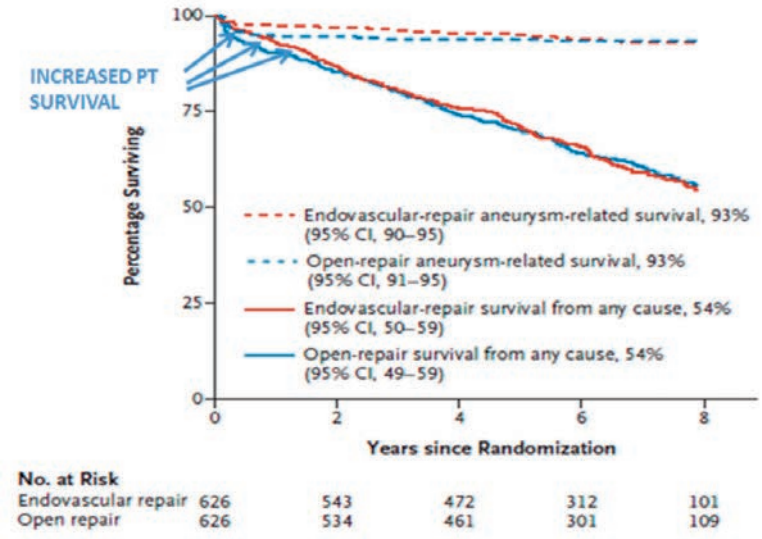
The optimal treatment of ruptured AAAs remains controversial. Several reports, including some controlled studies, claim that early and mid-term mortality is the same after EVAR and OR for ruptured AAAs. On the other hand, other groups and population based studies indicate that EVAR is associated with a lower 30-day mortality than that after OR. Some argue that this lower mortality for EVAR is due largely to patient selection, with EVAR being used in more stable patient groups. All these points of views are summarized in a recent report which also documents that in 13 centers using EVAR on every patient with suitable anatomy, even those that are unstable, the 30-day mortality after EVAR was lower than after OR (19.7% vs 36.3%, $p<.0001$.(16) This article also indicates that optimal results of EVAR for ruptured AAAs requires the use of a variety of strategies, adjuncts and techniques which have been shown to be helpful. These include having a protocol, appropriate use of supraceliac aortic balloon control and aggressive diagnosis and treatment of abdominal compartment syndrome. (16)

Nevertheless, the issue remains controversial, and many call for level 1 evidence to settle it. Accordingly 3 RCTs comparing EVAR and OR in the ruptured AAA setting are ongoing. One is the AJAX trial in France; a second is the ECAR trial in the Netherlands; and the third is the IMPROVE trial in the UK.(17) All 3 trials have methodological problems. AJAX and ECAR exclude some or all unstable patients who are most likely to benefit from EVAR. IMPROVE has had difficulty recruiting patients and requires some patient transfers before randomization. Nevertheless the results of these trials are awaited with interest.

If EVAR proves to have a lower mortality than OR in the IMPROVE trial, the issue will be settled. However, if no such improvement is shown, as appears to be the case in the ECAR trial (not yet published), many will not accept such negative level 1 evidence because of difficult methodological issues with all 3 RCTs. Centers, which are enthusiastic about EVAR in this setting and which treat all possible ruptured AAA patients in this way with excellent results, believe it is unethical to randomize such patients and refuse to participate in an RCT.(16) Two of these institutions have recently shown that, with the use of chimney and periscope grafts and other newer adjuncts, it has been possible to treat 100% of all presenting ruptured AAAs by EVAR with only a a 24% (17/70) overall 30-day mortality.(18)

Conclusion

It therefore appears reasonable to conclude that, despite some level 1 evidence to the contrary, EVAR is the best procedure for elective AAAs that require invasive treatment in fit and unfit patients. EVAR is also the best current treatment for ruptured AAAs. These conclusions come with the provisos that those performing these treatments have the necessary skills, experience, facilities, and equipment to perform these procedures effectively and that the patients have anatomical features suitable for treatment by these skills and equipment. In most institutions currently, there is still a need for OR in some AAA patients, and some others will still best be treated conservatively.



LEGEND FOR FIGURE 1

Overall patient survival (solid lines) and aneurysm related survival (dashed lines) after EVAR and OR.(4) The area between the solid lines indicated by the arrows is indicative of increased patient survival after EVAR.

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Keynote

2: Thursday, December 13th

Ronald L. Dalman, MD:
"Circulating biomarkers of aneurysms"

The Walter C. Chidester Professor of Surgery Vice-Chairman, Research and Quality, Stanford Cardiovascular Health Chief, Division of Vascular Surgery Director, Stanford Aortic Disease Treatment Center

Biomarkers in AAA Disease

Ronald L. Dalman MD

Definition

Biomarkers – expression of phenotypic characteristics either causative for, or reflective of, pathological processes relevant to disease – have been of great interest in abdominal aortic aneurysm (AAA) disease management. When discussed in the context of AAA disease, the term "biomarkers" is frequently used as a shorthand description for "circulating markers of disease presence or progression".[1] Considered more broadly, biomarkers may include any phenotypic characteristic representative of the disease feature of interest; in the case of AAA disease, including predilection for, progression of, symptomatic evolution of existing disease or sudden death. The concept of biomarkers of AAA disease has matured significantly over the last decade, in part due to continuous advances in understanding disease pathogenesis and pathophysiology. Current advances in biomarker development will be most relevant in early disease in patients already recognized to have, or be at significantly heightened risk for AAA.

Environmental exposures and phenotypic characteristics

A marked and consistent decline in AAA-related mortality has been recognized in the last ten years throughout the developed world[2-4], most likely related to concurrent or preceding declines in the prevalence of cigarette smoking.[5] Previous large screening studies recognized that smoking accounts for 70% or more of AAA risk in a population of older men.[6] Worldwide consensus guidelines now recommend that the core constituency for

abdominal ultrasound screening for AAA include men over 65 years of age with a positive history of "ever smoking", and that this screening rubric is sufficient to reduce AAA-related death by 50%.[7] *Thus the most significant biomarker for AAA is the presence of nicotine stains on the fingers or teeth of older men*. When population-based screening algorithms stray from these core criteria (including women or non-smokers), the presence of aneurysm disease drops three-fold in tested individuals. Certainly AAA can and do develop in non-smokers and women, and refinements have been proposed to existing guidelines to account for the differential influence of dozens of other risk factors (including BMI, serum glucose levels, diet, daily activity patterns, etc.) that influence AAA risk.[8] To date, however, age, sex, and smoking status serve to define the population most at risk for AAA disease.

Other manifest phenotypic biomarkers of AAA risk include height, weight (particularly distribution of excess body fat), and sibling-associated risk. After correcting for adiposity, blood pressure, lipids, inflammatory biomarkers, diabetes mellitus, or socio-economic factors, for persons born between 1900 and 1960, hazard ratios per 6.5cm greater height were negatively associated with death from coronary disease, strokes, and heart failure but positively associated with death from aortic aneurysm rupture (thoracic vs. abdominal location not specified).[9] In regards to weight or distribution of adiposity, in 318 men with AAA identified through screening, waist circumference (OR 1.14, CI 1.06 to 1.22) and waist to hip ratio (OR 1.22, CI 1.09 to 1.37) were independently associated with AAA after adjustment for other known risk factors, as were the adipokines resistin (1.53, 1.32 -1.76) and adiponectin (1.26, 1.07 to 1.50), as compared to age- and risk-factor matched controls. The anthropometric association(s) were strongest for AAA $\geq$ 40mm in diameter.[10] Increased prevalence of AAAs among siblings of AAA patients has been recognized for several decades; in a recent study from Stockholm, all siblings < 80 years of age of patients treated for AAAs for a two year period through December 2010 were approached for AAA screening. In this cohort, 11% were found to have AAA, an approximately 5-fold increase over the yield rate of population-based screening in Sweden. This included 17%

of brothers, and 6% of sisters. The mean age of the screened cohort was 66.4 years, and only 1/16 siblings was younger than 65 years of age. Of interest, an ever smoking history was present in 81% of AAA siblings compared to 59% of non-AAA siblings.[11]

Presence vs. Progression?

In regards to utility in identifying persons at risk, epidemiologic and population-based studies examining millions of individuals in case/control cohorts have successfully defined most if not all phenotypic and environmental risks associated with the presence of AAA disease. Unlike intracranial (IC) arterial or thoracic aortic (TA) aneurysms, confirmation of abdominal aortic aneurysmal enlargement is quickly and inexpensively obtained via transcutaneous ultrasound imaging. Furthermore, a single negative study at age 65, regardless of other risk factors, is highly effective in preventing aneurysm-related death. So while reduction in disease-associated death in IC or TAs cohorts may require "serial" screening for at risk individuals, a single negative screening study significantly reduces lifetime mortality risk for AAA disease. Thus the addition of more expensive and invasive biomarker alternatives is not likely to improve the efficacy or efficiency of current ultrasound-based AAA screening programs. For the foreseeable future, then, the recognition of AAA disease will remain largely ultrasound-based, within populations of persons recognized to be at increased risk based on known heritable or environmental risk factors.

The real and necessary guidance to be obtained from additional biomarker development in AAA will apply to identification of patients at risk for rapid disease progression and clinical evolution when the disease is already known to be present. For some time clinician have recognized that AAAs enlarge at individualized and time-dependent rates.[12] More recently it has become apparent that within the cohort of persons recognized to have early AAA disease, the likelihood of symptomatic evolution or progression to surgical repair will vary greatly. Data from over 15 thousand patients in 18 completed trials were included in a meta-analysis to determine the influence of relevant co-variables on aneurysm growth and rupture rates. Mean arterial pressure, anti-hypertensive or other cardioprotective medications did not

significantly influence rates of AAA enlargement. In multivariate modeling, only active smoking (increased by 0.35 mm/year, or 16%) and the presence of diabetes mellitus (reduced by 0.51 mm/yr, or 23%) significantly influenced AAA growth rate. Overall the presence of diabetes had the most significant influence on AAA enlargement of all variables included in the model. In regards to rupture, women were at four fold greater risk; smoking and high blood pressure both also increased rupture rate significantly.[13]

Beyond active smoking or the presence of diabetes, however, environmental and/or inherited influences on AAA progression are poorly understood. Aneurysm size, demographics, blood pressure and medication history were recorded from over 1,600 AAA patients identified via surveillance in the Chidester UK screening program from 1984 to 2007. Using flexible, hierarchical modeling, AAA growth rates were adjusted for the presence of confounding risk factors. Twelve hundred thirty one subjects met inclusion criteria of having at least one follow-up ultrasound study and a surveillance interval of at least one month. In this series of small AAA (overall mean diameter of 35 mm, interquartile range 31-42 mm), linear growth rate was 2.81 mm/yr (adjusted growth rate 1.43, CI -2.26 to 6.06 mm/yr). Overall, adjusted growth rates demonstrated a bimodal pattern, with nearly 50% of all AAA identified at screening in this age range never progressing to symptomatic status or requiring surgical repair. Participants whose AAA became symptomatic in follow-up experienced growth rates of 2.99 mm/yr (2.80 to 3.18) vs. 1.08 mm/yr (0.89 to 1.27) in those without significant clinical evolution.[14] Results from both these reports suggest that within the population of patients with AAA identified at screening (as opposed to those referred to surgical practices for consideration of repair), significant differences exist in terms of risk of ultimate rupture or need for surgical repair. In addition to the recognized influences of smoking, diabetes, gender and hypertension (the last two related to risk of rupture rather than enlargement), ideally, the recognition of readily identifiable biomarkers that track clinical progression will significantly improve aneurysm care by targeting treatment (surgical or potentially medical) to patients who need it most, regardless of absolute aortic diameter at the time of diagnosis.

The Genetic Basis of Heritable Risk

In the "omic" era, the ultimate biomarker is represented by at-risk alleles present within each individual's genome. Genetic influences on AAA disease were comprehensively reviewed recently by Harrison and colleagues.[15] Heritable risk patterns demonstrated in AAA disease are most consistent with multifactorial (complex) associations rather than Mendalian inheritance. Candidate gene studies have identified single gene polymorphisms (SNPs) in loci related to regulation of the renin-angiotensin system and folate metabolism that consistently associate (albeit weakly) with increased AAA risk. Using genome-wide association studies (GWAS) comparing cases to controls, SNPs at chromosome 9p21 have also been identified that predict risk for AAA disease (as well as coronary disease and intracranial aneurysms), with likelihood of aneurysm development increasing by approximately 30% per at-risk allele.[16] Again, the effect size though significant is small, with ORs ranging between 1.22 to 1.38 per at-risk allele present. A subsequent GWAS has reported additional associations between AAA disease and SNPs in the DAB21P gene on 9q33, which also identified cohorts at risk for coronary disease, venous thromboembolism and peripheral arterial disease.[17] The common mechanism responsible for increased aneurysm risk at both sites on chromosome 9 seems to be related to influences on vascular smooth muscle cell (VSMC) proliferation and senescence.[15] More recently, variations in expression of microRNAs, non-protein coding cellular regulatory elements expressed in response to environmental stimuli, have been recognized to influence VSMC proliferation and senescence in cultured human VSMCs[18], modulate progression of experimental AAAs (esp. in association with nicotine exposure), as well as also be differentially expressed in human aortic aneurysm surgical samples.[19] These examples underscore the growing significance of regulation of VSMC proliferation and senescence in AAA pathophysiology, a pathological mechanism rarely investigated in human disease cohorts to date and recognized only through the considerable power for novel gene discovery provided by whole genome or exome association studies. Most importantly for the purposes of this review, with genotyping available from multiple commercial ventures starting at USD $299/person, in the near future AAA patients may be

able to gain significant insight into their individual risk for disease progression and specific subsequent clinical events based simply on a sputum sample (see 23andme.com).

Cellular and molecular imaging

Modern methods of molecular imaging enable localization and quantification of specific ligands of interest within diseased tissue. In AAA disease, the ability to localize mural inflammatory macrophages or regions of increased matrix turnover may help predict patients at risk for rapid enlargement or clinical evolution.

Cellular Imaging

Increased F18-fluorodeoxyglucose (FDG) uptake in resident inflammatory cells has been associated with aortic wall inflammation, instability and symptomatic evolution of large AAA when co-registered with computed tomographic aortography (CTA)[20]; this technique may also identify areas of increased local wall stress AAA and TAA.[21] We and others have failed to demonstrate significant tracer uptake in smaller, asymptomatic aneurysms regardless of growth rate, however, and FDG/PET-CTA does not lend itself well to serial surveillance imaging. Alternative methods to localize and quantify inflammatory macrophages have measured iron-based contrast agents such as small or ultrasmall paramagnetic iron oxides (SPIO, USPIO) nanoparticles using magnetic resonance imaging (MRI). Differential aortic mural uptake of USPIOs has identified subsets of small AAA patients who subsequently experience more rapid growth[22], and refinement via ligand-based targeting (such as that provided by folate receptor expression on activated macrophages) promises to further improve imaging specificity.

Angiogenesis/Matrix Imaging

In the angiotensin II/apolipoprotein E deficient (AngII/ApoE-/-) mouse model, we employed the fluorescent dye Cy5.5 to label single-chain vascular endothelial growth factor (VEGF) to target VEGF receptor expression in areas of inflammation, mural neoangiogenesis and aneurysmal aortic enlargement. In this construct, signal intensity increased as a function of aortic diameter in diseased segments.[23] Using the same model, we created nanoparticles by conjugating Arg-Gly-Asp peptides to

human ferritin nanocages to target the $\alpha_v\beta_3$ integrin expression in areas of aortic mural inflammation. In situ and ex vivo fluorescent imaging demonstrated increased uptake of Cy5.5-labeled targeted nanoparticles in macrophages and adjacent areas of neoangiogenesis.[24] More recently we used activatable fluorescent probes to image spatial distribution of relative protease activity (MMPSense 680 and ProSense 750) in the AngII/ApoE-/- and porcine pancreatic elastase infusion murine models following aneurysm creation. MRI at 4.7T was used to quantify luminal motion before and after Ang II or PPE infusion. In the AngII model, AAAs form near the location of maximal abdominal aortic curvature, and these experiments the direction/magnitude of expansion was correlated with the direction of suprarenal aortic motion. Similar site-specificity was not observed in alternative murine models that develop more distal aneurysms of the abdominal aorta. Protease-activated fluorescence correlated with areas of maximal expansion and inflammation. These results provided further experimental evidence that aortic geometry, wall motion and luminal flow conditions influence aneurysmal pathologic features.[25] Taken together, cellular and molecular markers of angiogenesis, $\alpha_3\beta_3$ integrin expression, proteolysis or similar structural or inflammatory markers may prove useful in tracking disease progression if these technologies can be successfully translated to clinical application.

Circulating markers of pathogenesis and progression

Being able to readily identify circulating markers of AAA presence and progression would greatly facilitate disease monitoring as well as potential responses to proposed pharmaceutical inhibition strategies. Based on the characteristic features of AAA disease, investigators have examined circulating lipids, thrombosis-related proteins, markers of extracellular matrix metabolism and inflammatory cytokines as candidate biomarkers, either alone or in combination, as potential plasma-based biomarkers. Additionally, proteomic strategies have been employed to identify differentiating proteins in case/control studies. Candidate biomarkers identified from these analyses include the carboxyterminal propeptide of type I procollagen, the amino terminal propeptide of type III procollagen, and

tenascin-X; MMPs 1,2,3 & 9, α 1-antitrypsin and cathepsins; HDL, LDL or triglyceride lipid fractions, apolipoprotein B and lipoprotein (a); interleukins 1B, 2, 6, 8, tumor necrosis factor-α, interferon-γ, hsCRP, osteopontin, osteoprotegerin, resistin, leptin, adiponectin, sCD28 and 86, sCTLA-4, sVACM, sICAM, endothelin 1&2, neutrophil gelatinase-associated lipocalin (NGAL) and antibodies to *C . pneumoniae.* Methodologic issues complicate the interpretation and significance of nearly all these studies, and to date none of these markers have proven useful for monitoring disease and predicting clinical evolution in asymptomatic patients.[1] As an example, when studied in 206 patients for up to five years follow-up, neither endothelin-1, tumor necrosis factor – α, IL-6, CD40 ligand, and the APC-PCI complex levels (all found to be increased in AAA patients in prior case/control studies) demonstrated any correlation with AAA growth in Swedish patients, and levels did not distinguish patients who did or did not experience rupture during followup.[26] High sensitivity C-reactive protein (hsCRP) is also illustrative in this regard. Although modestly elevated hsCRP levels distinguish cases from controls in population-based screening studies, and that larger aneurysms are associated with increased levels, Norman and associates were not able to correlate absolute level with disease progression.[27] More recently, quartiles of CRP level variation, however, have been shown to predict AAA progression, e.g. an increase of >1.4mg/L was associated with an expansion rate of 4.8 mm during the followup interval vs. 3.9 mm in patients whose CRP increased by less than that amount. Incorporating all relevant variables into a multivariate age-adjusted logistic regression model, only initial AAA diameter and variation of CRP level were predictive of AAA expansion, with ORs of 6.3 (95% CI 3.1-7.5) and 3.4 (2.1-5.6), respectively.[28] To date the most comprehensively evaluated circulating biomarker for AAA presence and progression is D-dimer, a fibrinolytic byproduct potentially associated with aortic luminal thrombus remodeling and biologic activity. Unlike almost all other putative circulating biomarkers, D-dimer has been associated with both the presence and progression of AAA, in distinctly different at-risk populations. The utility of D-dimer when integrated in a comprehensive risk factor algorithm was highlighted most dramatically via classification and regression tree (CART) analysis,

where a model sequentially incorporating D-dimer levels > or ≤190 ng/ml, smoking status, D-dimer levels > or ≤400, and C-reactive protein > or ≤ 3.4 mg/L were able to define subgroups of patients whose AAA prevalence ranged from 3 to 82%, in both patients identified via population screening as well as those referred to a surgical practice for operative management. Measured in both average growth per year in millimeters, as well as average growth per year in percentages of initial AAA diameter (to account for the known influence of diameter on growth rate), plasma D-dimer levels segregated into quartiles between <150 mg/ml, >150 to ≤300, >300 to ≤900, and >900 were highly statistically significantly associated with increasing growth rates.[29] This study for the first time illustrated how a specific circulating biomarker, when integrated into a evaluation rubric incorporating existing clinical and biochemical risk factors could play a significant role in improving screening efficiency and tracking disease progression.

In summary, distinct genetic and phenotypic variants associated with AAA progression and symptomatic evolution are being recognized across a broad range of measurement modalities. Some markers directly reflect aortic pathologic processes, such as neoangiogenesis, while others more generally track systemic influences such as C-reactive protein. The most significant impact of biomarker assessment will likely be realized by integration into comprehensive risk assessment algorithms incorporating relevant clinical, demographic and environmental variables. Future advances in disease management, from diagnosis to suppression to potential restoration strategies incorporating stem cell technology, will depend on development and validation of emerging AAA biomarker science.

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Keynote

3: Thursday, December 13th

Cesare R. Sirtori, MD, PhD: "New drug/biotech approaches to arterial disease"

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New drug/biotech approaches to arterial disease

Prof. Cesare Sirtori, Professor of Clinical Pharmacology,
Università degli Studi di Milano;
Director, Center for Dyslipidemias,
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Risk factors for arterial disease are well known to any specialist as well as to the public. High cholesterol, elevated blood pressure, diabetes, smoking and others are certainly causative factors (1). The end product of these is, however, largely the same, ie cell proliferation in the wall of arteries, associated with cholesterol deposition and proliferation of monocytes/macrophages (2). The "inflammatory" picture, underlined by many authors as characteristic of the atherosclerotic arterial disease is, however, in large part consequent to the presence of cholesterol in the arterial wall. Cholesterol, a crystalline molecule, tends in fact to induce inflammatory reactions by activating *inflammasomes*, in particular the NLRP3 inflammasome (3) (Fig. 1). This leads both to plaque growth as well as to plaque instability (4). Thus, in spite of the frequent mentioning of inflammation as a feature of atherosclerotic vascular disease, inflammation is mainly the consequence of just excess cholesterol crystals in the arterial wall.

In view of this and other similar observations, a therapeutic approach to arterial disease may rely on drugs/biotechs that:

- can remove arterial cholesterol;
- can reduce the inflammatory reaction;
- can induce lipoprotein changes, in the long run resulting in reduced arterial cholesterol content/reduced inflammation.

In addition, and looking into a more distant future, microRNA (miRNA) therapeutics may provide a novel approach. MiRNAs as well as miRNA antagonists, eg antagonists of miRNA-33,

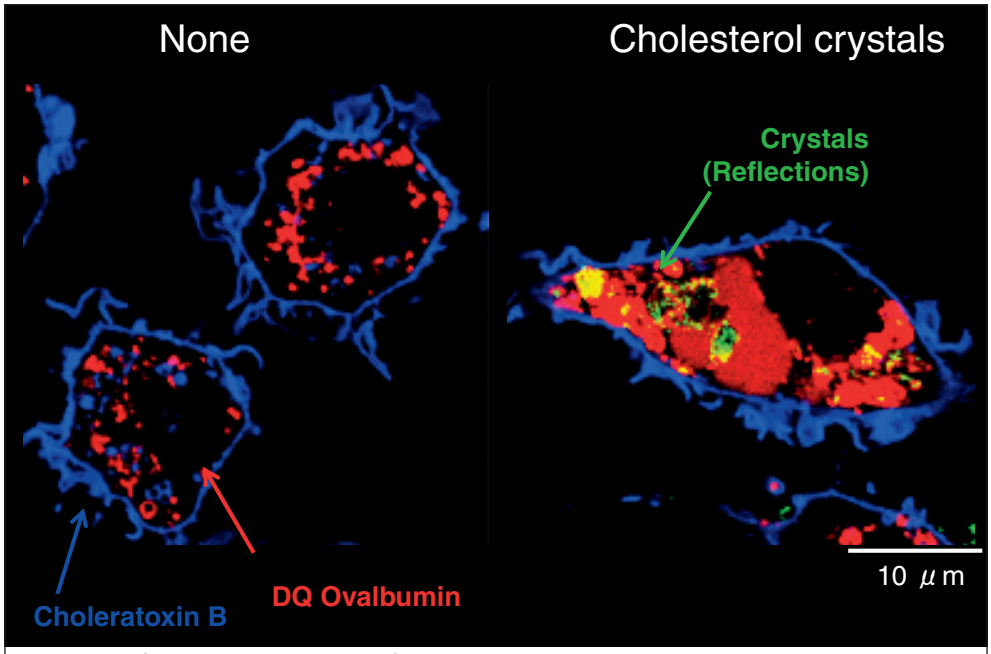

Fig.1 - Inflammatory properties of crystalline cholesterol on macrophages, mediated by the inflammasone NLRP3. While (left) albumin exposure does not lead to cell membrane (choleratoxin) damage, exposure to crystalline cholesterol leads to cell membrane damage and phagolysosomal swelling and rupture. *Duewell et al, Nature 464, 1357, 2010 (modified)*

increasing HDL-cholesterol, and of miRNA-126, potentially improving vascular regenerating capacity after myocardial infarction, are novel targets of biotech therapeutics for arterial disease (5).

Drugs/biotechs reducing arterial cholesterol

The major mechanism of cholesterol removal from tissues is by way of high density lipoproteins (HDL). There is clear evidence, from epidemiological studies, that individuals with elevated HDL-cholesterol (HDL-C) have a reduced risk of arterial disease, conversely, individuals with low HDL-C are at increased risk (6).

HDL provide a powerful circulating mechanism for tissue cholesterol removal. This allows the body to dispose of cholesterol from different tissues, and it is crucial in cholesterol removal from the artery (7). As pointed out, cholesterol is crystalline and leads

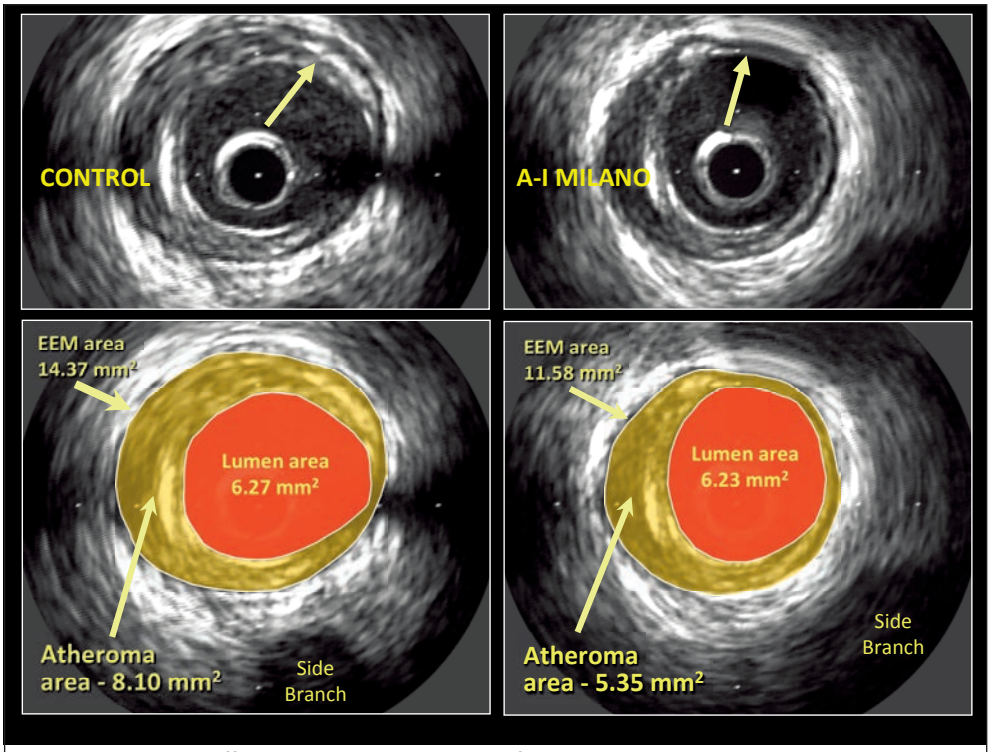

Fig.2 - Striking effects on coronary lesions of A-I Milano, as assessed by intravascular ultrasound. Area of atheroma is reduced by about 40%, particularly in lipid rich sites. *Nissen et al, JAMA 290, 2292, 2003 (modified).*

both to lipid accumulation and to plaque frailty, consequently to an enhanced risk of acute thrombosis.

HDL can effectively remove arterial cholesterol, thus explaining their potential clinical benefit, both directly, generally under the form of apo A-I liposomes (HDL-therapy), or indirectly by drugs increasing HDL-C levels. This latter aspect will not be considered in this review.

The major breakthrough in HDL-therapy has been the development of a recombinant apo A-I, named apo AI-Milano, reproducing a genetic mutation of apo A-I first discovered in a small Italian village, Limone sul Garda. The apo A-I Milano is present in blood as a monomeric and dimeric form. This latter shows a prolonged plasma residence and a very powerful

capacity to remove cell cholesterol (8,9) as well as to exert other effects, eg enhanced thrombolysis (10). Recently, a wild-type recombinant apo A-I has been also made available, associated with different phospholipids and an extractive apo A-I from blood is undergoing clinical development (11).

While the apo AI-Milano has shown a very exciting capacity to reduce coronary plaques, as determined by intravascular ultrasound (12) (Fig. 2), this same capacity has been shown to a lesser extent by the extractive apo A-I liposomes (11), while there are at present no real data on recombinant apo A-I complexed with phospholipids, mainly sphingomyelin. Thus of the three products, the A-I Milano dimers seem to provide the most promising therapeutic approach, now undergoing clinical development in the hope of obtaining a direct approach to arterial plaque removal.

Arterial inflammation: a real target?

While cholesterol is indeed an inflammatory molecule and there are data indicating that, eg, statins can reduce cholesterol crystals directly (even in vitro!) in appropriate conditions (13), it has as yet not been brought to real life the idea that just reducing inflammation may prove a beneficial approach to arterial disease.

Results of the JUPITER study with rosuvastatin indicated that individuals with elevated C reactive protein (CRP) appear to benefit from statin treatment in terms of event reduction (14). Unfortunately, these individuals also had a definite LDL-cholesterol reduction during therapy and dissociation between the two biochemical endpoints could not be achieved (15). Two recent papers criticized the concept of CRP reduction, based on other large clinical studies, where this parameter appeared not to be reduced in parallel with cardiovascular prevention (16, 17).

The hypothesis that a direct inhibitory intervention on inflammation (without a major effect on LDL-cholesterol or other components of the atherosclerotic process) is, however, being tested in two large randomized trials. The CANTOS

(Canakinumab Anti-Inflammatory Thrombosis Outcome Study) evaluates the potential activity of canakinumab, a fully humanized monoclonal IL-1β antibody, indicated for other chronic inflammatory conditions (18). Canakinumab will be injected sc as 50, 150 or 300 mg every three months and compared with placebo in 17,200 participants, stable post-MI patients. These remain at elevated risk, as gauged by raised levels of CRP (> 2 mg/L), despite the usual optimal therapy including statins. The average follow up will be 3.4-4 years.

Another ongoing study is the Cardiovascular Inflammation Reduction Trial (CIRT) (19) sponsored by the US Heart Lung and Blood Institute. CIRT will test low dose methotrexate compared to placebo, in the secondary prevention of major cardiovascular events. Methotrexate will be given in the same dose ranges commonly used to treat rheumatoid arthritis, ie 15-20 mg weekly. CIRT will enroll 7,000 patients in the US and Canada beginning in 2013 and will involve 3.5-4 years of trial follow up.

Should these trials prove neutral for the primary endpoint, they may indicate either that inflammation is not the causative pathway of atherosclerosis, or that the mechanisms of inflammation suppression are suspect. Of course, should these trials prove positive, they will likely usher in an entirely new era of therapy for CHD, perhaps somewhat akin to the widespread application of statin therapy.

Other potential approaches: lipoprotein oxidation and phospholipaseA2 inhibition

Explanations of the inflammatory role of cholesterol or other lipid components in atheroma development have taken into account the toll-like receptor (TLR) pathways in plaque initiation and progression. The presence of TLRs within plaques and on infiltrating leukocytes gave clear evidence of the involvement of innate immunity in atherogenesis (20). TLR4, besides being expressed in areas of plaques prone to rupture, may increase risk because of polymorphisms of TLR4 genes, associated with the susceptibility to coronary events in response to statin treatment (21). A special role is that of oxidized LDL (oxLDL) exerting a pro-inflammatory role, in part by binding to TLR4; knock-out (KO) of

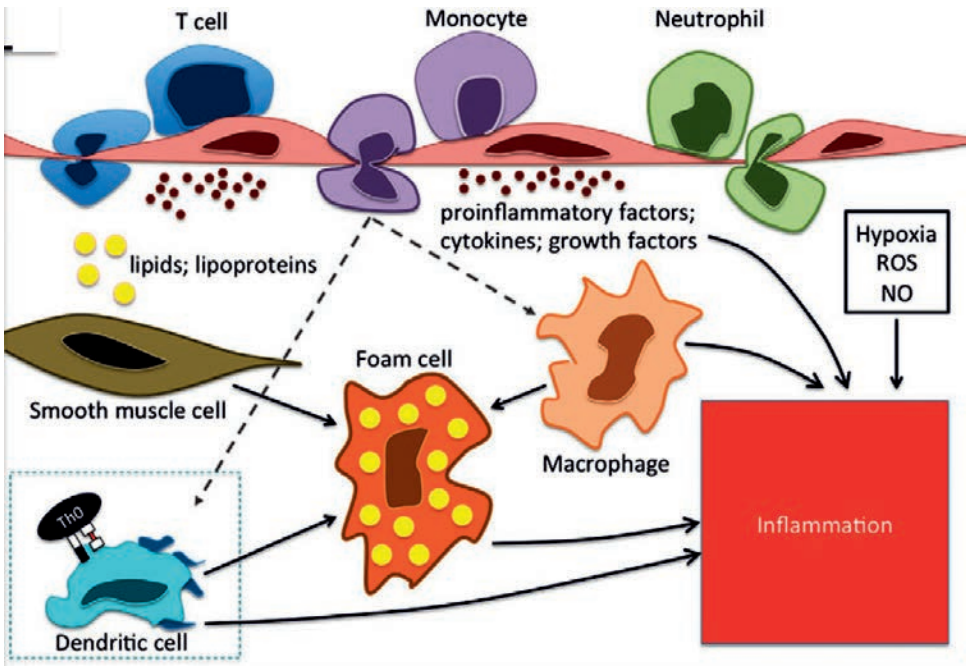

Fig. 3 - Involvement of numerous cell types in the arterial inflammatory response, which is part of atherosclerosis. Of particular note is the participation of immune-regulating cells, such as T lymphocytes and dendritic cells. *Wong et al, Can J Cardiol 28, 631, 2012 (modified)*

the downstream effector of TLR4 (myD88) has been shown to reduce the atherosclerosis burden (22).

While a statin can downregulate TLR4 expression in monocytes, thus reducing expression of downstream inflammatory mediators, a special interest is now placed on treatments targeting innate immunity/T cell regulation in the setting of atherosclerosis (Fig. 3).

Phospholipase A2 (PLA2) associated with lipoproteins can modify phospholipids in particles, thus generating atherogenic species (20). Two members of the PLA2 superfamily, ie lipoprotein associated PLA2 (Lp-PLA2) and secretory PLA2 (sPLA2) have both been linked to atherosclerosis (23). Lp-PLA2 is generated by inflammatory cells including monocytes, macrophages and T lymphocytes thus being linked to innate immunity control; it

is associated particularly with LDL and expression is increased in complex plaques. sPLA2 is instead an acute phase reactant, expressed in hepatocytes and smooth muscle cells. It acts by modifying phospholipids, thus generating pro-inflammatory lysophosphatidylcholine and oxidized non esterified fatty acids (25). Both enzymes modify lipoproteins and lead to more highly oxidized LDL particles. OxLDL induce inflammation by stimulating endothelial cells to release chemotactic proteins with consequent increased recruitment of inflammatory leukocytes to the plaque site and increased differentiation of monocytes into macrophages, thus contributing to the formation of foam cells (26). In addition to their contribution to plaque growth, Lp-PLA2 and sPLA2 have been found to be effective risk markers for coronary disease and adverse CV events (27). Development of inhibitors of PLA2 has thus become a promising area of research in atherosclerosis (28).

A number of agents have been tested for their potential to inhibit Lp-PLA2 and reduce plaque development, although the number of enzyme isoforms within this superfamily remains a challenge. Among direct/selective inhibitors of Lp-PLA2, darapladib (SB-480848) has provided evidence of therapeutic activity in swine models of diabetes and hypercholesterolemia (29). Drug treated animals show reduced coronary lesions and, in particular, reduced fibroatheromas. These findings have been supported by studies in coronary patients, indicating a moderate reduction of LDL-cholesterol and a marked decrease of both CRP and IL-6 (28).

In a phase II human study, in patients with angiographically documented coronary disease a sustained reduction of Lp-PLA2 activity was shown in the darapladib group, without differences in LDL levels (30); an apparent significant decrease in the progression of the necrotic core size was noted in drug treated patients (31). A phase III randomized study (Stabilization of Atherosclerotic Plaque By Inhibition of darapLadIb TherapY (STABILITY) involves 15,500 patients in 638 locations. The study is ongoing and should be completed in 2013 (32).

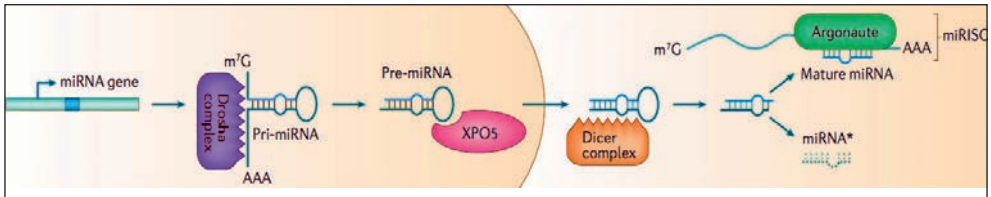

Fig. 4 – MicroRNA (miRNA) genes are transcribed into primary miRNA (pri-miRNA) transcripts that undergo processing by Drosha-containing complexes. The resulting hairpin precursor miRNAs (pre-miRNAs) are transported to the cytoplasm and the Dicer complex removes the loop region from pre-miRNAs, and one strand of the resulting duplex is bound by Argonaute to form a miRNA-induced silencing complex (miRISC), which targets mRNAs for regulation. *Pasquinelli, Nature Rev Genetics 13, 271, 2012 (modified)*

The Future: MicroRNA therapeutics

MiRNAs are a large class of short single-stranded RNA molecules (19-25 nucleotides). They negatively regulate the translation of different proteins, by binding to complementary sequences in the 3'untranslated region of mRNAs, thus inhibiting translation without affecting stability (32). The negative regulation of mRNA translation occurs by assembling into a complex known as miRNA RNA-inducing silencing complex.

A scheme of miRNA activity is reported in Fig. 4. It includes the RNA-specific endonuclease Dicer, involved in the processing of pre-miRNA into the mature form; the Argonaute protein, consisting of four isoforms, one of which, the Slicer, can cleave target mRNA; the P-body protein PW182; the HIV transactivating response RNA-binding protein, recruiting the Slicer to the miRNA-inducing silencing complex, and others whose miRNA RNA-inducing silencing complex-related functions have not been fully elucidated (33). The complex binds a target gene via partial sequence complementarity between the miRNA and preferentially, a conserved site within the 3' untranslated region of the gene.

A number of potential targets for miRNAs have been reported in cardiac diseases (33). Some of these have to do with cardiac hypertrophy and failure. MiR-23a is upregulated during cardiac hypertrophy and downregulation by KO or by an antagomir is sufficient to bring back heart size to normal (34). In the field of atherosclerosis and ischemic heart disease miR-21 is an inhibitor

of apoptosis in myocytes and other cell types. It is acutely downregulated during myocardial ischemia, specifically within the ischemic zone, where its overexpression can reduce infarct size and retard progression to failure (35). Similar to miR-21, miR-494 is also reduced in the infarct zone: normalizing levels by transgenic overexpression reduces infarct size and improves contractility (35). MiR-126 is highly expressed in epithelial and endothelial cells: it can be antagonized during ischemia resulting in enhanced angiogenesis (36).

Finally, and most interesting in the field of arterial disease, miR-33 targets the ATP-binding cassette A1 (ABCA1) cholesterol transporter, that mediates cell cholesterol efflux to HDL. Treatment of LDL-receptor deficient mice with anti-miR-33 resulted in upregulation of ABCA1 in the liver and macrophages, increased HDL-C and ultimately reduction of plaque size and inflammatory gene expression (37). These results were replicated in primate models: an anti-miR-33 raised HDL-C and reduced also levels of very low density lipoprotein-associated triglycerides (38).

While development of miRNA therapeutics is only approaching clinical outcome studies, a number of companies are focusing their efforts into different therapeutic areas, eg, cancer, metabolic disorders and atherosclerosis (33). Findings from these ongoing developmental studies are awaited with high interest.

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Keynote

4: Friday, December 14th

John A. Elefteriades, MD: "Genetics and genomics of aortic disease"

William W.L. Glenn Professor of Cardiothoracic Surgery and Chief of Cardiothoracic Surgery at Yale University and Yale New-Haven Hospital

Director of the Center of Thoracic Aortic Disease at Yale

Past President of the Connecticut Chapter of the American College of Cardiology and member of the national Board of Governors of the College

Past President of the International College of Angiology

Walter Bleifeld Memorial Award for Distinguished Contribution in Clinical Research in Cardiology

John B. Chang Research Achievement Award

Socrates Award from the Thoracic Residents Association, Thoracic Surgery Directors' Association, and the Society of Thoracic Surgeons

Genetics and genomics of thoracic aortic disease

Pawel Pomianowski, MD
John A. Elefteriades, MD

Hippocrates first described a clinical syndrome consistent with Ehler-Danlos and its accompanying easy bruising and bleeding. Writing in his "Airs, Waters, and Places", he noted that Nomads and Sythians had lax joints and easy bruising. The Danish dermatologist Ehler in 1901 and the French physician Danlos in 1908 refined the clinical description of the disorder. These were the first clinical reports of a disease which we now appreciate as genetically heterogeneous.

Thoracic aortic aneurysms (TAA) and aortic dissections (TAAD) are responsible for 15,000 deaths in the United States annually [1]. Despite progressive dilatation, aortic aneurysms usually remain asymptomatic until dissection or rupture occurs. While there are highly effective prophylactic surgical interventions, their implementation is hampered by the difficulties in identifying at-risk subjects. Indeed, there are no high-yield risk factors that can be used for screening the general population. Identification of the underlying genetic basis of aortic aneurysms should lead to better screening, early intervention, and better clinical outcomes.

Thoracic aortic aneurysms are divided into two broad categories: syndromic (associated with abnormalities of other organ systems) and non-syndromic (with manifestations restricted to the aorta) [2]. Syndromic aortic aneurysms occur in patients with: Marfan syndrome, Loeys-Dietz syndrome (LDS), Aneurysm Osteoarthritis Syndrome (AOS), Arterial Torturosity Syndrome (ATS), Ehlers-Danlos Syndrome (EDS) [2-3] and TGFβ mutations. Many of the syndromic aneurysms can be diagnosed

Table 1

Classification	Chromosome	Gene	Protein	Location	Frequency	Inheritance
Syndromic						
Marfan	15q21.1	*FBN1*	Fibrillin 1	ECM	1:5000-10,000	AD
Loeys-Dietz	3p24-25 9q33-34	*TGFBR2,* *TGFBR1*	TGFβ-R2 TGFβ-R1	Cell surface	Rare	AD
Ehlers-Danlos	2q24.3-31	*COL3A1*	Type III collagen	ECM	1:10,000-25,000	AD
ATS	20q13.1	*SLC2A10*	GLUT10	Intracellular	Rare	AR
AOS	15q22.2-24.3	*Smad3*	SMAD3	Intracellular	Rare	AD
TGFB2	1q41	*TGFB2*	TGFβ2	Intracellular	Rare	AD
Non-Syndromic						
TAAD2	3p24-25	*TGFBR2*	TGFβ-R2	Cell surface	~3 % of TAA	AD
TAAD4	10q23-24	*ACTA2*	Smooth muscle actin	Intracellular	10-15% of TAA	AD
TAAD5	9q33-34	*TGFBR1*	TGFβ-R1	Cell surface	~2 % of TAA	AD
TAAD-PDA	16p12-13 3q21.1	*MYH11* *MYLK*	β-MHC MLCK	Intracellular Intracellular	1-2% of TAA ~1% of TAA	AD

AD – Autosomal Dominant; AR – Autosomal Recessive

by their characteristic dysmorphic features and gene testing (Table 1, Table 2).

Over a century ago, Antoine Marfan, a French pediatrician, described a hereditary connective tissue disorder which came to bear his name. His report was made in 1896 the Bulletin of the Medical Society of Paris and described a five-year-old girl with long limbs and digits[4]. It was not until over 50 years later that the syndrome was fully described, including the involvement of aneurysms of the ascending aorta. In 2006, Loeys and Dietz described the syndrome of early, malignant arterial dilatations and unique facial features which characterize the syndrome that bears their names [5].

Marfan syndrome (MFS) is the best known aortic aneurysm syndrome and is caused by heterozygous mutations in the *FBN1* gene. It occurs worldwide with an estimated incidence of 1 in 5000 individuals and affects both sexes equally. Clinically MFS is a multisystem disease affecting the aorta (aortic aneurysm/

Table 2

Gene mutations

Recessive mutations - Almost always reduce or eliminate gene function

- Hypomorphic - Partial loss of function
- Amorphic – Complete loss of function
- Loss-of-function mutations - Produces a non-working protein.
- Examples of loss-of-function mutations include:
- **Point mutations that create premature termination when the gene transcript is tranlated into protain -** small (but significant) changes in a single nucleotide base.
- **Deletions -** remove information from the gene. A deletion could be as small as a single base or as large as the gene itself.
- **Insertions -** occur when extra DNA is added into an existing gene. Frequently the extra DNA represents a duplication of a portion of the gene.

Insertions and deletions often shift the "reading frame" causing all subsequent amino acids to be erroneous and almost always leading to premature termination of the protein.

Dominant mutations

- **I. Haploinsufficiency - Reduce gene function to 50%**
- **II. Gain of function**
- **Three types of gain-of-function mutations**
- **A. Hypermorphic mutations – Increase gene activity**
- **B. Antimorphic mutations (dominant-negative mutations) - antagonize wild-type gene function.**
- **C. Neomorphic mutations – Novel function**

dissection), the heart (mitral/aortic valve insufficiency), the eyes (ectopia lentis), and the musculoskeletal system (overgrowth). The diagnosis of Marfan syndrome is made based on the revised Ghent Nosology, which incorporates clinical criteria (based on a point score system), family history, and molecular genetic testing of the *FBN1* gene (Table 3).

Marfan syndrome follows an autosomal dominant pattern of inheritance with high penetrance (the probability of manifesting a disease) and significant inter/intra familial variability in disease expression[6]. In the majority of MFS patients, the disease is caused by a mutation in *FBN1* gene on chromosome 15q21.1, which encodes an extracellular matrix protein, fibrillin-1[7]. Over 600 *FBN1* gene mutations have been identified to date, and the detection rate for the *FBN1* mutations by DNA sequencing ranges from 70-93% in patients who meet the clinical diagnostic criteria [8]. Various types of mutations in the *FBN1* gene have been identified including nonsense, deletion/insertion, splice-site mutations, and missense mutations[9] with some genotype-

Table 3

2010 Revised Ghent Nosology for Marfan Syndrome

In the absence of FHx

Ao (Z>2) and EL = MFS
Ao (Z>2) and FBN1 = MFS
Ao (Z>2) and Syst (>7 pts) = MFS
EL and FBN1 with known Ao enlrgement = MFS

In the presence of FHx

EL and FH of MFS = MFS
Syst (>7 pts) and FHx of MFS = MFS
Ao (Z>2 above 20, >3 below 20 yrs) + FHx of MFS = MFS

A total score of 7 or higher is a Positive Systemic Score

Wrist and thumb sign:	3
Wrist or thumb sign:	1
Pectus carinatum:	2
Pectus excavatum	1
Hindfoot deformity:	2 [med rotation of med malleolus]
Pes planus:	1
Pneumothorax:	2
Dural ectasia:	2
Reduced upper/lower segment and incr. Armspan to height:	1
Scoliosis or kyphosis:	1
Rduced elbow ext.	1
3/5 facial features*:	1
Skin striae:	1
Myopia:	1
MVP:	1

BSA formula (Dubois and Dubois formula)
BSA (m^2) = 0.007184 x H^0.725 x W^0.425 with H height in cm, W weight in kg
Z-scores for diameters at the sinuses of valsalva in diastole and leading edge to leading edge (up to age 18)
Boys Z = [ln(d) - 3.1 - 0.49 x ln(BSA)] / 0.1
Girls Z = [ln(d) - 3.1 - 0.44 x ln(BSA)] / 0.09
With d = diameter in mm

- Facial features: dolichocephaly, downward slanting palpebral fissures, Enophthalmos, retrognathia, and malar hypoplasia

phenotype correlations. The most severe forms of Marfan syndrome are associated with *FBN1* mutations between exons 24-32 causing in-frame loss or gain of central coding sequences. Mutations causing premature stop codons result in rapid degradation of mutant transcripts and usually present with a milder phenotype[10].

A subset of patients previously thought to have Marfan syndrome do not have identifiable mutations in *FBN1*. Most of these patients are now classified as having Loey-Dietz syndrome (LDS)[5, 11]. LDS is an autosomal dominant disorder of connective tissue with multisystem involvement [2]. Patients with typical dysmorphic features (hypertelorism, craniosynostoses, cleft palate) are classified as LDS type 1; those with mild dysmorphic features (only hypertelorism) without other dysmorphic findings but with velvety, translucent skin, easy bruising, and atrophic scars are classified as LDS type 2 [12]. The natural history of both types of LDS is marked by early and rapid onset of thoracic aortic aneurysms (originating at the level of the sinuses of valsalva) and death at an early age (mean age 26.1 years)[12].

LDS is caused by a heterozygous mutation in one of the transforming growth factor beta receptor genes (*TGFβR1* or *TGFβR2*). *TGFβR2* mutations on chromosome 3 (3p24.1) account for the majority of LDS mutations (75%), and *TGFβR1* mutations on chromosome 9 (9q22.33) account for the remaining 25%[12]. Direct sequencing of both *TGFβR1* and *TGFR2* allows for the identification of a causal mutation in more than 95% of individuals. Although most LDS mutations are missense, other types of mutations have been seen including: splice-site, nonsense, deletions, and insertions. In LDS, de-novo mutations are found in 75% of patients. Both *TGFβR1* and *TGFβR2* gene mutations are thought to result in the overall up-regulation of TGFβ signaling.

The classical TGFβ signaling pathway involving the Smad-mediated cascade has been characterized by signals that induce extracellular matrix (ECM) deposition but also matrix degradation. This implicates the pathway as being critical to the structure and composition of ECM [13]. Enhanced TGFβ signaling with downstream canonical pSmad2 upregulation has been described as the predominant mechanism in both Marfan and Loeys-Dietz aneurysm formation[11].

Aneurysm Osteoarthritis Syndrome (AOS) is a newly described autosomal dominant syndrome with variable expression which presents with aortic aneurysms in the setting of atypical osteoarthritis and dysmorphic features. The frequency of AOS is 2% among TAA patients. AOS is caused by mutations in the Smad3 gene on chromosome 15 (15q22.33), which encodes a protein critical for cellular signaling downstream of the TGFβ receptors [14].

Mutations in Smad3 result in aortic aneurysms, dissections, arterial tortuosity, early onset osteoarthritis, and cutaneous anomalies. In one series, aortic aneurysms were present in 71% of patients with Smad3 mutations, mainly at the level of the sinus of valsalva but also affecting the abdominal aorta and/or other arteries such as the splenic, common iliac, mesenteric, renal, vertebral, and pulmonary arteries. The mean age of death, due to aortic dissection, was 54 +/- 15 years and occurred at mildly increased aortic diameters (4.0-6.3 cm)[15].

Arterial tortuosity was diagnosed in 48% of patients. Velvety skin, striae, and umbilical/inguinal hernias are common and joint abnormalities: osteochondritis dissecans (OCD), meniscal abnormalities, intervertebral disc degeneration, and early-onset osteoarthritis have been reported in all cases of AOS[16]. Cerebrovascular abnormalities were also noted to be common, and in 18% of patients concentric left ventricular hypertrophy (LVH) was observed. Importantly, LVH was not a consequence of hypertension as most patients were normotensive without treatment [17].

Arterial tortuosity syndrome (ATS) is an autosomal recessive disorder caused by mutations in the *SLC2A10* gene on chromosome 20 (20q13.1) which encodes the facilitative glucose transporter GLUT10[18-20]. GLUT10 is localized to the gene promotor region of decorin, a natural inhibitor of TGFβ. Mutations in the *SLC2A10* gene are thought to result in down-regulation of decorin and thereby up-regulation of TGFβ signaling. The mutations which cause this syndrome are loss-of-function mutations. The clinical spectrum of ATS includes: arachnodactyly, joint laxity or contractions, hypertelorism, cleft palate, bifid uvula, micrognathia, down-slanting palpebral fissures, blepharophimosis and arterial tortuosity with aneurysm formation[18].

Ehlers-Danlos Syndrome Type IV (EDS IV) is an autosomal dominant disorder with a prevalence of 1:10,000-25,000 in the US [21] caused by highly penetrant mutations in *COL3A1* (2q32.2). EDS IV is characterized by cutaneous findings (thin translucent skin, easy bruising) and arterial, intestinal, or uterine rupture. In childhood, inguinal hernias, pneumothoraces, and recurrent joint and hip dislocations are common. Vascular aneurysms/dissections or gastrointestinal perforation constitute the presenting signs in a majority of adults with EDS IV. The average age for the first major arterial or gastrointestinal complication is 23 years. Among patients with EDS IV ascertained because of a medical complication associated with the disorder, 25% had that complication by age 20 and 80% by age 40[22]. The median age of death in patients with EDS IV is 48 years. The diagnosis of EDS IV is made on clinical grounds (using major and

minor diagnostic criteria) and is confirmed by genetic testing or protein based testing[23]. Surgical intervention is notoriously dangerous in EDS IV, due to excess vessel fragility.

About 50% of EDS IV patients have a *de novo COL3A1* mutation. To date, at least 700 mutations in *COL3A1* have been reported. Using direct sequence analysis 98% of individuals with a clinical diagnosis of EDS IV are shown to have a mutation in *col3A1*. The majority of mutations are missense mutations resulting in an amino acid substitution for glycine residues in the $[Gly\text{-}X\text{-}Y]_{343}$ triplets of the triple helical domain or splice-site mutations and mutations resulting in mRNA instability. A small proportion of patients (2-3%) carry a genomic deletion[23]. Biochemical (protein-based) testing on cultured cells from a skin biopsy is recommended when a mutation is not identified by sequence analysis in a patient with a clinical diagnosis.

TGFβ2 (1q41) is the gene most recently identified as a cause of TAA. *TGFβ2* proteins are synthesized as peptides that form homodimers cross-linked through disulfide bonds which are cleaved before secretion. Mutations identified (frame-shift and nonsense) are predicted to cause haploinsufficiency. Clinical features in TGFB2 mutation carriers are similar to those of other syndromes causing thoracic aortic disease including: cardiovascular (aortic root aneurysm [74%], cerebrovascular disease, and arterial tortuosity), skeletal (pectus deformity, joint hyperflexibility, scoliosis, and arachnodactyly), cutaneous (striae, herniations), and pulmonary (pneumothorax, dural ectasia). Median age of aortic disease presentation is 35 years, with the majority of patients presenting with aneurysms at the sinuses of Valsalva (4.7-5.4 cm). In a small series reported to date, no aortic dissections occurred in individuals younger than 31 years of age [24].

For non-syndromic inherited aneurysmal disorders, a less heralded breakthrough occurred at Yale University in 1981. One of us (JAE) was a young resident in the audience when the distinguished Professor M. David Tilson, together with his resident protégé Chau Dang, presented at Surgical Grand Rounds their original observation that aneurysmal disease was

distinct clinically from occlusive vascular disease—and that *abdominal* aneurysmal disease tended to run in families. These truly original and iconoclastic observations laid the foundation for much work that was to come [25-26]. In 1997 and 1999, Dr. Diana Milewicz in Texas and our team at Yale reported, independently, that non-syndromic thoracic aortic aneurysms tended to run in families. Both teams, remarkably, reported the same likelihood—20%--that any given proband would have a relative with a known aortic aneurysm [27-28]. In the years since those observations of familial patterns in thoracic aortic disease, Milewicz and colleagues have gone on to identify via linkage analysis and other genetic techniques, the specific mutations that underlie many cases of familial thoracic aortic aneurysm and dissection [29].

Non-syndromic Aortic Aneurysms are thus divided into Familial Thoracic Aortic Aneurysms (FTAA) – where more than one person in the family is affected and sporadic TAA where only a single person in the family is known to have an aneurysm. FTAAs typically present earlier in life than sporadic aneurysms, have a higher annual growth rate then sporadic aneurysms, and do not demonstrate association with traditional risk factors for aortic disease such as dyslipidemia or coronary artery disease [28, 30]. Cases of non-syndromic TAA primarily involve the thoracic aorta, a region from the aortic root to the thoracic descending aorta.

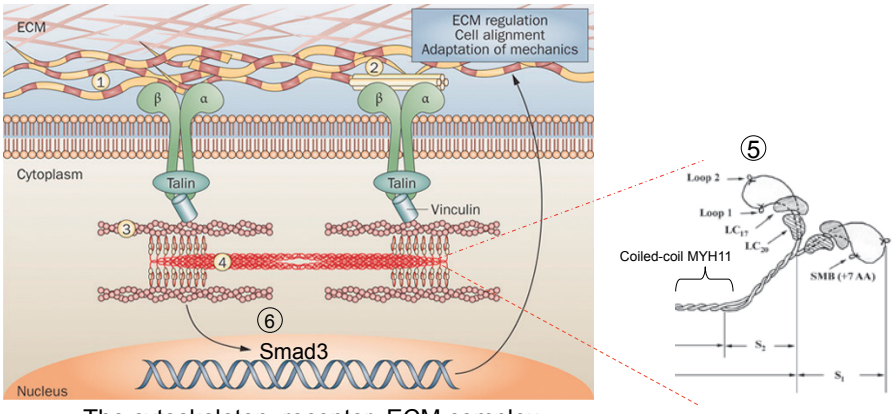
Non-syndromic Familial Thoracic Aortic Aneurysms and Dissections (FTAA and FTAAD) are also genetically heterogeneous. Mutations in five genes (*MYH11, TGFβR1, TGFβR2, MYLK, and ACTA2*) have thus far been identified and all have autosomal dominant inheritance. Together these account for only 23% of familial non-syndromic cases. Two additional chromosomal regions have been implicated (5q13-14 and 11q23.3-24) but no genes have as yet been identified. Novel genes have been difficult to map by linkage analysis, probably because of incomplete penetrance and/or locus heterogeneity [2, 31-32].

Mutations in the MYH11 gene (chromosome 16p13.11) account for 2% of non-syndromic TAADs, and have been often

associated with patent ductus arteriosus (PDA)[33]. The myosin superfamily is composed of a large class of motor molecules which interact with actin filaments and result in force generation through ATP hydrolysis. The *MYH11* gene is composed of 42 exons and encodes MYH11 protein. The vertebrate smooth muscle myosin is composed of a hexameric complex of 2 myosin heavy chains (SM-MHC coded for by *MYH11*), 2 essential light chains, and 2 regulatory light chains (RLC). Myosin heavy chains consist of a globular head domain composed of ATPase and actin-binding subdomains, a linker region with Ig repeats that bind light chains, and a variable tail region which specializes each myosin to its cellular functions. SM-MHCs coiled-coil domain in the tail region enables the protein to first dimerize and then polymerize to form thick filaments that interact with actin thin filaments. The coiled-coil domain is composed of a 28 residue charge repeat of alternating positive and negative residues. Most of the identified pathogenic MYH11 mutations are located in the coiled-coil domain of the protein[33-34] (Figure 2).

Figure 1

Non-syndromic Familial TAA/TAAD



The cytoskeleton–receptor–ECM complex

1-FBN; 2-COL3A1; 3-ACTA2; 4-MYH11; 5-MLCK; 6-Smad3

LC20 - Regulatory light chain – inv in contractility

El-Hamamsy I and Yacoub M H (2009) Cellular and molecular mechanisms of thoracic aortic aneurysms *Nat Rev Cardiol* doi:10.1038/nrcardio.2009.191

Heterozygous MYH11 mutations result in thoracic aortic aneurysms and are thought to act via a dominant negative mechanism. Mutations in MYH11 identified in FTAAD families are predominantly splice-site mutations resulting in in-frame deletions and missense mutations. Identification of MYH11 mutations responsible for FTAAD is often difficult as in the general population, rare, non-synonymous (nucleotide mutations resulting in an altered protein) variants are frequent. According to the Exome Rare Variant database, 0.6% of such variants have been identified for *MYH11* (http://evs.gs.washington.edu/EVS/) [35] (Table 3).

Mutations in *ACTA2* gene are the most common mutations resulting in aortic aneurysms and account for 10-15% of all FTAAD mutations. They are heterozygous mutations which encode the smooth muscle cytoskeletal protein actin alpha 2 (actin α2). Actin α2 is the vascular smooth muscle specific isoform involved in vascular smooth muscle cell contraction, where actin a2 interacts with β-myosin heavy chain (encoded by *MYH11*)[36].

The *ACTA2* gene is localized to chromosome 10 (10q23.31). Mutations in *ACTA2* act via a dominant negative mechanism with reduced penetrance and variable expressivity. Half of mutation carriers have no aortic disease. *ACTA2* mutations (to date ~ 30 mutations have been identified) resulting in aortic aneurysms have been predominantly found to be missense, [37]although deletions and splice-site mutations have also been described[36, 38-44].

Patients with *ACTA2* mutations present with acute ascending (type A) or descending (type B) aortic dissections, and a median survival of 67 years [36]. Although the aortic diameter is variable prior to rupture, most studies looking at *ACTA2* mutations found the majority of aortic aneurysms to be < 5.0 cm prior to dissection. For this reason, early surgical intervention should be considered even when minimal changes in aortic diameter are recognized. Histologically, *ACTA2* mutations demonstrate vascular smooth muscle hyperplasia but not hypertrophy. This vascular smooth muscle hyperplasia has been associated with a

possible increased risk of stroke and coronary artery disease (up to 25% in some studies)[38].

The MYLK gene is localized on chromosome 3 (3q21.1) and accounts for 1% of all FTAA muatations. Mutations in *MYLK,* a gene which encodes myosin light chain kinase (MLCK), have been exclusively associated with thoracic ascending aortic dissections (TAAD). MLCK is a ubiquitously expressed kinase whose target of phosphorylation is a 20 kDa regulatory light chain (RLC) of myosin II[45]. In smooth muscle cells initiation of myogenic response to mechanical stretch is a result of Ca/calmodulin complex activating MLCK. MLCK in turn phosphorylates RLC and this increases actin-activated myosin II ATPase and initiates the physiologic contraction of smooth muscle[37].

MYLK mutations follow an autosomal dominant pattern of inheritance, and are thought to cause disease as a consequence of haploinsufficiency. Because the pathophysiology of *MYLK* mutations is that of dissections and not aneurysms, it is difficult to counsel as to the time of intervention[37].

Medical science has made substantial progress in elucidating the genetic basis of aortic diseases since Marfan's original observations a century ago. The identification of specific mutations underlying syndromic and non-syndromic thoracic aortic aneurysms now permits precise identification of affected patients and confirmation of clinical diagnoses. Further, it is becoming clear that specific mutations lead to subtly different patterns of disease progression. Soon, we will enter an era of personalized aneurysm care, in which specific mutations will determine the appropriate size criterion for surgical intervention. Despite the great complexity of interpreting the wealth of information generated by whole genome sequencing, it is indeed this understanding that will allow aortic care to evolve beyond the current surgical plane--which, while delicate, intricate, and challenging is essentially human "plumbing".

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Keynote

5: Friday, December 14th

Joseph S. Coselli, MD: "History of Aortic Surgery"

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Antoine Marfan Award, by the National Marfan Foundation

Michael E. DeBakey Excellence in Research Award

Honorary President. Shandong Qianfoshan Hospital International Heart Center, Jinan, China

Award for Excellence in Surgery and Taking the Difficult Cases. Ehlers-Danlos National Foundation

Award for Exceptional Accomplishments in the Field of Cardiovascular Disease, American Heart Association

Lifetime Achievement.
Society of Brasilian Cardiothoracic Surgeons

Distinguished Scientist Award.
MacDonald Fund Committee, St. Luke's Episcopal Hospital

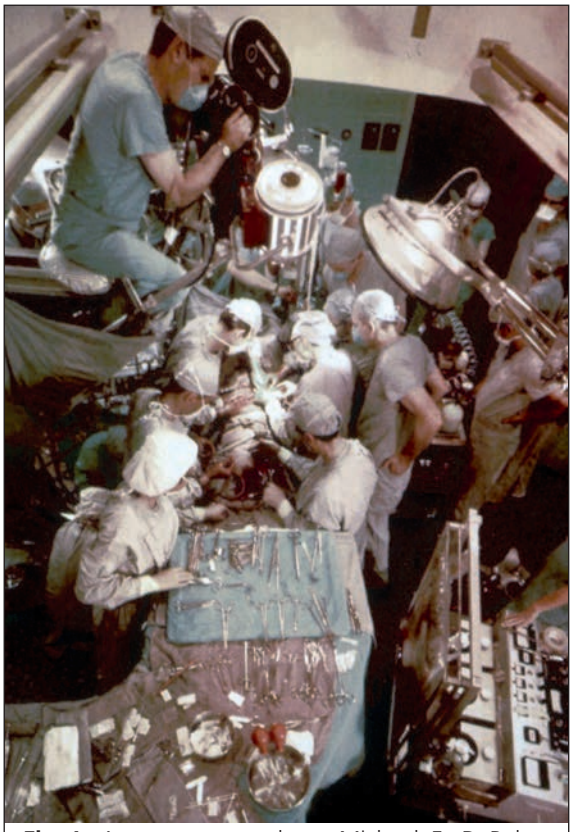


Fig 1. Among many others, Michael E. DeBakey in the operating room in the early 1960s. Image courtesy of the Baylor Archives and *LOOK* magazine.

The History of Aortic Surgery

Susan Y. Green, MPH, Scott A. LeMaire, MD, Joseph S. Coselli, MD

From the Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas, and the Department of Cardiovascular Surgery, Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas

It is difficult to fathom the extraordinary advances that have been made in aortic surgery in the last century (and nearly as difficult to acknowledge them all succinctly within the limits of this chapter). This monumental achievement is possible only with the contributions of a great many early visionaries, who themselves built on the work of their predecessors [1-3].

By the early to mid 20th century, several specialized cardiovascular surgical centers were emerging. In North America, these included Tulane, Johns Hopkins, Columbia, Chicago, Mayo Clinic, Massachusetts General Hospital, Harvard, Stanford, Toronto, and, in Houston, Baylor College of Medicine. In Europe, cities such as Stockholm, Lyon, Paris, London, Strasbourg, and Milan were at the forefront of aortic and vascular surgery. Additionally, there was generous cross-fertilization of technique as newly minted surgeons brought new concepts to their institutions from their residencies and from grand tours and training fellowships abroad. Undoubtedly, surgical experience gathered during World Wars I and II advanced aortic surgery on both sides of the Atlantic.

Houston's Baylor College of Medicine benefited especially from this cross-fertilization. DeBakey [Fig. 1] was mentored at Tulane by Ochsner and benefited from the rich heritage Matas had created there.

DeBakey also trained in Europe with vascular specialists such as Leriche and Kirschener. Cooley [Fig. 2] completed his residency under the direction of Blalock at Johns Hopkins and

Fig 2. Joseph S. Coselli (left) and Denton A. Cooley (right) attend the 26th annual meeting of the National Marfan Foundation, held in Houston, Texas, 2010. Image courtesy of the National Marfan Foundation.

assisted him in the first "blue baby" cardiac operation; later, Cooley supplemented his cardiac training in London under the tutelage of Lord Brock. Crawford [Fig. 3] graduated with highest honors from Harvard Medical School and served as chief resident under Churchill and Allen at Massachusetts General Hospital. Houston was at the epicenter of aortic surgery in the 1950s and 1960s [4]; as Chamberlain jokingly recalled, "Dr. DeBakey has a pair of hands that are unusual and I am sure that he can do better things and anastomose blood vessels faster than most of us . . ." [5].

Early Aortic Interventions

Introduced by dos Santos and colleagues in 1929 [6], aortography greatly facilitated the detection of aortic abnormalities; however, it was long thought that definitively repairing aortic aneurysms was nearly impossible. Thus, the commonly used treatments in this era were largely palliative techniques such as ligation, endoaneurysmorrhaphy, endoluminal wiring, and cellophane wrapping [7]. A tremendous body of experimental work involving vascular surgery, much of it performed by Carrel and Guthrie and most often on canine models, also developed in the early 20th century.

Aortic ligation repairs involved partially or fully occluding an aneurysm by wrapping a band (made of metal, tape, suture, tissue, or other materials) around the aorta just proximal to the aneurysm and without resecting the aneurysm. The goal was to obliterate the aneurysm through the gradual deposit of clot. Sir Cooper is widely considered to have been the first to use ligation to treat an abdominal aortic aneurysm (in 1817), and Tuffier is commonly credited with first applying this approach to a thoracic

aortic aneurysm (in 1902); however, both of these early attempts were unsuccessful [8, 9]. Later, Halsted [10] used an aluminum band as ligature material (which had a tendency to cut through the aortic tissue), and Matas, even as late as 1940 [11], advocated using proximal ligation to reduce the aortic stream to a fraction of the caliber of a normal aorta. Although ligation repairs were occasionally successful, many—especially those performed before 1920—resulted in death from necrosis, shock, rupture, or hemorrhage [8].

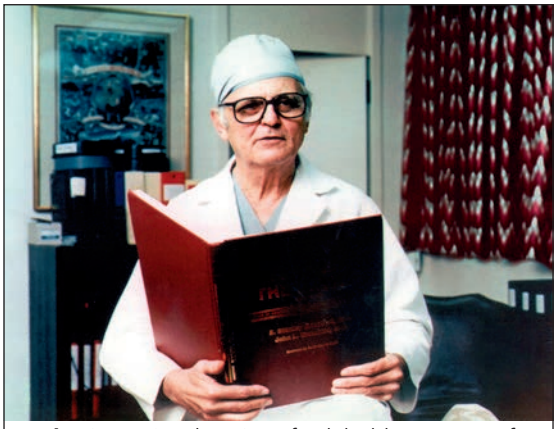


Fig 3. E. Stanley Crawford holds a copy of *Diseases of the Aorta*, his landmark atlas of aortic repair, which he wrote with his son, John L. Crawford [104]. Although this book was published in 1984, it remains an inspiration and is highly sought by contemporary collectors. Image from private collection.

Matas was best known for promoting an alternative technique: endoaneurysmorrhaphy, the reshaping of an aortic or peripheral aneurysm with 1 or 2 series of continuous suture. Endoaneurysmorrhaphy did not compromise any developed collateral circulation because the aneurysm was not resected but rather infolded and secured with suture. (Often, a rubber catheter was inserted into peripheral aneurysms to guide the repair.) In 1902, Matas presented his experience with 4 patients [12], and by 1909, when his technique appeared in *Keen's Surgery*, this approach was commonly considered superior to existing techniques [13].

Although using wire to treat aortic aneurysms had been attempted as early as 1864 by Moore [14], it was Blakemore at Columbia University who revived this approach in the 1940s and 1950s [15, 16]. The principle of aneurysmal wiring was to strengthen the entire sac wall by inserting enough wire to stimulate thrombosis. Up to 500 feet of wire could be inserted through either a small skin incision or full operative exposure [15]. The results were mixed; early attempts such as Moore's were often complicated by sepsis, whereas later cases such as

Blakemore's, often involving much more wire than in the past and the use of electric heating, often successfully relieved patients' symptoms for several years [15, 16]. In a modified form, wiring is still used today to treat endovascular aortic complications such as type II endoleak.

The purpose of cellophane wrapping was to irritate and scar the outer aortic layer, strengthening it and reducing its vulnerability to additional growth or rupture. Pearse [17] demonstrated this concept experimentally in 1940, and soon afterward this approach was successfully used clinically by Harrison and Chandy [18] to repair aneurysms of the subclavian artery in 2 patients. This technique was popularized by Poppe in the mid 1940s and was largely used to treat syphilitic aneurysms [19]. Although this treatment had limited success, it did prolong the lives of several patients, including Albert Einstein, who survived an additional 7 years after his symptomatic abdominal aneurysm was repaired [1].

Carrel, born and educated in Lyon, France, was both flamboyant and brilliant; his steadfast belief in a miraculous healing at Lourdes ruined his career and led him to America. His experimental work, particularly his studies of blood-vessel transplantation with Guthrie [20-22] at the University of Chicago, resulted in numerous joint papers.

The techniques he tested included reattaching blood vessels with direct anastomosis after resection, in which arterial continuity was maintained with short sections of interpositioned vein. Suturing was facilitated by using the principle of triangulation (using 3 tacking sutures to reshape the vessel) to simplify anastomosing the round vessels.

This and his use of button or patch reattachment strategies for branching blood vessels, as well as his work on organ transplantation, earned Carrel the Nobel Prize for Physiology or Medicine in 1912—the first ever awarded for work performed in the United States [23]. Carrel was convinced that aortic replacement was feasible, writing that "It seems possible that the aneurisms of the thoracic aorta could be extirpated and the circulation re-established by a vascular transplantation, if a proper technique was developed" [24].

Nonsuture Anastomosis

During this early period, there was parallel development of a nonsuture anastomosis technique (also called permanent intubation) to repair arteries, including the aorta. Various materials were used in these approaches, which generally involved creating a tube with grooves at both ends; silk suture and other material could be wound around the grooves to secure the tube, thereby rapidly replacing a short section of the aorta. Carrel experimented with using glass, aluminum, and gold-plated tubes to replace the aorta, while Payr used both flanged magnesium tubes and magnesium rings that were similar to the ivory rings used by Nitze decades earlier. Tuffier used silver tubes lined with paraffin, and Blakemore used vitallium tubes, including vein-lined ones. Commonly, these tubes either thrombosed or stimulated excessive fibrosis, so a more suitable, inert material was sought for arterial substitution [25].

Because many new plastics had been recently developed, Hufnagel and others tested Lucite (methyl methacrylate) as an arterial substitute in the late 1940s and early 1950s [26, 27]. Lucite was inert, strong, and inexpensive (vitallium, an inert metal, was considerably more costly) and was thought to have anticoagulant properties. Careful attention was paid to ensuring the smoothness of the tube's interior so as not to damage blood cells and induce clotting. Hufnagel's early canine experiments with nonsuture anastomosis [26] eventually led to the development of the Hufnagel aortic assist valve, which consisted of a ball-and-cage device inside a Lucite tube with metal rings designed to facilitate rapid, nonsuture attachment [27]. Beginning in 1952, this device was successfully used to prevent distal aortic regurgitant blood flow and replaced a short length of the descending thoracic aorta. This approach was used in at least 150 patients before mechanical replacement aortic valves were developed in the early 1960s. At least one of these patients experienced psychotic symptoms related to the excessive noise produced by the Hufnagel valve; Beall and Cooley [28] replaced this patient's Hufnagel valve with a homograft. In addition, the nonsuture method of blood-vessel anastomosis (with and without a vein inlay [29, 30]) continued to be promoted into the mid-1950s and was expanded to include other plastics such as polyethylene [25].

Aortorrhaphy

In the 1940s and early 1950s, emerging reports from Ochsner [3], Blakemore [31], and Monod [32] described the resection of saccular aneurysms that were then repaired with lateral suture to restore the continuity of the aorta. In 1952, Cooley and DeBakey published a small series of aortic and great-vessel repairs, including the successful repair of a saccular aneurysm of the subclavian artery by using aortorrhaphy. The paper described the complexities of surgical exposure and the limitations of contemporary approaches (such as wiring and cellophane wrapping), current surgical instruments, and adjuncts [33]. Shimert and colleagues used a nonsuture anastomosis approach to secure a shunt used during aortorrhaphy of the aortic arch [34]. Bahnson reported his success with using aortorrhaphy to repair a saccular aneurysm of the ascending aorta and one of the upper abdominal aorta (which had been previously wired but continued to enlarge). Bahnson comments that this repair was a poor choice in the latter patient because the aortic wall "was thin and badly diseased. Far better is substitution by a homograft" [35].

Emerging Use of Homografts

Fulfilling both Carrel's experimental work on arterial transplantation techniques and his fervent belief in the potential of aortic substitutes, Crafoord, Gross, and others successfully used suture-based and homograft-replacement techniques to repair aortic coarctation in the late 1940s [36-38]. This piqued other surgeons' interest in replacing aneurysmal sections of the aorta, but there was concern about the lack of developed collateral circulation in patients with aortic aneurysm, and about whether these patients could tolerate aortic clamping and related ischemia as well as the coarctation patients had [39].

As aortic technique was refined, surgeons could replace increasingly large sections of the descending thoracic aorta. In 1949, Swan used a 8-cm homograft (which had been refrigerated for 52 days in Ringer's solution) to repair a coarctation-related descending thoracic aneurysm in a 16-year-old boy [40]. And, in 1950, Oudot moved beyond the descending thoracic aorta and used a bifurcated homograft to replace an obstructed section

of the abdominal aorta and both iliac arteries in a 51-year-old woman [41].

Abdominal aorta (1951)

In 1951, Dubost and colleagues [42] successfully resected an abdominal aneurysm through a retroperitoneal approach in a 50-year-old man. A bifurcated homograft was not available, so the left common iliac artery was anastomosed in an end-to-side fashion. This repair was soon replicated by several other surgeons, including DeBakey and Cooley [43] in 1952 (although they used a transperitoneal approach). In these early cases, 60 minutes of ischemia appeared to be well tolerated, and a "clamp-and-sew" approach was generally applied. These promising results rapidly shifted treatment away from cellophane wrapping.

Descending thoracic aorta (1953)

In 1951, when Lam and Aram [44] attempted a homograft replacement of a true descending thoracic aortic aneurysm, concerns regarding tolerance to distal ischemia led them to use a Lucite shunt (in deference to Hufnagel). The authors described some difficulty with using this shunt, which hampered the suturing of the homograft. Sadly, this patient died of a mediastinal abscess caused by necrosis of the residual aneurysm, leading the authors to opine that if they had fully resected the aneurysm, the patient might have lived. In 1953, DeBakey and Cooley [45] successfully resected a descending thoracic aortic aneurysm (notably, in his recent memoir [46], Cooley revisits this complex case) and replaced it with a homograft by using a "clamp-and-sew" approach. The authors note, "Although the aorta was occluded for a period of 45 minutes during the anastomosis, there were no residual manifestations of ischemic changes in the spinal cord, the kidneys, or other organs." Additionally, because of Lam and Aram's failure, this and other early approaches to aortic repair favored full resection of the aneurysm.

Thoracoabdominal aorta (1955)

Attempts to repair thoracoabdominal aortic aneurysm (TAAA) were complicated by branching vessels, as well as the risk of distal ischemia. In their report of replacing the lower descending thoracic aorta with a homograft in 1953, DeBakey and Cooley [45] described using a thoracoabdominal approach to repair the aneurysm because it extended into the abdomen; notably, they clamped both the infra-celiac aorta and the celiac axis to secure distal vascular control, and they performed the distal anastomosis just above the origin of the celiac axis. In 1955, both Rob [47] and Etheredge [48] reported successful repairs involving homograft replacement of TAAA. In 1956, a series of 4 such repairs was reported by DeBakey and colleagues [5]. For the first patient, moderate hypothermia (32.8°C) was induced with a cooling blanket in the hope of reducing ischemic damage; however, this patient had excessive bleeding during rewarming and died within a few days. In the remaining cases, temporary shunts were used to reduce the threat of ischemia, and only 1 additional patient died. Aneurysms continued to be completely extirpated.

In 1955, DeBakey, Cooley, and Creech published their experience with 240 aortic resections performed because of aortic coarctation, aneurysmal disease, or occlusive disease [49]. Most of these cases were abdominal (204, of which 122 were aneurysmal), but a sizeable number for this era were thoracic (36, of which 21 were aneurysmal). The authors observed that tolerance to aortic ischemia was greatly diminished in the thoracic aorta, particularly for the spinal cord and kidneys. In contrast, ischemia was generally well tolerated in the abdominal aorta, perhaps because these aneurysms tend to arise below the renal arteries; for such repairs, the authors opined that few protective adjuncts were needed and endorsed a "clamp-and-sew" approach. Additionally, they surmised that the deaths in these abdominal repairs (20 of 122) were probably related to existing comorbidities such as advanced age, poor cardiac function, and renal disease and not to the aortic repair per se. However, the authors found thoracic aortic repair itself to be hazardous, especially in patients with aneurysm, who tended to lack sufficient collateral circulation (unlike coarctation

patients). Although imperfectly understood, important factors regarding operative success appeared to include the length of the resected aorta, the site of aortic clamping, and the duration of operative ischemia. The authors surmised that temporary shunts, hypothermia, and expeditious repair were beneficial in the more complex thoracic aortic repairs.

Ascending aorta (1956)

Resecting and replacing fusiform aneurysms of the ascending thoracic aorta remained challenging because clamping the most proximal section of the aorta induced left ventricular strain and systemic ischemia. Artificial heart-lung machines were a newly emerging technology in the mid-1950s; only a handful of surgical centers used them, primarily in pediatric cardiac repair. In 1956, Cooley and DeBakey used a modified DeWall-Lillehei pump oxygenator to resect and replace the entire ascending aorta with a homograft; venous blood was withdrawn through catheters in the venae cavae, while oxygenated blood was delivered through cannulas in the right femoral and right common carotid arteries. The patient tolerated a short period of cardiac arrest, and although ventricular fibrillation ensued after the aorta was unclamped and resuscitation began, it was easily corrected with electroshock (110 volts, 1.5 amp). The patient survived and had an uneventful recovery [50].

Aortic arch (1957)

Attempts to repair or replace fusiform aneurysms of the aortic arch began in 1951 [51], but none were successful until DeBakey's 1957 attempt. Barriers to success included left ventricular strain and atrial fibrillation (also encountered during ascending aortic repair), plus the risk of catastrophic cerebral ischemia. Schafer and Hardin's attempted repair involved placing small-diameter (3-mm) shunts in the aortic root proximally and in the innominate, left common carotid, and left subclavian arteries and the descending thoracic aorta distally; unfortunately, the patient's heart went into fibrillation, and he died soon afterward [51]. In 1954, Stranahan and colleagues attempted arch repair with a 10-mm bypass shunt to the descending thoracic aorta,

but their patient died of cerebral ischemia [52]. In 1955, Cooley, Mahaffey, and DeBakey reported Houston's attempt to surgically replace the entire aortic arch. Adjuncts included mild hypothermia (33.8°C) and a 14-mm Invalon© shunt with branches to the proximal right and left common carotid arteries. Cardiac arrhythmia developed shortly after the ascending aorta was clamped, but regular heart rhythm returned spontaneously after several minutes; however, the patient did not regain consciousness and died [53]. In 1956, Houston surgeons made 2 additional unsuccessful attempts to replace the aortic arch, using a 14-mm shunt and hypothermia in one case and a very large 20-mm shunt and no hypothermia in the other; both patients died [54]. In 1957, DeBakey and colleagues [55] successfully repaired the aortic arch in a 56-year-old patient by replacing it with a homograft. An early form of antegrade cerebral perfusion was provided by the same cardiopulmonary bypass system used in the previous year's repair of the ascending aorta.

Synthetic Arteries

Although many aorta banks were created in the 1940s and 1950s, using homografts as an arterial substitute was fraught with difficulties, including the complexity of preservation techniques, poor homograft availability, and emerging reports of early degeneration. Rarely, homografts would become atherosclerotic and, consequently, aneurysmal [56]. At least partly because Hufnagel had successfully used hard plastic tubes as aortic substitutes, woven plastic substitutes were now considered [57]. After Voorhees noticed the endothelialization of suture material, he searched for a suitable inert material that could be made into an aortic graft. Vinyon-N was brought to his attention by Blunt, a colleague at Columbia [1], and its clinical use as an aortic substitute was reported by Voorhees, Jaretzki, and Blakemore [58] in 1952. Many different materials were used as aortic substitutes (such as Orlon [acrylic fiber], nylon, taffeta, nylon-Dacron, crimped nylon tubes, plastic-dipped Orlon, Ivalon sponge, and Teflon), of which Dacron came to be widely considered the most suitable [59]. Disadvantages of synthetic grafts included the fact that twice as much blood seeped through synthetic grafts as through homografts, and

that synthetic grafts appeared to pose a greater risk of infection. To reduce their porosity, grafts were commonly preclotted in the patient's blood (to fill the interstitial spaces in the graft) before insertion [60].

Progression of Aortic Repair

Ascending aorta

In 1962, shortly after prosthetic "ball and cage" aortic replacement valves began to become available [61], Wheat and colleagues [62] performed the first repair that simultaneously replaced the ascending aorta and the aortic valve. The ascending aortic aneurysm was excised down to the annulus, but two "tongues" of aortic wall tissue were left; these contained the coronary ostia.

In 1968, aortic root replacement was further enhanced by Bentall and De Bono's [63] development of the composite valve graft—a replacement aortic valve directly sutured to a short tube made of Teflon graft material. In this repair, small holes made in the graft were connected to the ostia of the coronary arteries, and the opened aortic wall was then wrapped around the graft to facilitate hemostasis.

Over time, it became clear that there was a drawback to the Bentall procedure. In some patients, tension between the graft and the wrapped aortic wall containing the coronary arteries eventually caused them to pull away. In 1978, Cabrol [64] modified this technique by adding an interposition graft to the coronary arteries to reduce tension and by making a small opening in the wrapped aortic wall. In 1981, Kouchoukos [65] further modified the CVG approach by mobilizing the coronary arteries on buttons of tissue (and thus, abandoning the wrapped aortic wall technique) and reattaching them to the graft; this remains the preferred technique for full replacement of the aortic root [Fig. 4]. However, valve-sparing approaches to replacement of the ascending aorta are now used whenever feasible. These repairs have gone through several iterations, primarily at the hands of Yacoub [66] and David [67], and currently, the preferred approach uses the reimplantation approach rather than the

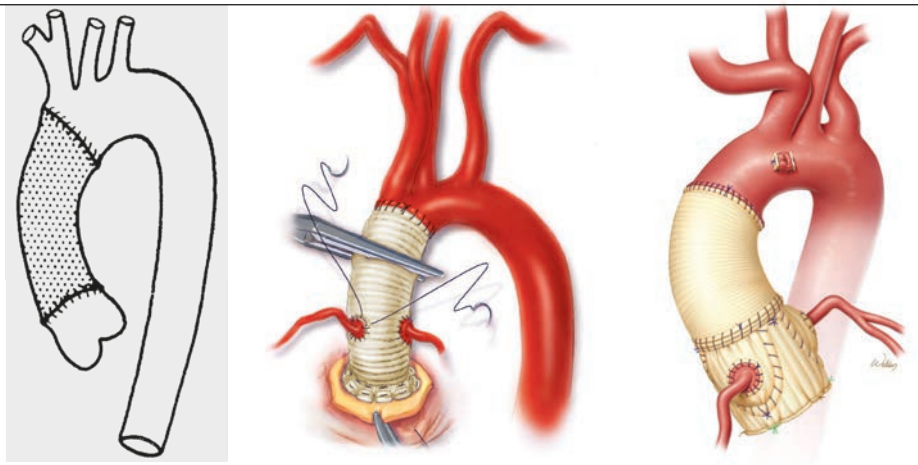
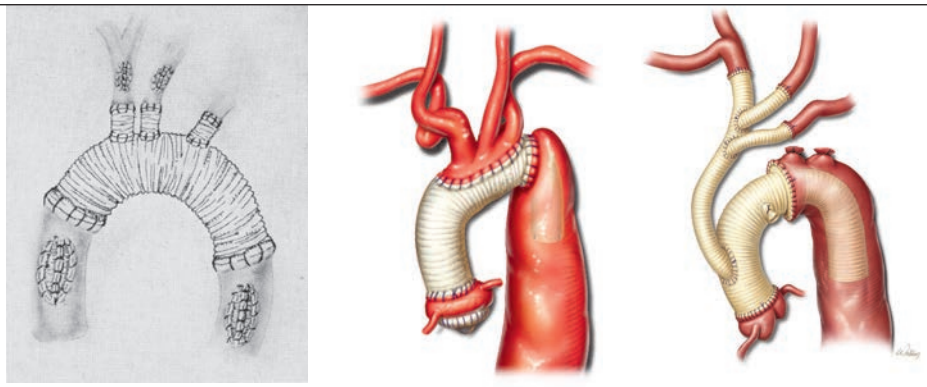


Fig 4. Illustrations showing the evolving approach to ascending aortic aneurysm repair. **(A)** The first successful ascending aortic repair, reported by Cooley and DeBakey in 1956 [50]. In this repair, a fusiform aneurysm was replaced with a homograft while an early form of cardiopulmonary bypass was used; this was the first such use in aortic repair. Used with permission, figure 2B [50]. Copyright © 1956, American Medical Association. **(B)** A composite valve graft repair. Here, the button technique of coronary artery reattachment is shown. This technique includes the Kouchoukos modification [65] of the original repair by Bentall and de Bono [63]. Used with permission from Brunicardi FC, Anderson DK, Billiar TR, et al. (eds.): Schwartz's Principles of Surgery, Ninth Edition. New York: The McGraw-Hill Companies, 2010, Chapter 22, Figure 22-5. **(C)** More recently, the use of valve-sparing aortic root replacement (VSARR) has become increasingly popular. Here, the completed valve-sparing aortic root replacement (which involved the reimplantation approach) and graft repair of the ascending aorta are shown. Used with permission of Baylor College of Medicine.

remodeling approach. Recently, this approach was expanded to include otherwise healthy bicuspid aortic valves [68].

Aortic arch

Early aortic arch repair commonly involved an extra-anatomic approach [Fig. 5] and was plagued by significant mortality rates, even in the best hands [69]. Eventually, an anatomically based repair began to be adopted, and in the late 1960s, Bloodwell, Cooley, and colleagues [70] introduced the island patch reattachment strategy for the brachiocephalic arteries; this approach greatly simplified repair and led to faster



A B C

Fig 5. Illustrations showing the evolving approach to aortic arch aneurysm repair. **(A)** Aortic arch repair as performed in the late 1950s and early 1960s. Here, the remnants of a bypass shunt (used to provide cerebral perfusion) are seen on the proximal aspect of the ascending aorta and the descending thoracic aorta; this shunt had smaller branches that attached to the innominate and left common carotid arteries. Repair includes individual branch grafts to the brachiocephalic arteries and follows the anatomic origins of these vessels. Note that the repair incorporates a relatively large portion of the descending thoracic aorta. Used with permission, figure 3D [69]. Copyright © 1962, Elsevier **(B)** An illustration of total arch repair using the island approach to brachiocephalic artery attachment as described by Bloodwell and colleagues in 1968 [70], which simplified and hastened repair. Additionally, the elephant trunk repair (first described by Borst [93] in the early 1980s) is shown; the distal anastomosis is performed just distal to the origins of the left subclavian artery. Image adapted from LeMaire et al [105], figure 2A. Copyright of The Society for Thoracic Surgeons. **(C)** Recently, Y-graft approaches to aortic arch repair have been introduced [79]. These approaches appear to aid cerebral perfusion; the brachiocephalic arteries are debranched and may then be perfused though the grafts. Additionally, the introduction of collared elephant trunk grafts has facilitated the shift toward performing the distal anastomosis at a more proximal location (just distal to the anatomic origin of the innominate artery), which is thought to aid hemostasis and better secure the anastomosis. Used with permission, figure 2G [80]. Copyright of The Society of Thoracic Surgeons.

anastomoses. In the mid-1970s, Griepp et al [71] first reported the use of profound hypothermic circulatory arrest (14°C) in a case series of 4 patients (3 of whom survived) who underwent aortic arch repair. In the early 1980s, Livesay, Cooley, and others [72] introduced the open distal anastomosis technique in their series of 18 patients; remarkably, all patients survived the repair.

The late 1980s and early 1990s led to improvements in cerebral perfusion strategies to protect patients from stroke. Frist and

colleagues [73] reintroduced antegrade cerebral perfusion, while Ueda [74] and others introduced retrograde cerebral perfusion; both techniques remain in use. Additionally, Kazui [75] adopted perfusion catheters with greater flexibility than previous models, and Crawford's experience [76] helped established a safe time limit (roughly 30 minutes) for hypothermic circulatory arrest. Bachet [77] modified cerebral hypothermia by developing a cold cerebroplegia technique. Cannulation techniques in arch repair have been modified to include the axillary artery [78] and, more recently, the innominate artery, both of which facilitate antegrade cerebral perfusion.

Spielvogel [79] radically changed aortic arch repair by developing Y-graft approaches, which essentially debranch the brachiocephalic vessels and move the distal anastomosis forward. With the addition of collared elephant trunk grafts, this technique has been adopted by several centers with good results, even in patients with acute dissection [80]. Today, most centers use antegrade cerebral perfusion rather than retrograde, and many centers are exploring the use of more moderate temperatures for hypothermic systemic circulatory arrest. Although open arch repair remains the gold standard, endovascular repair, particularly hybrid arch repair that combines open debranching strategies with endovascular approaches, provides an alternate treatment for severely compromised patients [81].

Descending thoracic aorta

In contemporary repair, the "clamp and sew" techniques of early descending thoracic aortic repair are essentially unchanged since the earliest days of their use; in select patients, adjuncts typically used in thoracoabdominal aortic repair (eg, cerebrospinal fluid drainage) may be adopted to reduce the risk of operative complications. However, since Volodos introduced endovascular thoracic stent-grafts [82] and Dake popularized their use [83], significant numbers of patients with DTA have been treated endovascularly. Although this approach has been rapidly adopted, it does not appear to have reduced the rate of open descending thoracic aortic repair; rather, the overall rate of repair has increased, which implies that patients previously

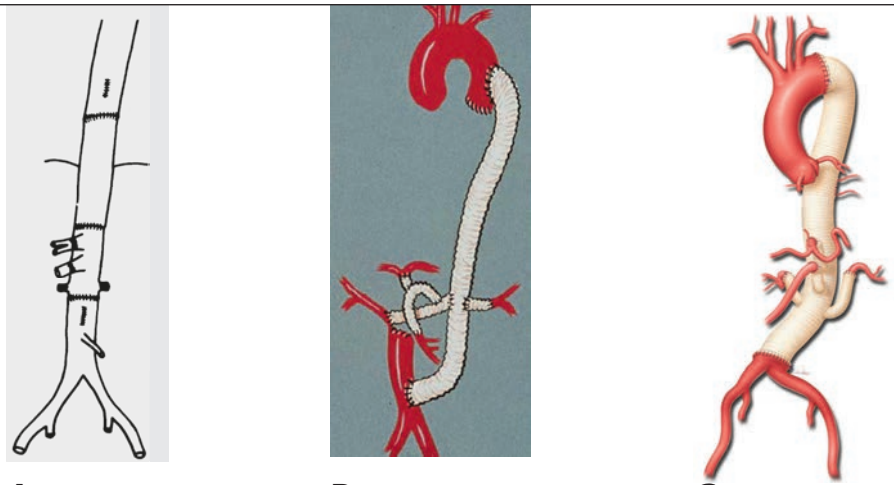


Fig 6. Illustrations demonstrating the evolving approach to thoracoabdominal aortic aneurysm (TAAA) repair. **(A)** In this early TAAA repair (the first successful repair performed in Houston), DeBakey and colleagues used a homograft to replace the resected aorta and restore continuity of the aorta. An end-to-side shunt, attached proximally to the descending thoracic aorta and distally to a section of aorta just above the inferior mesenteric artery, was utilized to maintain distal blood flow. Used with permission, figure 4 [5]. Copyright © 1956, Lippincott-Raven Publishers. **(B)** As synthetic grafts became available, TAAA repair shifted toward an extra-anatomic approach in which the graft is first used as a shunt around the aneurysm, and then the aneurysm is extirpated. Used with permission of Baylor College of Medicine. **(C)** In contemporary TAAA repair, an anatomic inclusion approach is used. In this illustration, a branched graft is used. Although many centers routinely use branched grafts, we tend to reserve them for patients with connective tissue disorders or when the origins of the patient's visceral vessels are far apart enough that patch reimplantation is undesirable. Used with permission of Baylor College of Medicine.

considered unable to withstand open repair are now being treated endovascularly [84, 85].

Thoracoabdominal aorta

Similar to aortic arch repair, early thoracoabdominal aortic repair also involved an extra-anatomic approach [86]. The graft was placed around the aneurysm and attached in an end-to-side fashion. This allowed its use as a shunt during repair, which reduced distal ischemia. Branched grafts were frequently used to reattach the visceral arteries [Fig. 6]; most commonly, the

renal arteries were reattached first. Because aneurysms were completely extirpated, intercostal arteries in the resected section continued to be sacrificed.

Beginning in the late 1960s and early 1970s, the need to fully resect the aneurysmal section of the aorta was beginning to be questioned. Crawford's landmark series of TAAA repairs [87] popularized an anatomic approach to repair that incorporated several key clinical and experimental techniques: reattaching branching vessels by directly suturing the vessel orifice to openings made in the graft, as suggested experimentally by Carrel and Guthrie [88] in 1906; wrapping the preserved aneurysmal aortic wall around the graft, which was inspired by the technique used by Javid and colleagues [89] to repair infrarenal aortic aneurysms; and reimplanting lumbar or intercostal arteries, as demonstrated experimentally by Spencer [90] in a canine model.

Over the next few decades, Crawford's original "clamp-and-sew" approach was modified to selectively incorporate several key adjuncts. Briefly, these included the use of cerebrospinal fluid drainage, introduced by Miyamoto [91] in Japan, cold renal perfusion, left heart bypass as introduced by Gerbode [92], and the selective perfusion of the celiac axis and superior mesentery artery, as well as Borst's elephant trunk approach to extensive aortic resection [93]. Honoring Crawford's legacy, we have conducted randomized trials of different renal perfusion techniques [94, 95] and of cerebrospinal fluid drainage [96], as well as an investigation regarding the use of left heart bypass to reduce distal ischemia [97]. Other important techniques include the use of prefabricated branched grafts in patients with connective tissue disorders or widely displaced visceral arteries, and the use of hypothermic circulatory arrest, both in cases of unclampable aortic aneurysms and as a standard technique in expert centers [65]. The contemporary use of these adjuncts is often determined by the Crawford extents of repair [98] and existing individual comorbidities. In severely compromised patients, both purely endovascular and hybrid techniques have been introduced in the hope of enhancing survival. Although the current experience with combined open and endovascular TAAA repair appears somewhat disappointing [99], the use of

experimental, purely endovascular techniques may yet prove to be a feasible repair strategy for otherwise inoperable patients [100].

Abdominal aorta

There has been a nearly complete paradigm shift in the treatment of abdominal aortic aneurysm (AAA). From its infancy, AAA repair opened the door to aortic surgery and allowed a novel field to flourish. Today, endovascular repair is more commonly used to treat AAA than is open repair [84]. In fact, European guidelines suggest endovascular repair unless the patient has unsuitable anatomic features or the aneurysm is exceptionally large [101]. Open surgery remains an important option in young patients due to the uncertain durability of endovascular repair in patients with a long life expectancy. Interestingly, data are now emerging that suggest that the early survival advantage endovascular repair has over open repair may not persist [102] and that endovascular repair may place patients at risk of late rupture [103].

Conclusion

During the last 6 decades, the techniques of aortic surgery have undergone significant metamorphosis, and dramatic progress in the treatment of aortic aneurysms has been made. In the beginning, we skirted around the aorta, but eventually we learned to tame it through operative resection and replacement. Now, we have entered the endovascular era, in which we are again attempting to avoid direct operative repair in the hopes of providing better care for our patients by minimizing repair-related complications.

Current trends suggest that greater numbers of sicker, older patients will seek treatment in the coming years. Providing these patients with the best care possible will depend on our ability to choose the best repair option for each individual patient—as well as our ability to develop new options for aortic repair. The future holds significant opportunity for innovation, just as it did in the beginning.

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Keynote

6: Friday, December 14th

Bart L. Loeys, MD, PhD: "The Loeys-Dietz Syndrome"

Professor at University of Antwerp, Belgium

De Swerts Award from the Royal Academy for Medicine, Belgium

Jacqueline Bernheim Prize, Belgium, Fund for Cardiac Surgery

Antoine Marfan Award for dedicated commitment to improving the length and quality of life for people with Marfan syndrome and related disorders through patient care and research from the National Marfan Foundation

Inbev-Baillet Latour Prize for excellence in clinical research

The Loeys-Dietz syndrome

Bart Loeys

Center for Medical Genetics
Antwerp University Hospital/University of Antwerp

Introduction

Loeys-Dietz syndrome (LDS, OMIM ID #609192) was first described by Loeys and Dietz in 2005. The initial paper presentedten probands with a novel aortic aneurysm syndrome characterized by the clinical triad of hypertelorism, bifid uvula/cleft palate and aortic/arterial aneurysms and tortuosity (1). Although these presented the most typical characteristics, a widespread involvement of different organ systems was also recognized. These included craniofacial (eg craniosynostosis), skeletal (joint laxity and contractures), integumental (skin hyperextensibility, dural ectasia) and ocular findings (eg strabismus). Although LDS shows clinical overlap with Marfan syndrome (MFS), it can be clinically distinguished from the latter. Shared features include aortic root aneurysm, pectus deformities, scoliosis and arachnodactyly. Distinguishing findings are craniosynostosis, hypertelorism, cleft palate or bifid uvula, cervical spine instability, club feet, and most importantly widespread arterial aneurysms with tortuosity and early aortic rupture. Since the initial description of LDS, families with aortic aneurysms without significant outward features have also been described (2, 3).

Signs and Symptoms

An overview of the clinical features of LDS is given in Table 1.

LDS is characterized by four major groups of clinical findings, affecting the vascular, craniofacial, skeletal and cutaneous system (1). Although some clinical overlap with MFS exists,

highly prevalent distinguishing features in LDS are cleft palate/bifid uvula, hypertelorism and arterial tortuosity. Interestingly, in some patients the bifid uvula is the only visible marker to identify people at risk for aortic aneurysms.

Cardiovascular Manifestations

In the vascular system, the most common and prominent finding is the dilatation of the aortic root at the sinuses of Valsalva, which if undetected, leads to aortic dissection and rupture. These dissections have been described in patients as young as six months of age. Moreover, dissections have occurred at smaller diameters than those generally accepted at risk in MFS (11). In addition to the aortic root aneurysms, aneurysms throughout the arterial tree have been described, most prominently in the side branches of the aorta and the cerebral circulation. Finally, another striking finding is the presence of arterial tortuosity, which is usually most prominent in the head and neck vessels. Vertebral and carotid artery dissection and cerebral bleeding have been described; however, isolated carotid artery dissection in the absence of aortic root involvement has not been observed (1, 4, 12).

Skeletal Manifestations

Marfanoid skeletal features can be observed, although the actual overgrowth tends to be milder in LDS patients compared to MFS patients. Most typical LDS skeletal findings include pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus and cervical spine malformation and/or instability. Arachnodactyly is present in some, but true dolichostenomelia (leading to an increase in the arm span-to-height ratio and a decrease in the upper-to-lower segment ratio) is less common in LDS than in MFS. The combined thumb and wrist signs are present in circa one-third of individuals with LDS. Joint hypermobility is very common and does include congenital hip dislocation and recurrent joint subluxations. Paradoxically, some individuals can show reduced joint mobility, especially of the hands (camptodactyly) and feet (club feet). Other recurrent skeletal findings include spondylolisthesis, acetabular protrusion and pes planus (1, 4).

Preliminary evidence suggests that individuals with LDS have an increased incidence of osteoporosis with increased fracture incidence and delayed bone healing (13).

(Cranio)facial manifestations

Most typical craniofacial features consist of ocular hypertelorism and the presence of a cleft palate, or its mildest presentation, a bifid uvula. Sometimes the uvula is not bifid but has an unusual broad appearance with or without a midline raphe. Another common presenting feature in the more severely affected patients is craniosynostosis. In the latter all sutures can be involved: most commonly the sagittal suture (resulting in dolichocephaly), but also the coronal suture (resulting in brachycephaly) and metopic suture (resulting in trigonocephaly). Other common craniofacial characteristics are malar flattening and retrognathia. Besides the hypertelorism, ocular manifestations include strabismus, blue sclerae and myopia, but the latter is less frequent and less severe than in MFS. Significant refractive errors can lead to amblyopia. Retinal detachment has been reported rarely (1, 4). In our experience, ectopia lentis is not observed, although in the literature minimal lens(sub)luxation has been reported (14). Less common associated findings requiring further exploration include submandibular branchial cysts and defective tooth enamel (4).

Cutaneous manifestations

In persons without craniofacial features, important cutaneous findings can provide the clue towards diagnosis. These skin findings show significant overlap with those observed in Ehlers-Danlos syndrome (EDS) and include velvety, thin, translucent skin, easy bruising (other than the lower legs) and dystrophic scars. Comparable to the vascular type of EDS, life-threatening complications, such as spontaneous bowel rupture and peripartal uterine rupture have been reported (4, 15). Although in the past, a type I and II of LDS were described based on the presence of these vascular EDS-like findings, we now believe these are the representation of a continuum within the LDS spectrum of disease.

Other findings

Finally, a minority of affected individuals present developmental delay. When present, developmental delay is most often associated with craniosynostosis and/or hydrocephalus, suggesting that learning disability is an extremely rare primary manifestation of LDS. The common neuroradiological findings are dural ectasia and Arnold-Chiari type I malformation (16). The precise incidence of those two findings is unknown.

Other recurrent findings that need further documentation include muscle hypoplasia, dental problems with enamel dysplasia, allergic disease with seasonal allergies, asthma/ sinusitis, eczema and important gastro-intestinal problems: food allergy, eosinophilic esophagitis, inflammatory bowel disease.

Clinical presentation of LDS-related diseases

Van de Laar ***et al.*** recently described another autosomal dominant variant of LDS, also called aneurysms osteoarthritis syndrome (AOS) (6). AOS is characterized by aneurysms, dissections and tortuosity throughout the arterial tree in addition to craniofacial (including hypertelorism and abnormal palate/uvula), skeletal (including arachnodactyly and scoliosis) and cutaneous (including striae and velvety skin) symptoms and thus perfectly fits in the phenotypic spectrum of LDS. A distinguishing feature, however, might be the presence of early-onset osteoarthritis. In the initially published series, about 50% of the patients present with osteochondritis dissecans and about 90% of patients have vertebral disc degeneration, suggesting that these findings are very common in ***SMAD3*** associated type of LDS (6). Since the initial publication, however, it has become clear that not all ***SMAD3*** mutation positive patients do present osteoarthritis (17, 18). The cardiovascular severity of AOS seems similar to classical LDS with early onset dissections at smaller diameters and marked tortuosity (19, 20).

Finally, patients with mutations in the ***TGFB2*** gene, also present an autosomal dominant disorder with many systemic features of both MFS and LDS. Features shared with MFS and LDS include aortic aneurysm, pectus deformity, arachnodactyly,

scoliosis and skin striae. Features shared with LDS but not with MFS, consist of hypertelorism, bifid uvula, bicuspid aortic valve (BAV), arterial tortuosity, club feet and thin skin with easy bruising. Ectopia lentis was not observed (7).

Most recently, mutations in ***SKI***, a functional repressor of TGFbeta signaling were identified as the cause of Shprintzen-Goldberg syndrome (SGS) (29). SGS is characterized by craniosynostosis, distinctive craniofacial features with dolichocephaly, retrognathia, high arched palate, marfanoid skeletal changes including dolichostenomelia, arachnodactyly, camptodactyly, pes planus, pectus excavatum or carinatum, scoliosis, joint hypermobility, and contractures. Cardiovascular anomalies with mitral valve prolapse, mitral regurgitation, and aortic regurgitation may occur, but aortic root dilatation is usually mild. Minimal subcutaneous fat, abdominal wall defects, cryptorchidism in males, and myopia are also characteristic findings. Nearly all SGS patients present with developmental delay, a finding that is rare in LDS. Molecular analysis of a series of individuals with typical SGS did not reveal mutations in the ***TGFBR1*** or ***TGFBR2*** (1).

The major clinical findings of MFS, LDS and SGS are summarized in a comparative table (Table 2).

Inheritance and mutational spectrum

LDS is an autosomal dominant disorder. About two third of cases are the consequence of ***de novo*** mutations, whereas the other one third are familial. In general, the more severe cases with marked craniofacial and skeletal findings are the consequence of a ***de novo*** mutation, whereas the milder cases tend to be familial. Both non-penetrance (4) and mosaicism (5) have been reported.

Two major genes have been initially associated with LDS. These genes encode the transforming growth factor b receptors 1 and 2, ***TGFBR1*** and ***TGFBR2***. ***TGFBR1*** is located on chromosome 9q and contains 9 exons, whereas ***TGFBR2*** is mapped to chromosome 3p and contains 8 exons. Most recently, mutations in the gene encoding ***SMAD3*** have been associated

with a condition called aneurysms osteoarthritis syndrome, showing a significant clinical overlap with LDS (6). Finally, also mutations in ***TGFB2*** have been identified in patients with LDS-like presentations (7).

One third of the ***TGFBR*** mutations are identified in ***TGFBR1*** whereas the remainder is found in ***TGFBR2*** (4). Mutations are primarily located in the serine-threonine kinase domain, the intracellular part of the TGFb receptor. Although occasional nonsense mutations or small intragenic deletions have been described in ***TGFBR2***, these were all predicted to escape nonsense-mediated-decay (4). Deletions involving ***TGFBR2*** lead to an LDS-like phenotype but patients lack significant aortic disease (8). Moreover, ***TGFBR1*** nonsense mutations or mutations predicted to cause a complete loss-of-function have been shown recently to lead to a skin cancer phenotype, multiple selfhealing squamous epithelioma (9). Both for ***SMAD3*** and ***TGFB2*** mutations, haplo-insufficiency and loss-of-function were suggested as mutational mechanisms. All findings hitherto suggest that although the ***TGFBR***-mutations in LDS are also predicted to lead to loss-of-function (10), some residual protein activity seems to be required to cause the LDS phenotype (see pathogenesis).

Diagnostic criteria for LDS

Although no formal diagnostic criteria have been developed, ***TGFBR1/2*** genetic testing should be considered in the following scenarios:

1) Patients with the typical clinical triad of hypertelorism, cleft palate/bifid uvula and arterial tortuosity/aneurysm
2) Early onset aortic aneurysm with variable combination of other features including arachnodactyly, camptodactyly, club feet, craniosynostosis (all types), blue sclerae, thin skin with atrophic scars, easy bruising, joint hypermobility, BAV and patent ductus arteriosus (PDA), atrial and ventricular septum defects (ASD/VSD)
3) Patients with a MFS-like phenotype, especially those without ectopia lentis, but with aortic and skeletal features not fulfilling the MFS diagnostic criteria (21)
4) Families with autosomal dominant thoracic aortic aneurysms, especially those families with precocious

aortic/arterial dissection, aortic disease beyond the aortic root (including cerebral arteries)
5) Patients with a clinical tableau reminiscent of vascular EDS (thin skin with atrophic scars, easy bruising, joint hypermobility) and normal type III collagen biochemistry
6) Isolated young probands with aortic root dilatation/ dissection

If patients present with premature onset of osteoarthritis in addition to any of the above clinical scenarios, ***SMAD3*** may be prioritized as the causal gene. If the clinical presentation is rather mild, ***TGFB2*** may also be considered. Although it should be stressed that the clinical overlap is so large, that it is impossible to predict the correct causal gene based on the clinical signs. If craniosynostosis and intellectual disability are associated features, ***SKI*** might be the first gene to be analyses.

Treatment and managment

Natural history

Comparison of the natural history of Marfan syndrome and Loeys-Dietz syndrome has lead to two important lessons. First, in the most severe cases of LDS (with more outward features of LDS) aortic dissections at smaller diameters as in MFS have been observed, leading to the need for earlier surgical intervention (see below). Secondly, it has been observed that the aortic disease is far more widespread in LDS with aortic disease beyond the aortic root and prominent involvement of aortic sidebranches, necessitating a complete imaging of the arterial tree from head to pelvis.

Medical treatment

Many of the treatment strategies in LDS are derived from knowledge derived from MFS patient management. The current treatment for aortic aneurysms in MFS is not causal and purely symptomatic. Preventive treatment with beta-blockers is believed to slow down the aortic root growth but in general this does not prevent aortic surgery at later age. Based on initial experiments that demonstrated the rescue of the lung phenotype in Marfan

mouse models through the use of TGFb neutralizing antibodies (39), it was hypothesized that similar treatments may be beneficial for the aortic phenotype in MFS patients. Proof-of-principle was obtained from a Marfan mouse trial (40). The intraperitoneal injection of TGFb neutralizing antibody blocked aortic root growth in these mice. Subsequently, similar results were obtained using an angiotensin II type 1 receptor blocker, losartan. Losartan does not only have an effect on the renin-angiotensin-aldosterone axis but has also an effect on TGFb signaling. It is believed to reduce both the total and active amount of TGFb in the extracellular matrix, probably through effects on thrombospondin, a TGFb activator. In a placebo-controlled trial on Marfan mice, losartan resulted in significantly reduced aortic growth compared to atenolol, despite the similar hemodynamic effect. In addition to a major effect on the aortic growth, the histology of elastic fibers in the aortic wall of the losartan treated MFS mice was also indistinguishable from wild type mice (40).

The beneficial effect of angiotensin receptor blocker treatment on aortic growth was confirmed in a preliminary observational study in severely affected pediatric MFS patients. Similar to the MFS mice, a significant decrease in rate of change of aortic root dimension after starting angiotensin receptor blocker therapy was observed. Again, as there was no difference in the effect of hemodynamic parameters, the data suggest that these achieved protective effects were likely to be attributed to TGFb antagonism (41). This study has provided the first evidence for a significant benefit of angiotensin receptor blocking agents over current therapies in reducing aortic root dilation in severe pediatric MFS patients.

Based on the mouse data and the preliminary human study a large, randomized clinical trial in MFS patients has been initiated. This trial, supported by the Pediatric Heart Network through the U.S. National Heart, Lung and Blood Institute (NHLBI), compares atenolol with losartan treatment in more than 600 patients for a three-year treatment (42). In addition, a dozen other trials with different designs and inclusion criteria have been initiated in Belgium, France, Italy, The Netherlands, Taiwan and the United Kingdom (43-46). As some of these studies might be underpowered, it is anticipated that a meta-analysis of trials with similar design will be necessary (47).

Surgical treatment

Given the safety and the increasing availability of the valve-sparing procedure, the following recommendations have been issued for aortic surgery in LDS (48). First, for young children with severe systemic findings of LDS, surgical repair of the ascending aorta should be considered once the maximal dimension exceeds three standard deviations and the aortic annulus exceeds 1.8 cm, allowing the placement of a graft of sufficient size to accommodate growth. Second, for adolescents and adults, surgical repair of the ascending aorta should be considered once the maximal dimension approaches 4.0 cm. This advice is based on both numerous examples of documented aortic dissection in adults with aortic root dimensions at or below 4.0 cm and the excellent outcome of prophylactic surgery. An extensive family history of larger aortic dimension without dissection could alter this practice for individual patients (49).

Table 1. Clinical features at initial diagnosis of LDS.

Craniofacial features:	
– Craniosynostosis	15%
– Hypertelorism	48%
– Cleft palate/uvula	72%
– Exo/esotropia	18%
– Blue sclerae	23%
Skeletal features:	
– Pectus deformity	51%
– oint contractures	23%
– Joint hypermobility	50%
– Arachnodactyly	56%
– Club feet	22%
– Pes planus	51%
– Scoliosis	70%
– cervical spine abnormality	39%
Skin features:	
– Thin, translucent	33%
– Smooth, velvety	23%
– Easy bruising	24%
– Delayed wound healing	12%
– Herniae	25%
Vascular findings	
- Arterial tortuosity 92%	
- most common in head and neck vessels	
- carotids (55%)	
- vertebrals (56%)	
- intracranial (37%)	
- ascending aorta (5%), aortic arch (10%) descending thoracic (4%) or abdominal (7%) Ao, also other vessels (e.g. iliacs)	
- Aneurysms	
Aorta	
- root	87%
- ascending	27%
- arch	10%
- desc thoracic	15%
- abdominal	12%
Vessel beyond Ao	30%

Table 2. Differential diagnostic features of MFS, LDS and SGS

	MFS	LDS			SGS
Clinical feature	***FBN1***	***TGFBR1/ TGFBR2***	***SMAD3***	***TGFB2***	***SKI***
Ectopia lentis	+++	–	–	–	–
Cleft palate/bifid uvula	–	++	+	+	+
Hypertelorism	–	++	+	+	++
Craniosynostosis	–	++	–	–	+++
Tall stature	+++	+	+	++	
Arachnodactyly	+++	++	+	+	++
Pectus deformity	++	++	++	++	++
Club foot	–	++	+	++	+
Osteoarthritis	+	+	+++	+	–
Aortic root aneurysm	+++	++	++	++	+
Arterial aneurysm	–	++	+	+	+
Arterial tortuosity	–	++	++	+	+
Early dissection	+	+++	++	+	–
Bicuspid aortic valve	–	++	+	+	+
Mitral valve insufficiency	++	+	+	++	+
Striae	++	+	+	+	+
Dural ectasia	+	+	+	+	+
Developmental delay	–	–	–	–	++

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Keynote

7: Friday, December 14th

Piero Anversa, MD:
"Cardiac stem cells and myocardial repair"

Professor of Medicine, Director, Center for Regenerative Medicine, Harvard Medical School, Boston MA

Laurea ad Honorem of the University of Bologna Medical School

Research Achievement Award of the American Heart Association

Louis and Arthur Lucian Award

Distinguished Scientist Award of the Council on Basic Cardiovascular Sciences of the American Heart Association

Board of Scientific Counselors NIH/NIA

International Academy of Cardiovascular Sciences Medal of Merit

Notes

Keynote

8: Friday, December 14th

Roland Hetzer, Prof. Dr. med. Dr. h.c.mult: "History of artificial heart and cardiac assist devices"

Deutsches Herzzentrum Berlin
Director Department of Cardiac, Thoracic and Vascular Surgery
Federal Cross of Merit First Class
Honorary Professor of Shanghai Second Medical University
Honorary Doctorate from the University of Fujian
Honorary Doctorate of the Cardinal Stefan Wyszynski University in Warsaw
Urania Medal of the City of Berlin for the academic performance of public education
Honorary Doctorate from the Lomonosov Moscow State University

Notes

Keynote

9: Saturday, December 15th

Timothy A. M. Chuter, MD:
"History of endovascular aortic procedures"

Professor of Surgery
Division of Vascular and Endovascular Surgery
Director of the Endovascular Surgery Program
University of California San Francisco
Medal for Innovation in Vascular Surgery from the Society for Vascular Surgery

A brief history of endovascular aneurysm repair

Timothy A.M. Chuter, MD
UCSF Division of Vascular Surgery

The original concept of endovascular aneurysm repair (EVAR)

Widely used as it is, the term "endovascular aneurysm repair" is something of a misnomer: the aneurysm is not *repaired* in the surgical sense. Bypass or exclusion would be more accurate. This is not just a semantic distinction. In surgical repair, the aneurysm is opened and its branches are suture ligated. In endovascular repair, the aneurysm is left intact and its branches remain patent, at least initially; hence the potential for exclusively endovascular failure modes, such as endoleak or endotension.

EVAR relies on a series of assumptions: exclusion of the aneurysm from flow reduces the pressure in the aneurysm sac, reduced pressure causes the sac to shrink, and a shrinking aneurysm is unlikely to rupture. All these assumptions have proven to be correct. The presence (endoleak) or absence of flow within the aneurysm sac correlates with sac pressure, sac behavior, and the risk of rupture. These correlations form the basis for the use of surrogate endpoints to assess the success and durability of the repair. Their predictive value is important because EVAR is basically a prophylactic operation, and it is a bit late to declare the procedure a failure when the aneurysm ruptures.

Animal studies

The trans-femoral delivery and attachment of an endovascular graft relies could not have developed without two enabling technologies: fluoroscopic imaging and stent-mediated graft

attachment. Maass (1) was the first to suggest in-print that a stent might be used for endovascular aneurysm repair, and Cragg (2) was the first to demonstrate the feasibility of this approach experimentally. In both cases, the only barrier between the perfused lumen and the aneurysm was the stent itself possibly a lining of thrombus: there was no fabric covering. Balko et al were the first to use a true stent graft, combining Z-stents and a polyethylene covering (3). Lawrence et al were the first to insert a stent graft using fluoroscopic guidance (4). They were also the first to use percutaneous trans-femoral access. Meanwhile (unknown outside the Ukraine) Volodos et al was already starting to use a similar technique in patients (5, 6). Another notable pioneer, Parodi, used a balloon expanded Palmaz stent in a short series of animal experiments (7), before proceeding quickly to clinical use (8).

Aorto-aortic stent grafts

Parodi's 1991 paper, describing the first cases of EVAR, marked a turning point in the history of Vascular Surgery. After a short period of denial, vascular surgeons as a group realized that their proudest achievement, the surgical repair of an aortic aneurysm, was amenable to an endovascular approach and their widespread adoption of EVAR served a gateway to the wider world of endovascular intervention.

For all its impact, the technique initially described by Parodi ultimately failed. All 6 patients in this series required revision to treat migration and leakage from the unattached distal end of the graft. Even with the addition of a distal stent, this approach suffered from limited applicability and high rates of distal attachment failure. The realization that most patients lacked a non-dilated segment of aorta between the aneurysm and the bifurcation limited the use of tubular aorta-aortic graft. Endovascular repair of AAA required distal implantation in one or both common iliac arteries (9).

Although aorto-aortic stent grafts were unsuitable for use in AAA, they found a role in the endovascular treatment of thoracic aortic disease (TEVAR). The first such cases were probably performed by Volodos (5, 6). This work received very little attention at the time. Other, better-known, pioneers in TEVAR include Dake et al, who not only used homemade stent

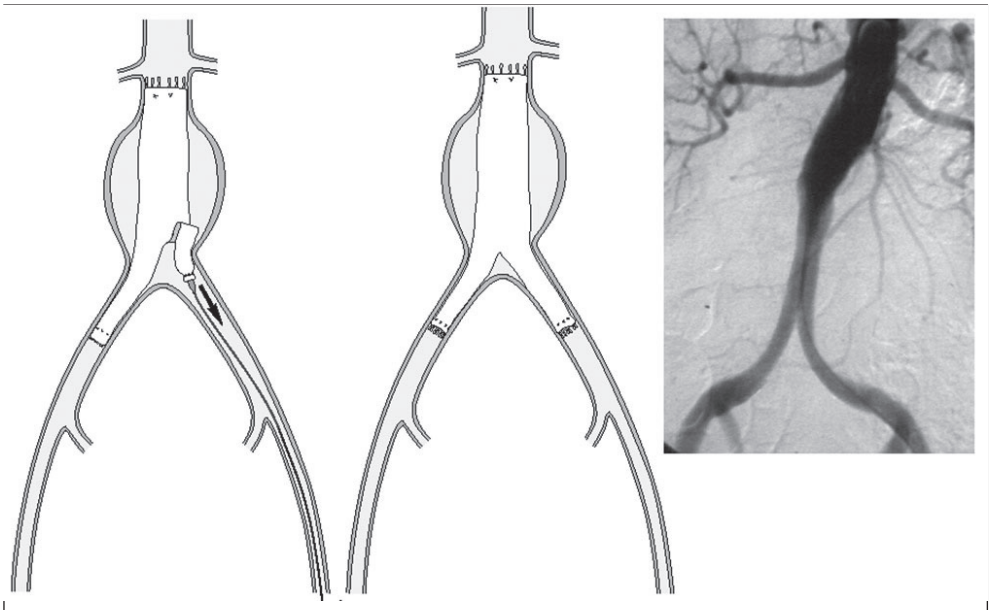

Figure 1. The first bifurcated stent graft.

grafts to treat aneurysms, traumatic rupture and dissection of the thoracic aorta (10).

Aorto-uniiliac stent grafts

Aorto-uniliac stent grafts are easy to make and easy to insert. They played a prominent role in the early history of EVAR, at a time when most surgeons made their own stent grafts. For example, the first stent graft implanted in the United States was of this design, as was the first stent graft for aneurysm rupture (11). Uni-iliac stent grafts require femora-femoral bypass and contralateral common iliac occlusion. The disadvantages of this form of hybrid repair include: the flow restriction of a single iliac outflow, the additional surgery of femoro-femoral bypass and the risk of graft infection. Aorto-uniiliac stent grafts are now used only in cases of distal aortic narrowing and unilateral iliac occlusion.

Bifurcated stent grafts

The first bifurcated stent grafts were of a unibody design (Fig. 1), which means they were inserted whole with both

limbs already attached and manipulated into position using a system of catheters. Early examples included the Ancure stent graft (Endovascular Technologies). Modular designs, which are assembled in-situ from two or more components have largely replaced unibody designs because they tend to be easier to make, easier to insert and more versatile. These days the only unibody design in widespread use is the one manufactured by Endologix, but even this incorporates modularity in the form of additional mating components that extend the trunk and allow precise infrarenal implantation.

The evolution of device design

The early stent grafts proved to be safe and effective in the short-term, but unstable in the long-term (12-15). The endosceptics had a point when they declared endovascular aneurysm repair "a failed experiment", but they were wrong to conclude that the evident instability of the early devices was an inevitable feature of the endovascular approach, rather than the device-specific consequences of faulty design.

Some early devices, such as the Stentor (later known as the Vanguard) showed every conceivable form of late failure, including: stent fracture, stent disconnection, fabric erosion, component separation and stent graft migration. Fortunately, the design of later generations of stent graft benefitted from the painful lessons of the early experience. We learned, for example, that loosely woven grafts develop suture traction holes, unattached stents damage the underlying graft, inadequate inter-component overlap causes separation, and that friction and column strength will not prevent migration, but barbed suprarenal stents will (15).

The result has been a convergent evolution of stent design and the elimination of failure-prone devices such as the Vanguard and AneuRx.

Because small (evolutionary) changes in stent graft design built on established principles, they rarely produced any surprises, good or bad. The current crop of widely used devices can all be expected to function reasonably well in the short and long-term. But devices that rely on radically different design features and different mechanisms of action sometimes encounter new failure modes. For example, the Ovation, which substitutes a

polymer filled balloon for the usual stent skeleton, depends on the stability of balloon dimensions, neck dimensions and suprarenal stent structure. If any of these change, the device will fail. Similarly, the Nellix, which also has a polymer filled balloon, depends on the dimensional stability of the neck, the mural thrombus and the endobag. On the other hand, if these devices work as intended they will have a prominent role to play because they offer reduced delivery profile and freedom from type II endoleak.

Endovascular repair of juxtarenal AAA

Once bifurcated stent grafts had eliminated the need for a distal neck, the main exclusion criterion for EVAR became the lack of a suitable proximal neck. Arbitrary as they were, the original instructions for use, requiring a neck length of at least 15mm, proved to be quite predictive of stent graft performance.

Several techniques evolved to allow pararenal stent graft implantation when the infrarenal neck was too short, too wide, or too angulated. They all involve creating a route for flow to the renal arteries - and possibly the mesenteric arteries- through (fenestration), or around (snorkel, or chimney), the stent graft.

The technical details and relative merits of the two approaches are beyond the scope of this paper. Suffice it to say that fenestrations are more difficult to construct, but more likely to succeed.

For a simple fenestration to work it had to be relatively small and placed right over the renal orifice. In the technique developed by Lawrence-Brown, Hartley et al (16) a catheter was inserted through a fenestration in the partially deployed stent graft and into the corresponding target artery (Fig. 2). This bridging catheter then guided the fenestration to the target artery and a bridging stent held it there. The substitution of a covered stent for the uncovered bridging stent converted a fenestration into a branch and permitted fenestrated stent grafts to be used to treat pararenal and thoracoabdominal aneurysms.

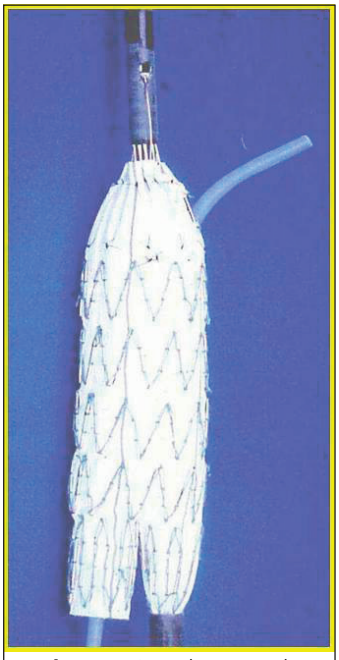

Figure 2. Photograph of a bridging catheter emerging through a fenestration in a partially expanded Zenith Figure

Endovascular repair of the aortic arch, thoracoabdominal aorta and common iliac bifurcation

Aneurysms of the aortic arch and thoracoabdominal aorta are difficult to treat by any means. One cannot exclude their walls without first making some provision for flow to their branches, either through the branches of a multi-branched stent graft, or through the limbs of an extra-anatomic surgical bypass.

The relative merits of multi-branched endovascular repair and hybrid endovascular/surgical repair depend on the accessibility of the branches. The supra-aortic trunks, for example, are readily accessible. So long as one does not have to go to the aorta for a source of inflow, hybrid repairs are easy to perform, well tolerated, and therefore widely practiced. The thoracoabdominal aorta and its branches occupy an inaccessible location. Hybrid repairs are poorly tolerated. Multi-branched endovascular repair is generally the better option. The same is true of bifurcated iliac repair in cases of common iliac artery aneurysm.

Like bifurcated stent-grafts, multi-branched stent grafts can be of unibody or modular design. The first reported cases of branched endovascular repair in the aortic arch and thoracoabdominal aorta employed unibody stent grafts. But the irreducible complexity of the unibody approach limited the number of branches and produced high rates of both embolism and endoleak. A completely endovascular multi-branched repair proved to be easier and safer using the simpler, more versatile modular approach. None of this required complex technology (17). The original homemade stent grafts show the same basic features as today's industry made stent grafts.

Since the first case in August 2000 (Figs. 3A-3C), multi-branched endovascular TAAA repair has been performed in more than a thousand patients worldwide. In general, the branches consist of covered stents attached to fenestrations or cuffs (short branches) one an aortic, or aorto-iliac, stent graft. Axially oriented cuffs have proven to be particularly forgiving and versatile. In-situ customization can be achieved by varying the length and orientation of the branch as it winds down the aorta from the cuff to the target artery. This has allowed a standard of-the-shelf stent graft to be used in a majority of cases.

Even though modular stent graft was first used to treat and aneurysm of the aortic arch over 8 years ago (18), endovascular

Figure 3A. The first multi-branched thoracoabdominal stent graft.

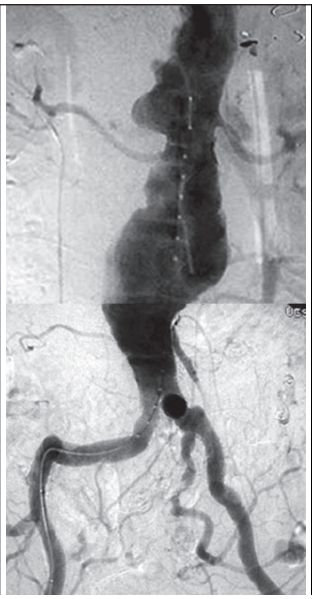

Figure 3B. Preoperative angiogram of the first patient to undergo aneurysm repair using a multi-branched thoracoabdominal stent graft.

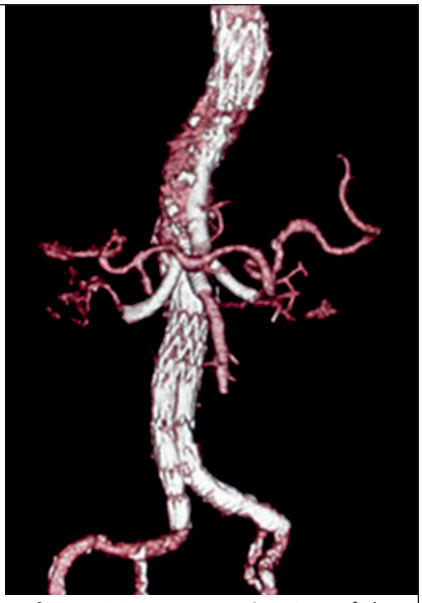

Figure 3C. Postoperative CTA of the first patient to undergo aneurysm repair using a multi-branched thoracoabdominal stent graft.

repair of the arch has been slow to progress. It is difficult to introduce, orient and deploy very large stent grafts in a segment of the aorta that is wide, far from the femoral arteries and close to the aortic valve. At the time of writing, the most widely used multi-branched stent graft (Figs. 4A-4D) has been used in approximately 40 cases. The complication rates showed a steep learning curve. There were 4 deaths in the first 10 patients, one in the next 10 and none since.

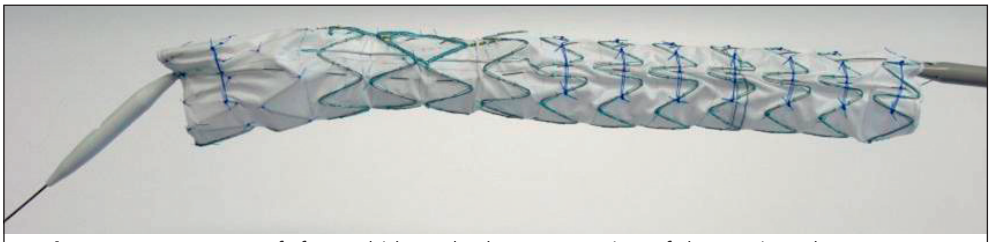

Figure 4A. A stent graft for multi-branched reconstruction of the aortic arch.

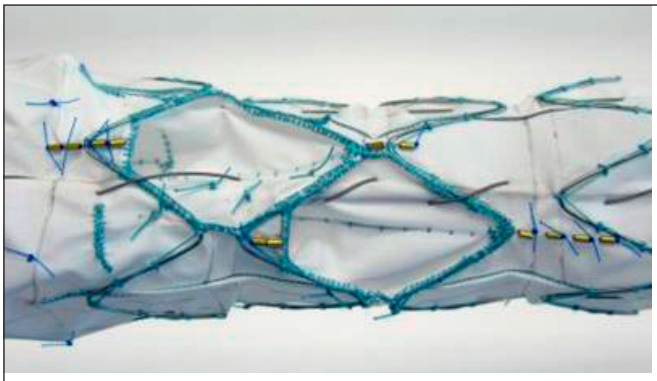

Figure 4B. A close-up of the cranial surface, showing access sites for internal branch attachment cuffs.

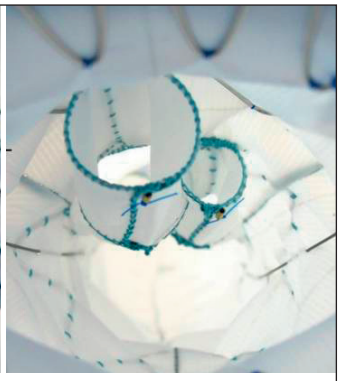

Figure 4C. An internal view, showing branch attachment cuffs.

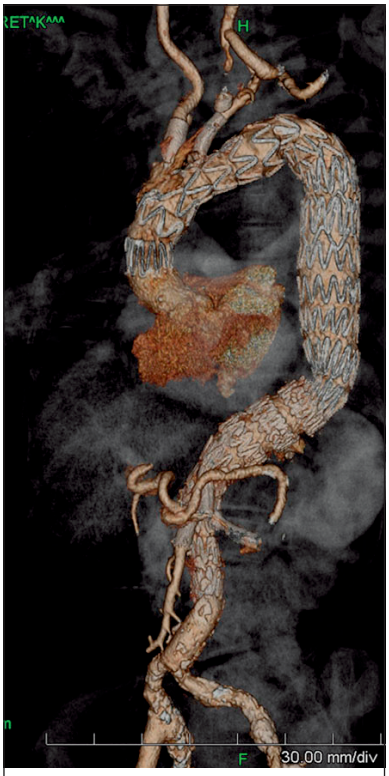

Figure 4D. Postoperative CTA of the first patient to undergo multi-branched endovascular repair of an arch aortic aneurysm. stent graft.

Trials and registries

Several randomized studies have shown that the short-term survival advantage of endovascular repair compared to open surgical repair is lost within 2 years (19). Although the phenomenon has been explained in a variety of ways, long-term instability of the repair certainly plays a role. However, one should bear in mind that stent graft technology has improved since 1999 when the EVAR studies were started. This is particularly true of long-term device performance, which evolves slowly because it depends on the observation, and correction, of late-occurring failure modes. It is hardly surprising that more recent studies, such as OVER, produced better results (14).

Early reports based on the Eurostar and Life-line registries were undermined by a lack of device-specific data. Later reports showed the importance of device designs as a determinant of the long-term performance. The exclusion of data on obsolete designs yielded a much more informative picture of current experience (14).

Conclusion

The history of EVAR makes one thing abundantly clear: the field is in a constant state of flux. Even now, 20 years after the first clinical application of the approach, stent graft design continues to evolve and every change in stent graft design confers a possible change in stent graft performance. Most long-term data relate to obsolete devices. Moreover, any conclusions regarding the role of EVAR have to be device-specific, center-specific and (given the regulatory landscape) country-specific.

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Keynote

10: Saturday, December 15th

Randall B. Griepp, MD:
"Insight in spinal cord ischemia"

Professor and Chairman Emeritus, The Mount Sinai School of Medicine, New York

Founder and Director of the Aortic Surgery Symposium 1988-2012

Earl Bakken Scientific Achievement Award, Society of Thoracic Surgeons

Distinguished Scientist Award from the Bicuspid Aortic Foundation

Past President New York Society for Thoracic Surgery

Giants of Thoracic Surgery Award, New York Society for Thoracic Surgery

Perspective

The anatomy of the spinal cord collateral circulation

Eva B. Griepp, Gabriele Di Luozzo, Deborah Schray,
Angelina Stefanovic, Sarah Geisbüsch, Randall B. Griepp

Department of Cardiothoracic Surgery, Mount Sinai School of Medicine, New York, New York, USA

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Spinal cord injury remains a devastating complication of the treatment of extensive thoracoabdominal aortic aneurysms (TAAA), whether by open surgery or endovascular strategies. Although the incidence and pattern of occurrence of spinal cord injury have been changing in recent years, the threat of possible paraplegia or paraparesis continues to deter patients from undergoing elective operations to prevent rupture of extensive TAAA. A better understanding of the anatomy and physiology of the spinal cord circulation have in recent years led to a reduction in the risk of postoperative spinal cord ischemia; further insights should soon enable us to make postoperative paraplegia and paraparesis a very rare complication of TAAA treatment.

A number of clinical and experimental findings led us to question the traditional view that spinal cord perfusion is dependent principally upon a single prominent branch from the descending aorta with a distinctive hairpin configuration, the so-called artery of Adamkiewicz (1). We proposed instead the existence of an extensive collateral network that supports spinal cord perfusion. This collateral network includes all the segmental arteries (SAs), both intercostal and lumbar: they send branches to the anterior spinal artery (ASA), the major artery within the spinal canal. In addition to multiple SA inputs, the ASA is also potentially fed by an extensive epidural arterial network, and by a dense array of small vessels which supply the paraspinal musculature. All these vessels are interconnected, and have major anastomoses with the subclavian arteries cranially, and the hypogastric arteries caudally. This extensive collateral network

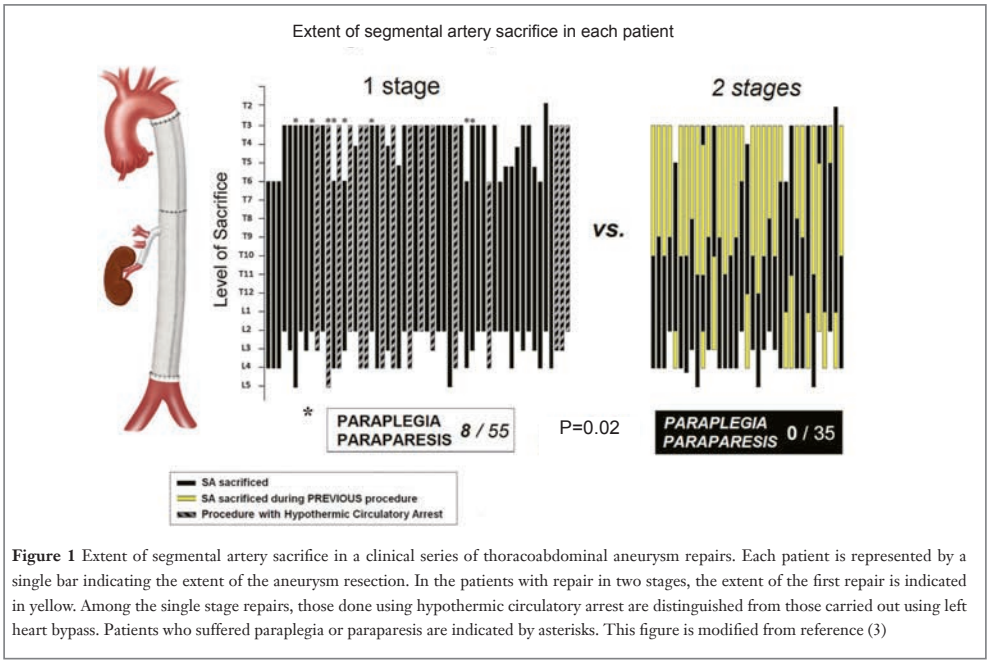

Figure 1 Extent of segmental artery sacrifice in a clinical series of thoracoabdominal aneurysm repairs. Each patient is represented by a single bar indicating the extent of the aneurysm resection. In the patients with repair in two stages, the extent of the first repair is indicated in yellow. Among the single stage repairs, those done using hypothermic circulatory arrest are distinguished from those carried out using left heart bypass. Patients who suffered paraplegia or paraparesis are indicated by asterisks. This figure is modified from reference (3)

allows compensatory flow to the spinal cord when some of the direct inputs to the ASA are compromised during repair of TAAAs.

The observation that spinal cord injury occurs more frequently in TAAAs of great extent—type II in the Crawford classification—was documented more than 20 years ago (2). More recently, we and others noted that when such extensive resections are carried out in two stages rather than during a single procedure, the risk of spinal cord injury is reduced sharply, Figure 1 (3,4). Although in our retrospective study the two-stage procedures were dictated by the various circumstances of the evolution of each patient's disease, we reasoned that the protection from spinal cord injury that resulted in each instance likely reflected a similar physiological adaptation by the collateral network to the loss of SA input. We have carried out a series of studies which have begun to illuminate the process by which complete recovery of spinal cord perfusion after extensive SA sacrifice is usually achieved, and to explain the mechanisms for the occasional occurrence of spinal cord injury following extensive TAAA resection.

The first series of experiments in pigs with regard to the

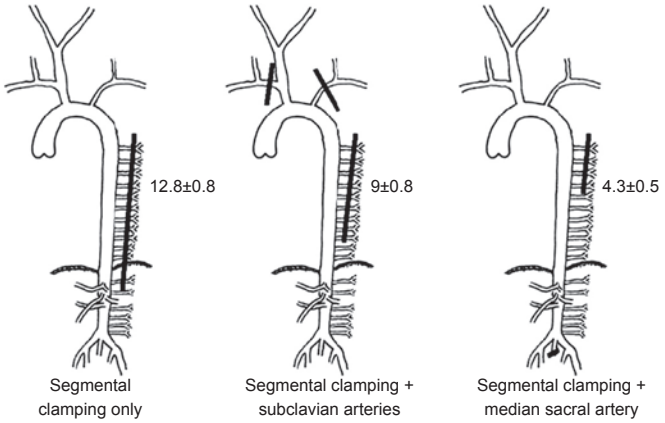

Figure 2 Shown are studies under various circumstances of the average numbers of segmental arteries—intercostal or lumbar—which could be serially clamped without provoking an ischemic change in the motor evoked potential signals in juvenile pigs. A higher number of segmental arteries can safely be clamped in the previously untouched control than after subclavian artery or after median sacral artery clamping. This figure is modified from reference (5)

spinal cord circulation demonstrated that the subclavian and median sacral arteries (equivalent to the hypogastric arteries in humans) are important components of the collateral network. If the subclavian arteries or the median sacral arteries are eliminated as inputs to the collateral network, fewer SAs can be sacrificed during simulated TAAA resection without spinal cord ischemia [monitored by motor evoked potentials (MEP)] as shown in Figure 2. In the native pig, as many as 13 intercostal and lumbar artery pairs can be sacrificed without any impact, but fewer can be eliminated without MEP loss if there has been prior subclavian artery sacrifice, and fewer still after median sacral artery sacrifice (5).

The importance of the total extent of SA sacrifice as the principal predictor of the risk of subsequent paraplegia has been confirmed in two clinical studies. In the initial study, at a time when few intraoperative measures to enhance spinal cord protection were routine, paraplegia was very rarely seen if fewer than 11 segmental arteries were sacrificed during TAAA resection, Figure 3 (6). Up to the present day, based on 609 patients, the highest risk of paraplegia is incurred when more than 13 SAs are sacrificed. When between 8 and 12 SAs are involved, the risk of spinal cord injury depends upon their location, with the greatest vulnerability occurring with lower thoracic and lumbar SA sacrifice (Figure 4) (7).

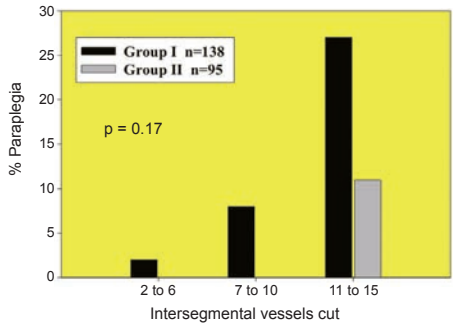

Figure 3 Comparison of the incidence of paraplegia before (in 138 patients) and after (in 95 patients) various adjuncts to increase spinal cord protection were routinely employed. Fewer cases of paraplegia were seen when adjuncts were utilized, but in both groups, cord injury depended upon the number of segmental arteries sacrificed. When fewer than 11 segmental arteries were sacrificed in the presence of adjuncts to protect the spinal cord, spinal cord injury did not occur. This figure is modified from reference (6)

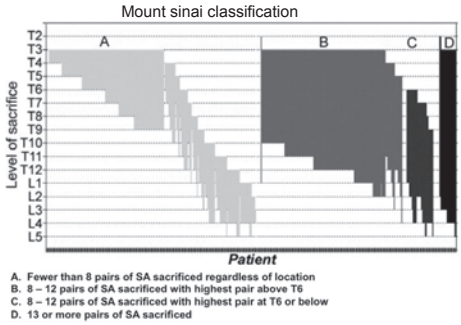

Figure 4 A proposed classification scheme for risk of paraplegia based on the extent and location of segmental artery (SA) resection during thoracic and thoracoabdominal aneurysm repair. For limited resections, especially those in the upper thoracic segments, the risk is quite low, but it rises sharply when more than 8 SAs are sacrificed, especially in the lower thoracic and lumbar area. The diagrams represent the extent of resection of the aneurysms in each group. The incidence of ischemic cord injury was 1.2% in Group A, 3.7% in Group B, 15% in Group C, and 12% in Group D. This figure is modified from reference (7)

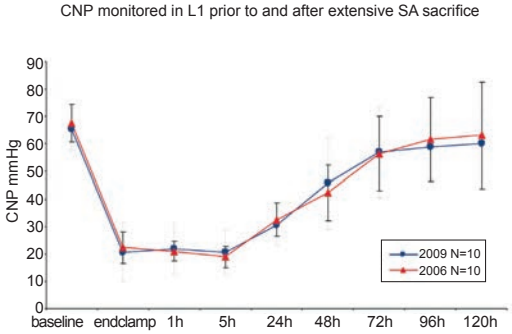

Figure 5 When pressure is monitored in the stump of a segmental artery (SA) after sacrifice of all SAs, the collateral network pressure (CNP) falls initially, reaches its lowest point about 5 hours after SA sacrifice, and recovers reliably between 72 hours to 5 days even in pigs that subsequently exhibit signs of functional spinal cord injury (8)

Measurement of pressure in the collateral network—by means of a catheter in the stump of a divided SA—permits an appreciation of the dynamic response of the circulation to SA sacrifice. Pressure in the collateral network is 60-80% of mean arterial pressure (MAP) at baseline, and falls after extensive SA sacrifice, reaching its nadir about 5 hours later, during awakening from anesthesia. Gradual recovery of collateral network pressure begins within the first 24 hours. In the experiments shown in Figure 5, return to baseline pressure was invariably seen between 72 and 120 hours after complete SA sacrifice, even in pigs that showed functional evidence of spinal cord injury (8).

Intraoperative clinical measurement of collateral network pressures has also been possible in a few patients, Figure 6 (9). These clinical recordings reveal that, as in the pig, baseline collateral network pressure is less than baseline MAP. The

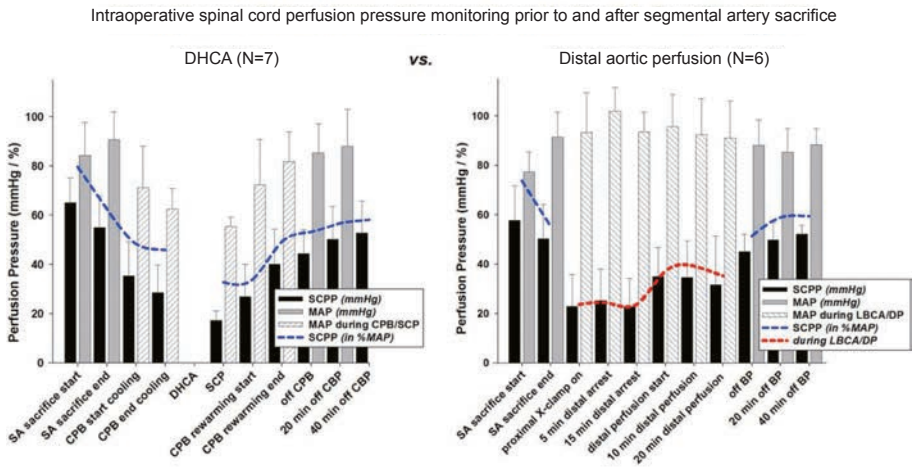

Figure 6 Intraoperative collateral network pressure, thought to be roughly equivalent to spinal cord perfusion pressure (SCPP), can also be monitored clinically in patients undergoing resection of thoracic and thoracoabdominal aortic aneurysms. As in pigs, SCPP is initially less than mean MAP at baseline and falls with segmental artery (SA) sacrifice; SCPP is very low in the absence of pulsatile perfusion, including the interval of left heart bypass. Partial recovery is seen for the first 72 hours postoperatively (not shown) (9). CPB = cardiopulmonary bypass; DHAC = deep hypothermic circulatory arrest; DP = distal perfusion; LBCA = lower body circulatory arrest; SCP = selective cerebral perfusion

perfusion pressure in the collateral network drops after SA sacrifice, and remains quite low until pulsatile perfusion is restored after discontinuation of cardiopulmonary bypass. Notably, perfusion pressure in the collateral network remains quite low despite what is generally considered effective partial left heart bypass. The lowest pressures, demonstrated in a few patients whose collateral network pressures were monitored

Figure 7 The perfusion of the spinal cord depends upon a vascular network which also provides flow to the paraspinal muscles, whose needs dwarf the flow to the spinal cord. In this view, the aorta is seen giving off paired segmental arteries which course around the vertebral body to supply the paraspinal muscles and, in the midline, the small anterior spinal artery

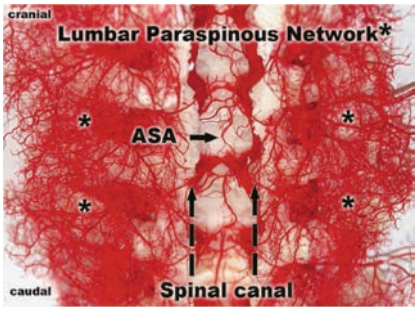

Figure 8 In this longitudinal section of a pig after injection of methyl methacrylate, the ASA is seen, with its multiple connections with the extensive vasculature of the paraspinal muscles adjacent to the spinal cord

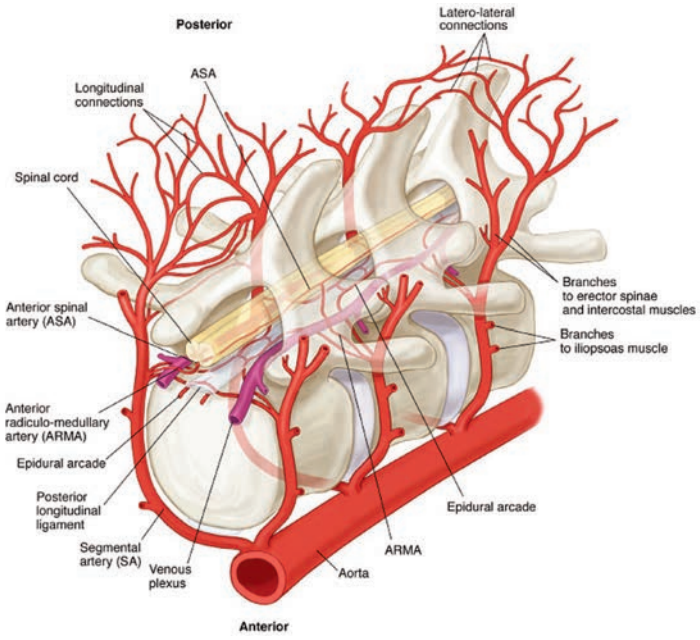

Figure 9 A diagrammatic reconstruction the blood supply to the spinal cord. The multiple inputs into the anterior spinal artery, and the rich matrix of longitudinal and lateral interconnections between the intraspinal and epidural systems are shown

for 24 hours postoperatively, occur—as in the pig—during rewarming and awakening from anesthesia, several hours after completion of SA sacrifice. This may explain a recent clinical trend toward a preponderance of delayed rather than immediate paraplegia.

To document and possibly explain these physiological observations, we undertook a series of anatomical studies of the collateral network (10). In the initial studies, a mixture of methyl methacrylate was injected at physiologic pressure into the circulation of juvenile pigs in the native state, and subsequently in other pigs after sacrifice of all intercostal and lumbar SAs. The digestion of surrounding tissue revealed a cast of a vast network of interconnected small arteries and arterioles surrounding the spinal cord: a matrix of vessels connects the relatively modest spinal cord perfusion circuit with the much more extensive network of vessels supplying the paraspinal muscles, Figures 7 and 8 show the interconnecting vessels within the spinal canal which provide continuity between intraspinal and extraspinal circuits, and the presence of longitudinal as well as lateral

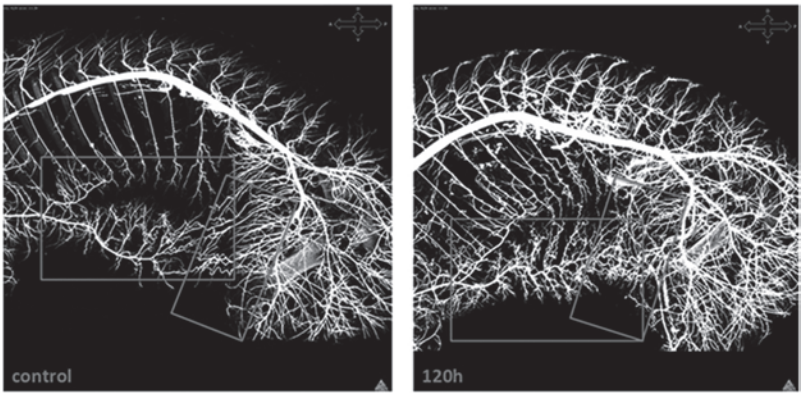

Figure 10 A CT scan of a sagittal section of a juvenile pig infused with a barium/latex mixture shows the normal distribution of vessels in the collateral network surrounding the spinal cord, and then the increased numbers and density of these vessels in a pig 120 hours after interruption of all segmental arteries

interconnections. From this picture, it is possible to imagine how the loss of a few SAs can be compensated by flow via alternative routes within this rich anastomotic network.

An idealized reconstruction of the details of the structure of the spinal cord perfusion network can be seen in Figure 9 (10). There are multiple inputs into the ASA from the aorta via the SAs, but also connections to an extensive epidural network of vessels, which feature segmental epidural arcades which feed into the ASA periodically via radiculomedullary arteries (ARMAs).

Anatomic studies of the changes in the circulation after extensive SA sacrifice in the pig reveal enlargement of the ASA within 24 hours, and more extensive expansion of various components of the intraspinal circulation by 5 days (11). A refinement of the injection technique allows visualization of the collateral network in situ by means of CT scanning, using a radiopaque viscous barium/latex mixture in place of the acrylic to outline even small vessels within the collateral network (12). In Figure 10, the ligated SAs are seen, filled retrograde to the radiopaque clips: the density of the collateral vasculature 5 days after SA sacrifice is clearly greater than in the accompanying picture from a native pig with intact SAs. These studies, taken together, confirm the enlargement and proliferation of the collateral network within 5 days in response to SA sacrifice. The presence of a greater number of vessels and an increased capacity within the collateral network explains the reliable return

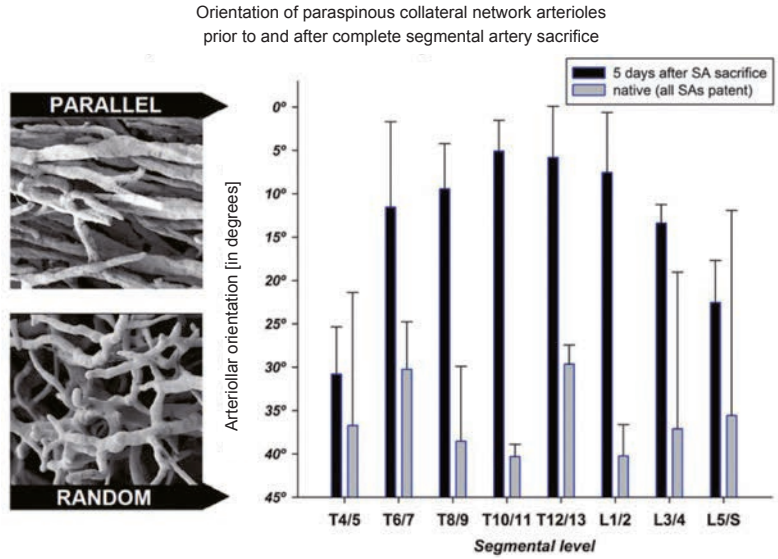

Figure 11 The change in the orientation of the small arterial vessels of the paraspinous muscles within 5 days after complete sacrifice of all intercostal and lumbar segmental arteries (SA) in the pig is shown. A scanning electron micrograph (top) illustrates the more parallel orientation of the vessels after SA sacrifice, which is obviously different from the random arrangement in the native pig (below). The graph reflects the quantification of these changes in vessel orientation. This figure is modified from reference (11)

of a stable network collateral pressure 5 days after extensive SA sacrifice.

More intriguing than the enlargement and proliferation of the vessels is a series of observations made by scanning electron microscopy of the original methyl methacrylate casts. These pictures show a gradual reorientation of the proliferating vessels after extensive SA sacrifice: from the random orientation characteristic of the native state to a configuration with vessels more parallel to the spinal axis, Figure 11 (11). We speculate that this reorientation facilitates flow from the cranial and caudal inputs into the mid-thoracic region of the spinal cord circulation, which is the area most seriously deprived of its direct blood supply as the result of SA sacrifice. We anticipate that further refinements of imaging techniques will eventually allow assessment and monitoring of the spinal cord circulation in patients before and following SA sacrifice.

The mechanisms that provoke the anatomic changes which occur within the collateral network after extensive SA sacrifice remain to be elucidated. It is likely that there is vasodilatation to account for the early ASA enlargement, probably in response

to mild ischemia. The subsequent proliferation of small vessels seems to involve generation of new vessels—angiogenesis—as well a transformation of smaller arterial conduits into larger ones by means of arteriogenesis. Clearly, an understanding of how this process is stimulated and controlled may allow manipulation to augment the response in advance of an aneurysm procedure, and thus reduce the chance of subsequent function-impairing spinal cord ischemia.

In the interim, knowledge of the anatomy and physiology of the spinal cord circulation can be helpful in directing the time course of staged interventions, and the duration and nature of measures to improve spinal cord protection. The vulnerability of the spinal cord circulation during the first few days after extensive SA sacrifice—until the observed adaptations in the collateral network have occurred—warrants vigilance to avoid hypovolemia, hyperthermia, high venous pressures, and other threats which may upset the temporarily tenuous balance between spinal cord blood supply and demand which prevails after SA sacrifice. Once the anatomic adaptations to a reduced segmental blood supply have been made, the system is once again quite robust, and the threat of postoperative paraplegia recedes.

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Disclosure: The authors declare no conflict of interest.

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Thoracic and thoraco-abdominal aortic disease: an overview.

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Introduction

This overview is based on data gathered from 1251 patients treated at our institution for thoracic and/or thoraco-abdominal aortic disease since 1993, including 308 patients with aortic arch disease, 507 patients with descending thoracic aorta disease, and 436 patients with thoraco-abdominal aortic disease. Roughly two-thirds of the patients received open surgical treatment and one-third endovascular or hybrid treatment.

In the same timeframe, 4347 patients were operated for an abdominal aortic aneurysm; this proportion however may not reflect of the actual distribution of aortic disease but rather it may be a consequence of the pattern of patients referral to our institution.

This paper will be divided into five sections:

I - Descending Thoracic Aorta;
II - Type B Aortic Dissection;
III - Aortic Arch;
IV - Thoraco-Abdominal Aorta, and;
V - Spinal Cord Ischemia.

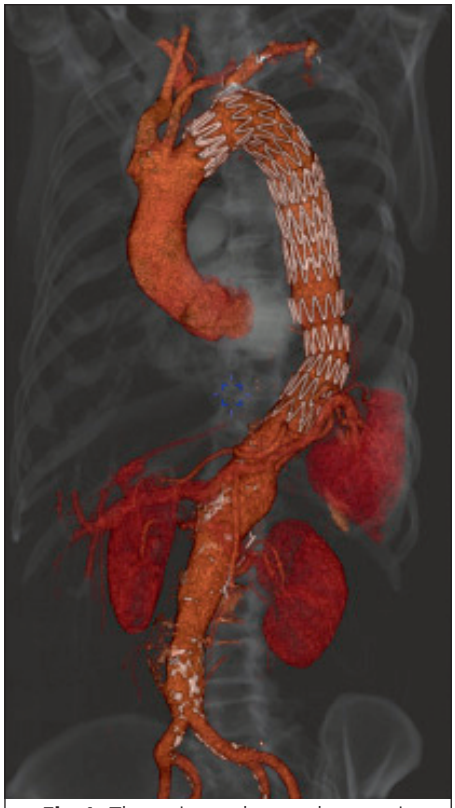

Fig.1 Thoracic endovascular aortic repair is nowadays commonly referred to with its acronym: TEVAR.

I - Descending Thoracic Aorta

While we sporadically evaluated and treated patients with thoracic aortic disease at our institution beginning in the mid-1980s, a formal program began only in 1993. Between 1993 and 2011, 254 patients with descending thoracic aorta (DTA) disease received an open surgical operation with 3.9% peri-operative mortality, 11.4% pulmonary complications, 6.3% cardiac complications, and 4.7% spinal cord ischemia (SCI). We began a thoracic aortic endovascular repair (TEVAR) program in 1998; since then 253 patients have been treated with an endovascular or hybrid procedure with 2.0% peri-operative mortality, 0.8% pulmonary complications, 0.4% cardiac complications, and 4.2% spinal cord ischemia (SCI).

In the last decade at our institution, TEVAR [Fig.1] gradually replaced open treatment in the majority of cases; a similar paradigm shift was observed throughout Europe[1]. Comparing results from open repair to the results of TEVAR, a reduction in mortality and major complications is apparent with the exception of SCI. On further analysis, however, most SCI events in open cases were immediate, severe, and unresponsive to treatment, while those associated with TEVAR occurred in a delayed fashion, several hours or even days after the procedure (often after a hypotensive event). SCI after TEVAR often manifest as a mild paraparesis rather than severe paraplegia and regressed after treatment (via cerebrospinal fluid drainage, blood pressure control, steroids, etc.) in a significant number of cases[2].

Although prospective, randomized trials are generally not available concerning TEVAR treatment, a large number of studies have been conducted, including industry sponsored trials

(FDA pivotal trials)[3, 4, 5], industry sponsored registries[6,7], voluntary base registries[8], multi-center, and single center studies[9]. By and large, many advantages of TEVAR over open treatment have been reported; in particular a meta-analysis by Cheng et. al.10 including 5,888 cases showed a reduced mortality with TEVAR as compared with open treatment (OR: 0.44 (95% CI 0.33 - 0.59)).

Based on the literature data available in 20[10], an ACCF/AHA task force issued recommendations for the treatment of patients with DTA diseases[11] suggesting TEVAR for DTA aneurysms over 55 mm in diameter, saccular aneurysms, and postoperative pseudo-aneurysms. Open treatment was recommended for chronic dissection with aortic diameter over 55 mm and for patients with connective tissue disorders. In other categories of patients, however, open treatment might be considered, including patients that are young, have a history of failed TEVAR, ruptured aneurysms, inadequate or absent landing zones, and patients with inadequate access vessels.

It is notable that while the mortality rate in the pivotal trials was between 1.5 and 2.1%, patients were highly selected for these trials in order to comply with the label instructions of each manufacturer (i.e. they were all aneurysms with good access vessels and landing zones and without severe vessels tortuosities). In our own experience, more than half of patients undergoing TEVAR were treated for "off-label" indications, similar to the 62% "off-label" indications recently reported by Hughes et al[12]. [Fig.2 A,B] Clearly real world results may be quite different, as reported in Cheng's meta-analysis of 1444 cases with 5.8% mortality.

In 2007 we showed that TEVAR results vary according to aortic segments treated, i.e. the DTA, the arch, and the thoraco-abdominal aorta (TAA)[13]. Statistically significant differences were found with regards to initial and 30 day technical success, type I endoleaks, mortality, and clinical success. Moreover, peculiar etiologies such as traumatic injury, aorto-esophageal fistula (AEF), and dissection may also affect TEVAR outcome.

Concerning traumatic aortic injury, the choice of treatment may be related to the clinical presentation, but also to logistical

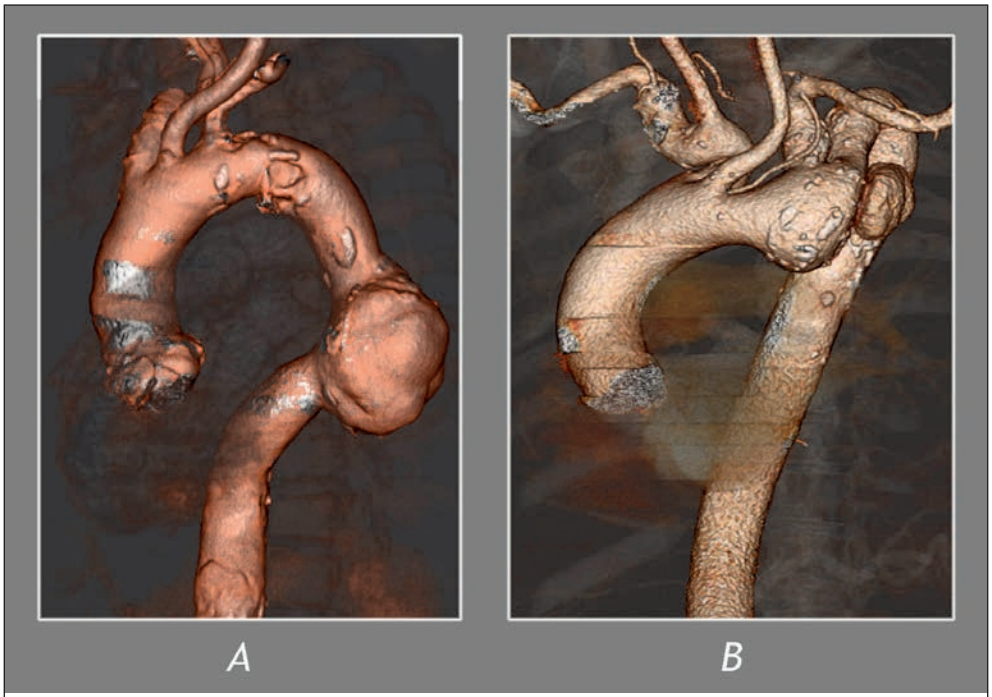

Fig. 2 - A. A typical "mid-thoracic" DTA that would suit well the inclusion criteria of the "pivotal trials ("on-label" indication for TEVAR)
B. A complex "real world" case with challenging aortic angulations and difficult landing zones ("off-label" indication for TEVAR)

problems, including the immediate availability of appropriately sized stent-grafts. The less invasive nature of TEVAR over open treatment, with no need for thoracotomy, aortic clamping, full heparinization, or extra-corporeal circulation may result in advantages that are particularly important in trauma patients such as reduced bleeding (also at the level of concomitant lesions), lower infection rate, and reduced length of stay in the intensive care unit. Several authors reported significantly reduced mortality and SCI with TEVAR in traumatic aortic injury. In particular, Lee's meta-analysis[14] of 7768 patients showed rates of death and SCI of 19% and 9% with open treatment and 9% and 3% with TEVAR, respectively.

We agree with Hoffer[15] that "endovascular repair can decrease the death rate by half and diminish the risk of paraplegia by 75% as compared to open repair" and we employ

TEVAR for traumatic aortic injury whenever technically feasible. [Fig.3] Debated issues in this field include the conformability of stent-grafts, especially in acutely angulated aortic arches, and long-term durability of the stent-grafts, particularly when used in younger patients. One uncommon but potentially catastrophic complication is collapse of the stent-graft: among its causes one should certainly consider excessive oversizing of the stent-grafts and acute curvature of the aortic arch with malapposition of the stent-graft (bird's beak)[16, 17].

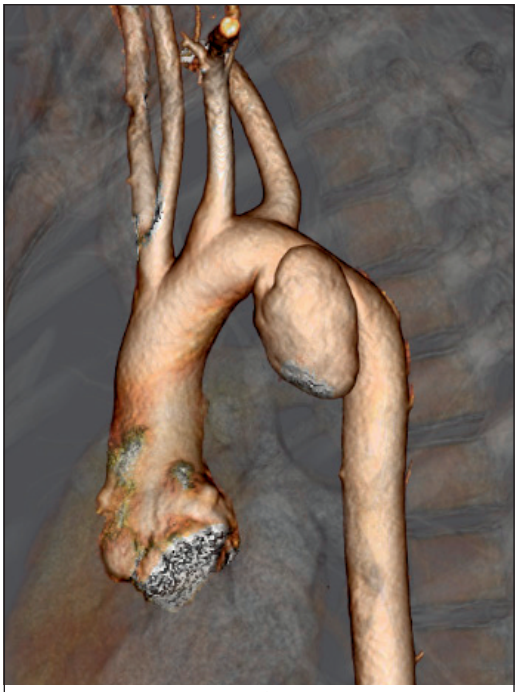

Fig. 3. A traumatic isthmic aortic injury in a young patient. Smaller aortic diameters and acutely angled arches (gothic arch) are common features of these patients.

Concerning AEFs, this condition is very serious but fortunately rather uncommon. Only a small number of reports regarding its open treatment can be found in the literature. Open treatment options include aortic "in situ" reconstruction with either synthetic grafts or homografts, or ligature of the thoracic aorta with extra-anatomic revascularization; similarly many different options have been described for the treatment of the esophageal lesion. Overall mortality ranges from 21 to 78%[18, 19]. Literature data for TEVAR treatment of AEF is scarce; Jonker et al.[20] could find only 14 anecdotal cases and 5 series with 12 or fewer cases. This lack of literature data prompted us to promote a multi-center survey[21] among 17 Italian institutions with a thoracic endovascular program in order to ascertain the frequency of AEF as an indication for TEVAR and outcomes. Between 1998 and 2008, 1138 patients received TEVAR at one of the 17 participating centers; in 25 cases (2.2%) TEVAR was performed for an AEF (14 cases) or an aorto-bronchial fistula (ABF) (11 cases). The etiology was primary in 18 cases (72%) and secondary in 7 (28%). Primary technical success was 100%, 30 day mortality 28%, and

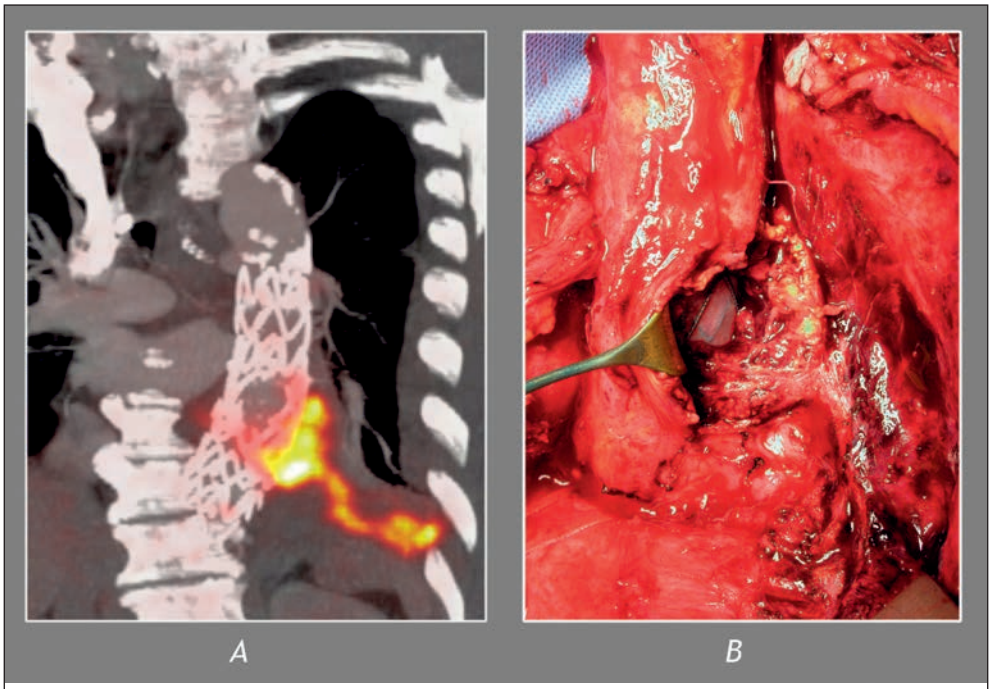

Fig. 4. - A CT-PET (Fluorodeoxyglucose) of thoracic endograft peri-aortic infection. **B** during thoracotomy the stent-graft fabric could be observed through the disrupted aortic tissue

follow up mortality at 23 months 44%. Interestingly, in the 15 patients who received TEVAR alone 30 day mortality was 40% and follow up mortality 53%, while in the 10 patients who also received an associated procedure (i.e. esophageal repair) the 30 day mortality was 10% and follow up mortality 30%. Therefore, while TEVAR may be a feasible alternative to control aortic bleeding especially in unstable patients, an associated esophageal/bronchial repair may improve outcome. [Fig.4 A,B]

In conclusion, open surgery for DTA disease is proven to be safe and effective and is recommended in patients with chronic dissection and Marfan disease. TEVAR seems to offers reduced mortality and morbidity; however, the hospital charges are usually increased, Long term outcomes need to be carefully assessed.

II Type B Aortic Dissection

We previously discussed how stent-graft repair of DTA aneurysms currently offers encouraging outcomes. Stent-grafts were initially designed and approved for aneurysmal disease were the goal is clear: to exclude the sac from arterial pressurization thus reducing or hopefully abolishing the risk of rupture. However, aneurysms currently represent only one-half to two-thirds of patients with indication for TEVAR.[22] Traumatic injury and AEF/ABF have also been previously discussed. Other TEVAR indications include complicated type B aortic dissection (TBD) as well as, less frequently, penetrating aortic ulcer and intramural hematoma. For TBD the goals are less clear; remodeling and complete healing of the dissected aortic wall is certainly a desirable outcome but it may actually be obtained in only a fraction of cases.[23]

Type B dissection usually initiates with an intimal tear allowing blood to penetrate into the aortic wall layers with creation of two lumina: a false lumen (FL) that expands and a true lumen (TL) that may contract or even collapse. Blood flows in both lumina, as may be observed in real time with trans-esophageal

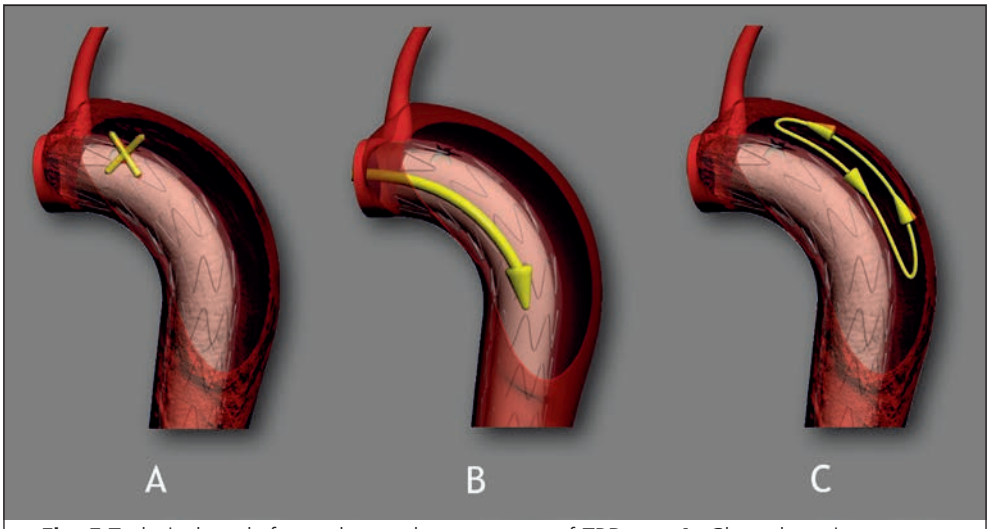

Fig. 5 Technical goals for endovascular treatment of TBD are: **A.** Close the primary entry tear. **B.** Re-direct the blood flow into the TL. **C.** Produce low turbulent flow and promote thrombosis in the FL.

echocardiography (TEE). The rationale of endovascular treatment of TBD is to exclude the FL from the circulation. Technical goals are:

1. Close the primary entry tear.
2. Re-direct the blood flow into the TL.
3. Produce low turbulent flow in the FL and eventually promote thrombosis of the FL. [Fig.5 A,B,C]

Another effect of re-directing blood flow into the TL and decompressing the FL is that a compressed or collapsed TL may expand, thus preventing or relieving dynamic malperfusion. Possible additional problems include:

1. Retrograde flow into the FL from the left subclavian artery; this may be treated percutaneously with a plug.
2. Presence of hi-flow secondary tears in the thoracic aorta; these are assessed intra-operatively with TEE, and may be treated with an additional stent-graft; this however has to be balanced against the increased risk of SCI.
3. Additional secondary tears in the abdominal aorta (often adjacent to the splanchnic vessels) are commonplace and are usually left untreated.
4. Flapping movements of the intimal lamella may contribute to preventing thrombosis of the FL.
5. A collapsed TL may fail to adequately expand with persistent distal malperfusion.

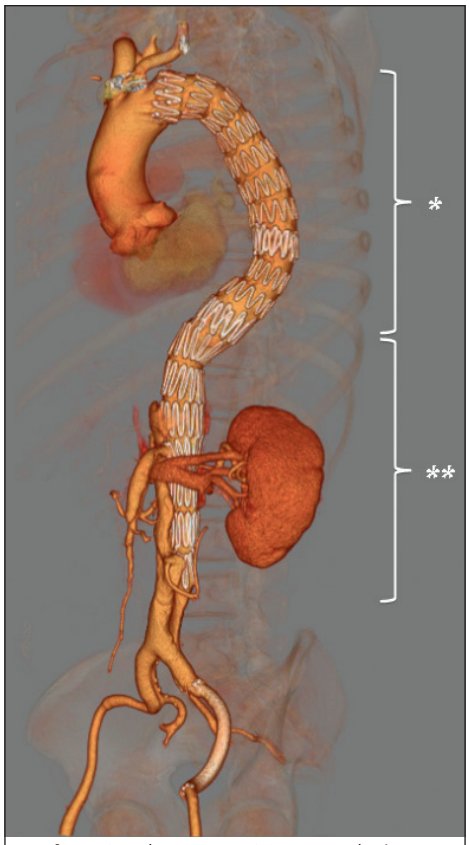

Fig. 6 The PETTICOAT technique employs a self-expandable bare stent (**) positioned in the TL distal to the covered stent-graft (*) in order to obtain expansion of the TL and stabilization of the intimal lamella without affecting the patency of the aortic side branches

To address the latter two problems, the PETTICOAT (Provisional Extension to Induce Complete Attachment) concept was first introduced by Nienaber et al.[24] in 2006. It employs a self-expandable bare stent positioned in the TL distal

to the covered stent-graft in order to obtain expansion of the TL and stabilization of the intimal lamella without affecting the patency of the aortic side branches (intercostal, visceral, renal). [Fig.6]

From a more clinical perspective, an endovascular approach is accepted by most authors for the treatment of acute and sub-acute TBD. However, for uncomplicated cases, best medical treatment (BMT) is still the treatment of choice. A recent prospective randomized trial (Instead) failed to demonstrate any advantage of BMT+ TEVAR over BMT alone.[25]

Since 1998, we have treated 93 patients with acute/sub-acute TBD at our institution. Indications included branch/vessel obstruction, persistent/intractable pain, resistant hypertension, severe peri-aortic effusion/hematoma, aortic growth > 5 mm (in < 3 months), and aortic diameter > 40 mm. The PETTICOAT technique was utilized in 31 cases with dynamic malperfusion after TEVAR and/or TL collapse (11 were previously published[26]). Peri-operative results were as follows: overall mortality 2.7%, clinical success 87%, and SCI 1.9%. For the PETTICOAT cases, results were: clinical success 84%, mortality 0%, SCI 3.2%, and malperfusion resolution 100%.

In TBD, bowel malperfusion is one of the most difficult complications to interpret when only soft and non-specific symptoms are present; however, waiting for hard signs and symptoms may result in fatal bowel necrosis. After an initial positive experience, in the last four years we have routinely used laparoscopy both preoperatively in patients with unclear abdominal symptoms and after TEVAR in all patients with unclear angiographic findings related to intestinal perfusion.

In a recent study[27] we performed a volumetric assessment on the CT datasets of 25 patients who underwent TEVAR + PETTICOAT with the Cook TXD dissection device followed for two years, in order to evaluate the fate of the TL and FL. A very significant increase in the TL volume of the thoracic aorta was observed postoperatively and at one and two years follow up.

In conclusion, TEVAR shows satisfactory safety and efficacy

in acute and sub-acute complicated TBD cases. The PETTICOAT technique promotes TL expansion, relieves malperfusion, and does not affect aortic side branches patency.

III Aortic Arch

With endovascular treatment in mind, we define involvement of the aortic arch when at least one of the supra-aortic trunks (i.e. the left subclavian artery) is deliberately covered by the stent-graft. Since the year 2000, we have treated 143 such patients with an endovascular or hybrid procedure. According to Ishimaru's classification[28], we have treated 77 cases with proximal landing zone (PLZ) 2 (coverage of only the left subclavian artery), 34 cases with PLZ-1 (coverage of the left subclavian and left common carotid arteries), and 32 cases with PLZ-0 (coverage of all the supra-aortic trunks). [Fig.7] Results up to 2007 were previously reported[29].

Patients with aortic arch involvement undergoing endovascular treatment at our Institutions are not good candidates for open surgical repair. Advanced age and poor pulmonary and cardiac function were common in this cohort of patients and many of them were actually referred by cardio-thoracic surgeons since they were unfit for open treatment. Etiology was degenerative in 122 cases, TBD in 15 cases, and residual dissection after open surgical repair of acute type A dissection in 6 cases.

In order to safely cover the origin of the supra-aortic trunks with the stent graft, we chose a hybrid approach, thus surgically "de-branching" the arch by means of one or more bypasses before stent-graft deployment. While the innominate and left common carotid arteries were always re-vascularized before coverage, the left subclavian artery was selectively re-vascularized. De-branching for PLZ-0 requires sternotomy but may be performed "off-pump" by means of side clamping of the ascending aorta. On the other hand, de-branching of the left common carotid and subclavian arteries may be performed with extra-anatomic bypasses that do not require sternotomy. As far as timing of the open and endovascular procedures is concerned, while extra-anatomic bypasses are often performed in a staged fashion, TEVAR is usually performed during the same procedure in PLZ-

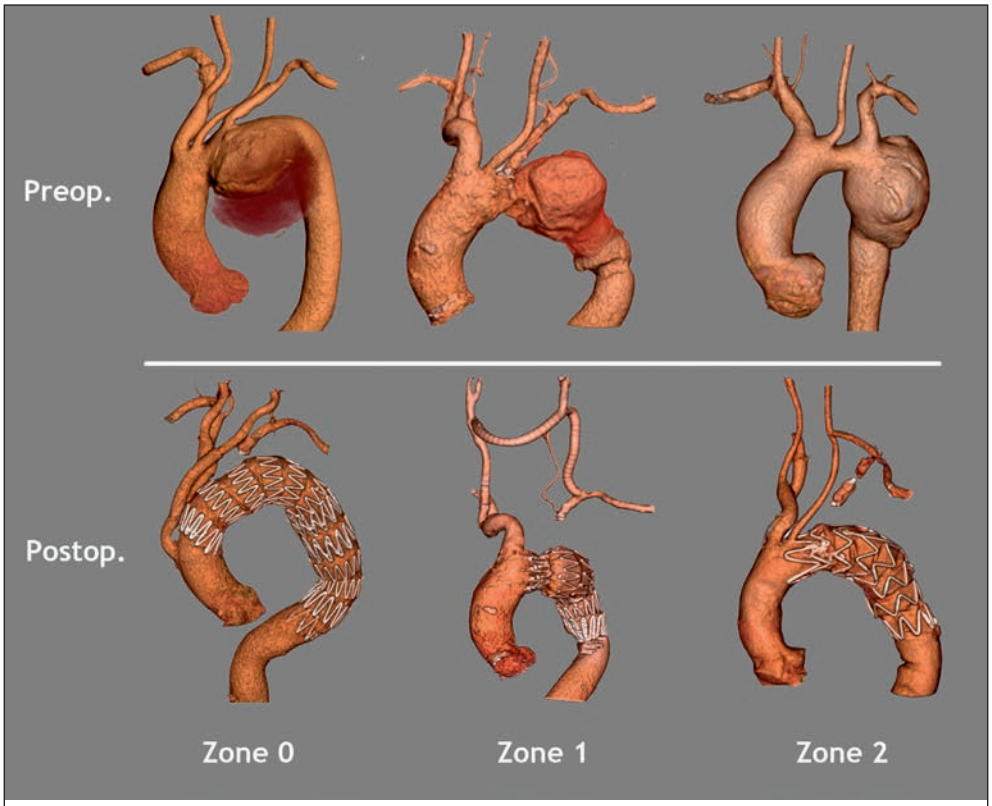

Fig. 7 Preoperative and postoperative examples of aortic arch aneurysms according to Ishimaru's classification of supra-aortic vessels involvement. Proximal landing zone PLZ-0 coverage of all the supra-aortic trunks, PLZ-1 coverage of the left subclavian and left common carotid arteries and PLZ-2 coverage of only the left subclavian artery.

0 cases while the sternum still opened. The main reasons for this is that potentially severe cardiac complications of TEVAR in PLZ-0 (such as ventricular fibrillation, left ventricular perforation, etc.) may be better managed with the sternum open. Moreover, if a type I endoleak is observed after correct placement of a stent-graft in PLZ-0, there is very little that can be accomplished endovascularly. On the other hand an additional procedure of banding or plicature of the aorta at the level of the PLZ may be performed surgically with resolution of the endoleak.

In our experience, aneurysms in PLZ-2 were saccular in 21/77 cases and the DTA was involved with proximal extension of the disease in 56/77 cases. The left subclavian artery was re-vascularized in 59/77 cases, particularly in the latter group with

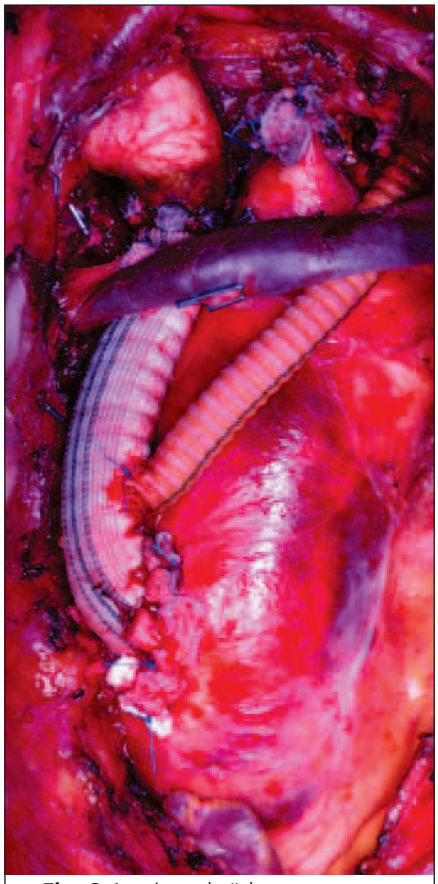

Fig. 8 Aortic arch "de-branching" for PLZ-0 is performed off-pump through median sternotomy with individually tailored Dacron grafts

more extensive aortic coverage, in order to provide additional collateral blood flow to the spinal cord through the vertebral artery. In 23 cases at higher risk of SCI, a cerebrospinal fluid drain (CSFD) was also inserted.

In patients with PLZ-1, the length of uninvolved aorta that may be obtained by de-branching the left common carotid artery is usually not very long and the proximal sealing may not be satisfactory. This procedure is therefore offered only to patients that are markedly unfit for sternotomy.

De-branching for patients with PLZ-0 was performed through median sternotomy [Fig.8] or, in a few cases, mini-sternotomy. The proximal anastomosis on the ascending aorta is located as proximally as possible in order to obtain a longer PLZ. The ascending aorta is side-clamped (off-pump, systemic heparin 70 UI/Kg) with a large Satinski or Dubost clamp with well-controlled arterial blood pressure. Bifurcated grafts are not used in order to avoid a large anastomosis in the ascending aorta. An 8-10 mm pre-clotted Dacron graft is anastomosed to the right side of the ascending aorta (4/0 polypropylene suture with Teflon pledgets), rather than anteriorly, in order to avoid retro-sternal bulging of the bypass; side branches are constructed in a custom fashion, individualized to the patient's anatomy.

Initial clinical success in arch patients was 88%, significantly lower than that of patients with DTA disease not involving the arch (94%). Overall mortality was also higher (4.2% vs. 2.0% for DTA patients). The main cause of mortality was stroke, which was observed in three PLZ-0 patients (9.4%) and one PLZ-2 patient (1.3%); this was also significantly higher than in patients

treated for DTA (1.1%). At a mean of 24 months follow up, we observed two cases of aneurysm-related deaths, both in patients with PLZ-2 (5.9%), likely related to loss of proximal sealing.

Whether an open, fully endovascular, or hybrid approach are used, stroke seems to be the main complication of aortic arch aneurysm treatment. In a recent review of 647 cases of aortic arch aneurysm treated with open surgical repair, Wolf et al. reported a 10.6% stroke rate. While several brain perfusion and brain protection techniques have been employed by various authors[30, 31], hemodynamic and embolic strokes remain a significant burden of this operation even in experienced hands. During the de-branching phase of our hybrid procedures, we used intraoperative EEG monitoring in all cases; since significant alterations were never observed at the time of clamping of the supra-aortic trunks, an embolic etiology therefore seems to be predominant in strokes that we observed. This is not surprising considering the amount of endovascular manipulation (wires, catheters, sheaths, devices) associated with delivering a stent-graft to the aortic arch.

Our overall stroke rate in aortic arch hybrid repair was 2.8% (4/143 cases) and all cases were observed before 2007. Three cases were cerebellar and one hemispheric; all were associated with multi-organ embolization and all had a fatal outcome. We retrospectively reviewed the scans of these patients and found shaggy aortas in two cases, a heavily calcified aorta in one case, and a floating thrombus in one case. The lessons learned from this experience were: first, better patient selection based on the quality of the (non-aneurysmal) aorta is needed, and surgical ligation or endovascular occlusion with a plug of all supra-aortic trunks before "endo-manipulation" should be performed when possible. While the small number of events did not allow for a formal statistical analysis, we observed that strokes were equally distributed in patients with or without left subclavian artery re-vascularization (2/2). However, all events occurred in patients in whom the left subclavian artery was not ligated or occluded before deployment of the stent-graft. These data were recently presented at the European Society for Vascular Surgery (ESVS) meeting in Athens[32].

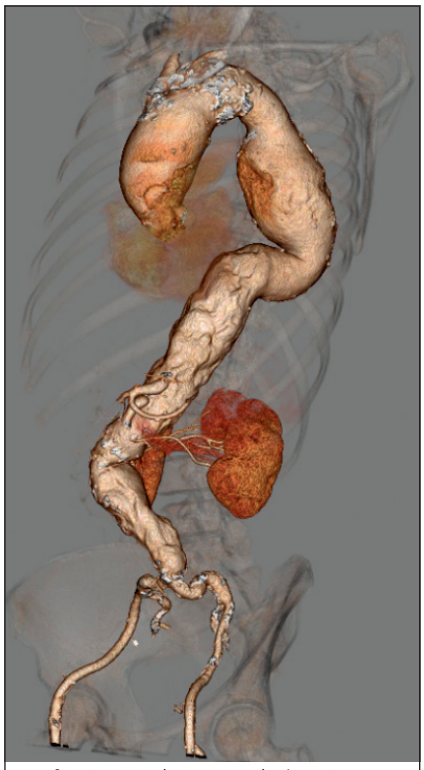

Fig.9 3D volume rendering CT scan of a extent II TAAA

In conclusion, hybrid repair of aortic arch pathology is an alternative to open surgery in selected patients producing acceptable results. Appropriate patient selection and stroke reduction strategies may improve outcomes.

IV - Thoraco-Abdominal Aorta

Among the founding fathers of thoraco-abdominal aortic surgery, we would like to mention Drs Michel E. De Bakey[33], Denton Cooley[34], and in particular Stanley E. Crawford[35], all from Houston, TX. These brilliant surgeons have devised and refined, in a truly pioneering way, all the basic techniques that we continue using over half a century later. We would also like to mention Dr Joseph S. Coselli[36], whom we had the privilege of observing many times performing thoraco-abdominal aortic surgery and whose contribution to this field is fully acknowledged by the vascular surgical community throughout the world.

We know that the natural history of untreated thoraco-abdominal aortic aneurysms (TAAA) is a very ominous one, with a high risk of dissection, rupture, or death when aortic diameter is greater than 5.8 cm[37]. Surgical repair, however, is also very challenging and it is important to stratify the operative risk according to potential dysfunction of different organs. Impaired renal function, for instance, as indicated by an impaired glomerular filtration rate (GFR), is a well-known predictor of peri-operative mortality[38, 39]. Preoperative assessment of co-existing coronary artery disease is also important and may be obtained by means of EKG-gated CT scan. Our patients usually receive a bi-phasic contrast media injection with prospective EKG-gating in the thorax and a regular helical scan in the abdomen. The same CT dataset may therefore be used, with appropriate post-

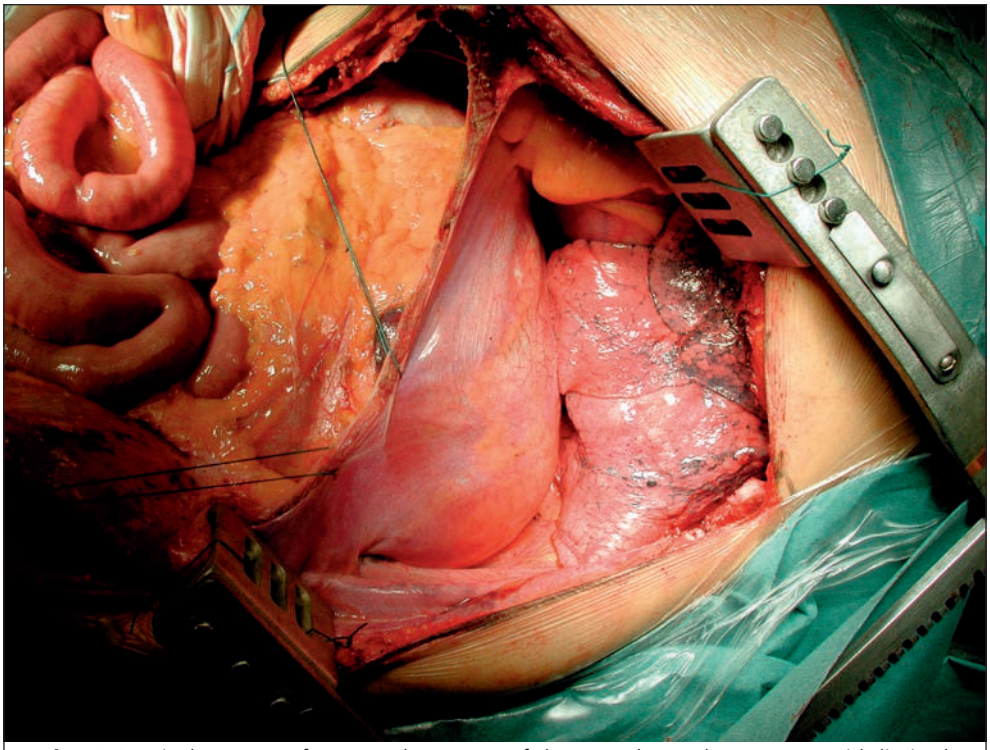

Fig.10 Surgical exposure for TAAA by means of thoraco-phreno-laparotomy with limited frenotomy

processing for evaluation of the aortic disease, coronary arteries, and also of the spinal cord vascularization (which will be discussed in Section V); appealing 3D reformatting may also be obtained [Fig.9]. Pulmonary function is also assessed preoperatively by means of spirometric tests. Appropriate screening of organ function also allows preoperative optimization by means of hydration, coronary revascularization, when indicated, and respiratory physiotherapy.

Highlights of the surgical procedure are the following:

1. Routine use of cerebro-spinal fluid drainage (CSFD) for extent I-III TAAA
2. Limited surgical exposure, tailored to the extent of the aneurysm
3. Limited phrenotomy sparing the phrenic center [Fig.10]
4. Left heart bypass with a centrifugal pump (non-occlusive cannulation of a pulmonary vein and of the left femoral

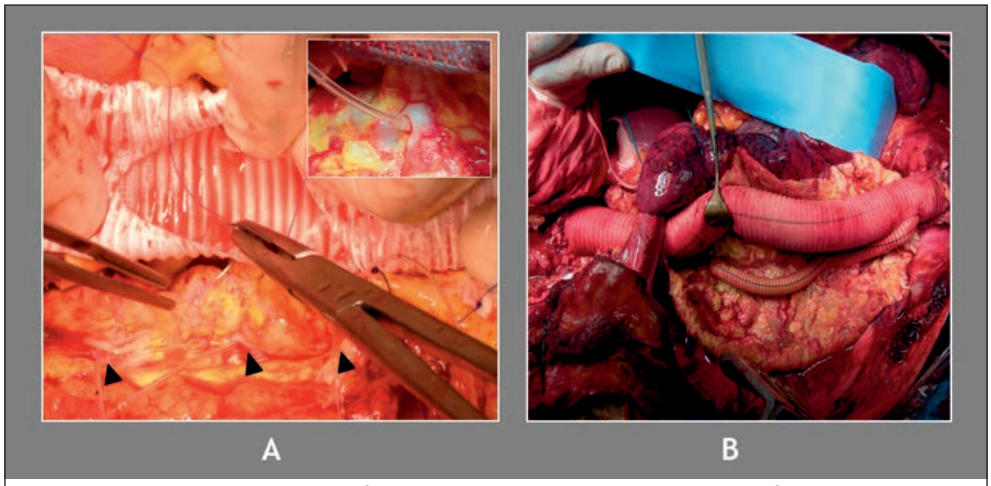

Fig. 11 - A. Re-implantation of critical intercostal arteries by means of Carrel patch or. **B.** selective bypasses in Marfan patients

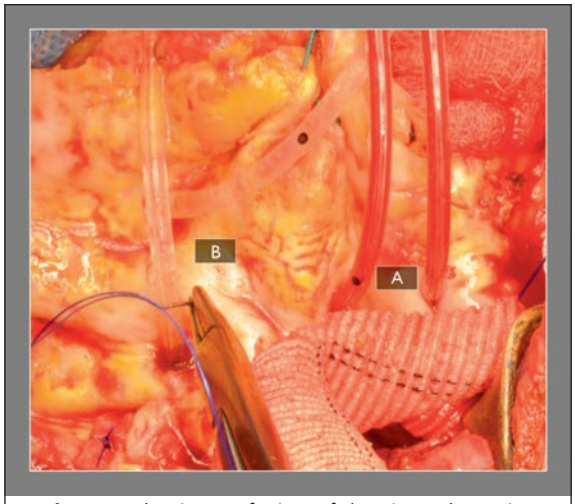

Fig. 12 Selective perfusion of the visceral arteries with warm blood from the pump **(A)** through 9 Fr occlusion-perfusion Pruitt-Inhara catheters and selective perfusion of the renal arteries with cold (4°C) Histidine-Tryptophan-Ketoglutarate solution (Custodiol) through 9 Fr occlusion-perfusion Pruitt-Inhara catheters **(B)**

artery) for extent I-III TAAA

5. Proximal aortic clamping between the left common carotid and left subclavian artery when a satisfactory neck is not available distal to the left subclavian (hypothermic circulatory arrest only if a suitable clamping site is not present)
6. Sequential clamping of short segments of the aorta
7. Circumferential division of the proximal aorta
8. Temporary occlusion of critical intercostal arteries with 4 Fr. Pruitt catheters and re-implantation by means of Carrel patch [Fig.11 A] or selective bypasses in Marfan patients [Fig.11 B]
9. Selective perfusion of the visceral arteries with warm blood from the pump through 9 Fr occlusion-perfusion Pruitt-Inhara catheters [Fig. 12]

10. Selective perfusion of the renal arteries with cold (4°C) Histidine-Tryptophan-Ketoglutarate solution (Custodiol) through 9 Fr occlusion-perfusion Pruitt-Inhara catheters [Fig.12]
11. Direct stenting of the renal and visceral arteries when ostial plaques are present [Fig.13]
12. Re-implantation of the visceral and right renal arteries with a Carrell patch and the left renal artery with a separate bypass. [Fig.14 A], or with individual bypasses to all vessels in Marfan patients. [Fig.14 B]

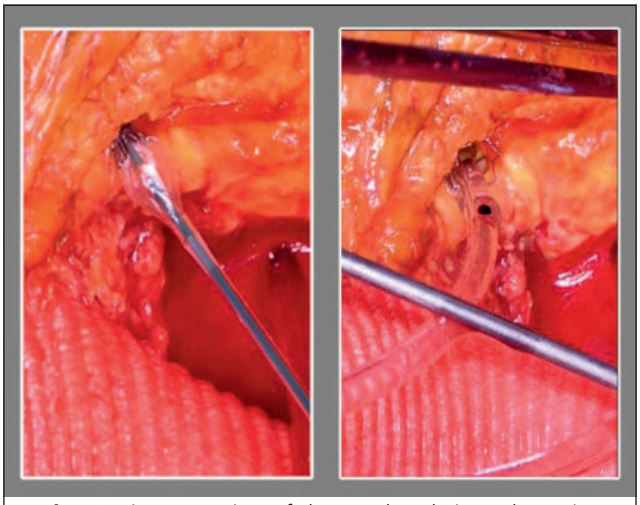

Fig.13 Direct stenting of the renal and visceral arteries when ostial plaques are present

When evaluating the surgical results reported in the literature one should be aware that TAA aneurysms of different extents have very different surgical results and that overall results always reflect patient selection and the composition of the case-mix. High volume centers (i.e. series with over 150 patients) report mortality in the 6-13% range, SCI in the 3-16% range, and renal failure in the 6-12% range[40,41,42]. In the NIS registry, however, a mean mortality of 22% was reported for 1542 patients, and a significant inverse correlation was found between hospital (and surgeon's) volume and mortality[43].

Between 1993 and 2011, 389 patients underwent open repair of TAA aneurysm at our institution. For the sake of this presentation however, we reviewed only the last 254 consecutive cases operated in the last five years (2006-2011). According to Crawford's classifications, we treated 52 patients with extent I, 59 with extent II, 80 with extent III, and 63 with extent IV TAA aneurysm. Overall 30 day mortality was 10.2%, ranging from 3.2% in extent IVs to 18.6% in extent IIs. Overall, SCI occurred

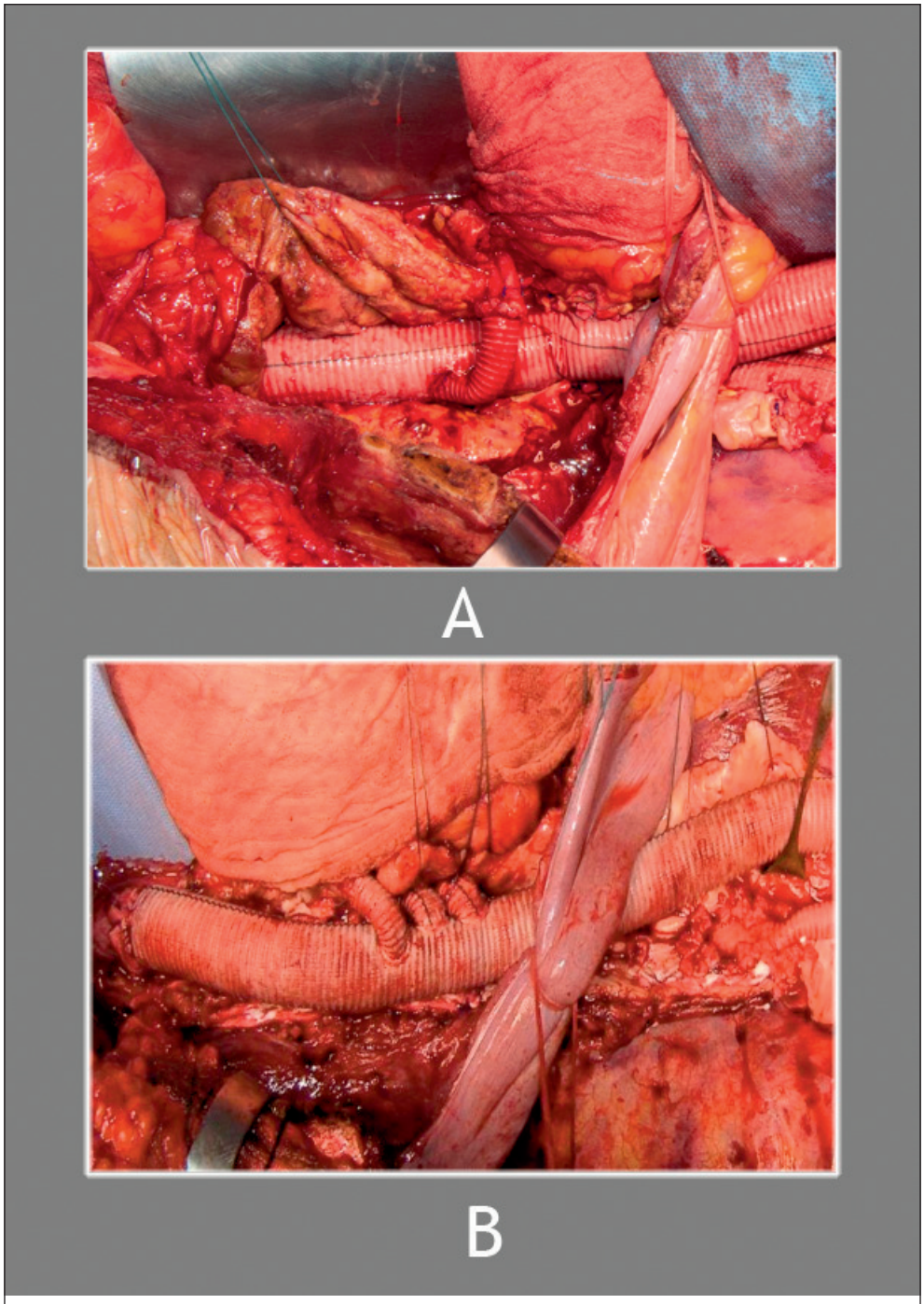

Fig.14 - A. Re-implantation of the visceral and right renal arteries with a Carrell patch and the left renal artery with a separate bypass, or **B**. with individual bypasses to all vessels in Marfan patients.

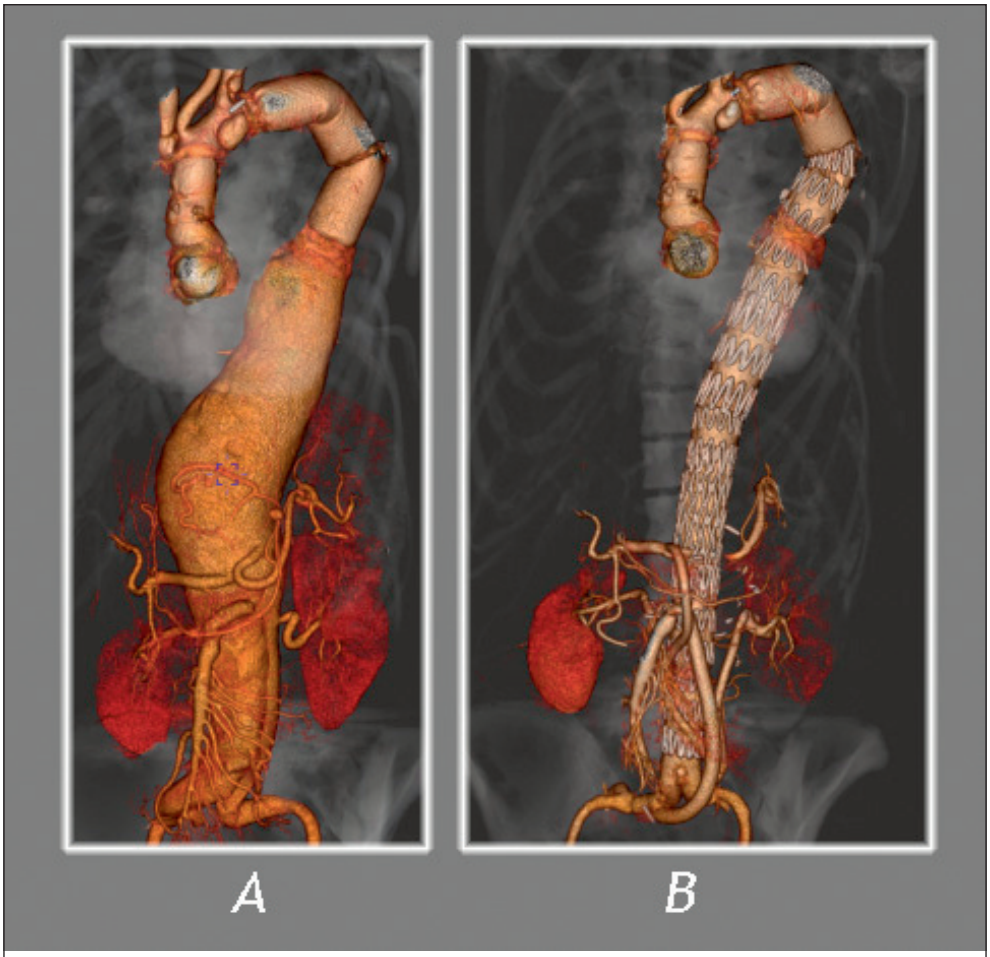

Fig.15 - A. Preoperative 3D volume rendering angioCT of a patient with complex TAAA and multiple previous thoracic open operations.
B. Hybrid treatment with open four vessels (renal and splanchnic) debranching + TEVAR

in 8.3% ranging from 1.6% in extent IVs to 16.9% in extent IIs. Adjuncts such as left heart bypass, cold renal perfusion, CSFD, etc. were used routinely in extent IIs and selectively in less extensive aneurysms. Improvements in mortality and major morbidity were observed for aneurysms of all extents as compared to historic series reported previously[44, 45].

Thoraco abdominal aortic aneurysms may also be treated with a hybrid approach by means of de-branching the splanchnic and/or renal arteries with individual bypasses prior to performing TEVAR with conventional thoracic stent-grafts. [Fig.15] At our

Institution this treatment is offered only to patients markedly unfit for conventional open surgery due to advanced age, severe chronic obstructive pulmonary disease (COPD), frozen chest (previous thoracotomy or other diseases), severe coronary or valvular heart disease with reduced ejection fraction, and renal failure. Visceral bypasses and deployment of the stent grafts may occasionally be performed in a single operation; however in most cases a staged approach was preferred. In a recent literature review from 2006, we found over 300 cases treated with this approach but with an array of very non-homogeneous variations both in the technique and case-mixes. Generally speaking, after initial enthusiasm for this approach, most centers that perform substantial number of cases have also reported significant mortality and major morbidity and have expressed words of caution[46, 47, 48, 49]. Thus far we have performed 47 such operations with 100% technical success, but 14.9% mortality and 6.4% SCI.

In conclusion, in our hands the results of open surgery for TAA aneurysms are rather satisfactory in relation to the severity of the disease; unfortunately the more extensive cases are still burdened by an elevated mortality and major morbidity, including paraplegia, which is probably the most devastating complication. A hybrid approach has also permitted reasonable results in a cohort of very sick patients; however it has not permitted, as initially hoped, the great advantages that we observed with TEVAR employed for DTA aneurysms. It should be noted that we deliberately omitted discussion of total endovascular techniques for both the aortic arch and the thoraco-abdominal aorta with both fenestrated/branched stent-grafts and chimney/parallel stent-grafts techniques, because our experience in these fields is only marginal.

V - Spinal Cord Ischemia

Knowledge of the blood supply to the spinal cord (SC) is clearly important for a better understanding of spinal ischemic complications after procedures that involve the thoraco-abdominal aorta. Regrettably, SC vasculature is complex and difficult to study for several reasons: it consists of very small vessels that run through three-dimensionally intricate planes with a substantial regional and inter-individual variability. Comparative anatomy studies are of limited help in this area. Gross anatomical studies are arduous due to the relative inaccessibility of the SC within the spinal column. In vivo angiography fails to describe the entire spinal circulation due to competitive flow from several feeding arteries. Selective angiography before thoraco-abdominal aortic surgery was proven to be dangerous in this clinical setting and was abandoned in spite of initially interesting results[50]. Most basic knowledge of the SC circulation comes from microinjections of different staining fluids and micro-radiological studies in post-mortem specimens[51]. Anatomy handbooks are vague and sometimes imprecise on this topic and there is still widespread uncertainty concerning SC angio-architecture; moreover much confusion arises from inconsistent nomenclature. Teaching is often based only on anatomical sketches that can be more or less accurate.

Spinal cord vessels provide remarkably efficient collateral pathways that make spontaneous spinal stroke exceedingly rare even when the origin of most intercostal and lumbar arteries is chronically obstructed. Impressively, early accurate anatomical descriptions were provided by Adamkiewiczs (1881) and Kady, among others[52]. They used a clearing method with clove oil (already mentioned by Virchow in 1857) that renders tissue sections transparent so that the stained vessels can be followed under the microscope. They described supply to the SC by one anterior and two postero-lateral anastomotic trunks that run longitudinally.

Inflow vessels include:

The subclavian artery through the vertebral artery, the thyrocervical trunk, and the costocervical trunk

Segmental feeders from the intercostal and lumbar arteries

3) The hypogastric arteries through the lateral sacral and ileo-lumbar arteries.

Arteries directly supplying the SC (intrinsic arterial system) are divided into:

A central (centrifugal) system fed by the sulcal arteries

A peripheral (centripetal) system, the pial plexus (or pial network) giving origin to perforating branches.

The pial network, which covers the SC in its entire length, forms an impressive secondary anastomotic system between the anterior and postero-lateral longitudinal vessels. Intra-parenchymal anastomoses have been rarely demonstrated.

Please note that the intercostal arteries divide three times before reaching the anterior spinal artery, the crucial vessel supplying blood to the spinal grey matter. The first branch of the intercostal artery is the nervo-medullary artery. The latter divides into anterior and posterior radicular arteries. The anterior radicular artery divides in a descending and an ascending branch. The anterior spinal artery can therefore be considered an anastomotic channel between ascending and descending branches of neighboring anterior radicular arteries. [Fig.16 A,B,C,D]

It is important to remember that the nervo-medullary artery division consistently supplies the anterior and posterior part of the vertebral canal, the nerve roots, and the dura; however, only at certain levels do the anterior and posterior radicular arteries cross the dura together with the anterior and posterior nerve roots to reach the surface of the medulla. In fact only a few (2-14, mean 6) of these segmental branches are left in the adult: a mean of two to three at the cervical level (L=R), two to three at the thoracic level (L>R), and zero or one at the lumbo-sacral level (L>R). Phylogenetic embryological studies showed that by the 16th week, development of the anterior spinal artery is followed by regression of most of the original 31 bilateral segmental feeders. In the thoraco-lumbar region, one (occasionally two or three) anterior radicular artery (the artery of Adamkiewiczs) is always distinctly dominant in caliber and is therefore called the great radicular artery (GRA). Division of the GRA is anatomically very characteristic: the radicular artery has a steep, cranially

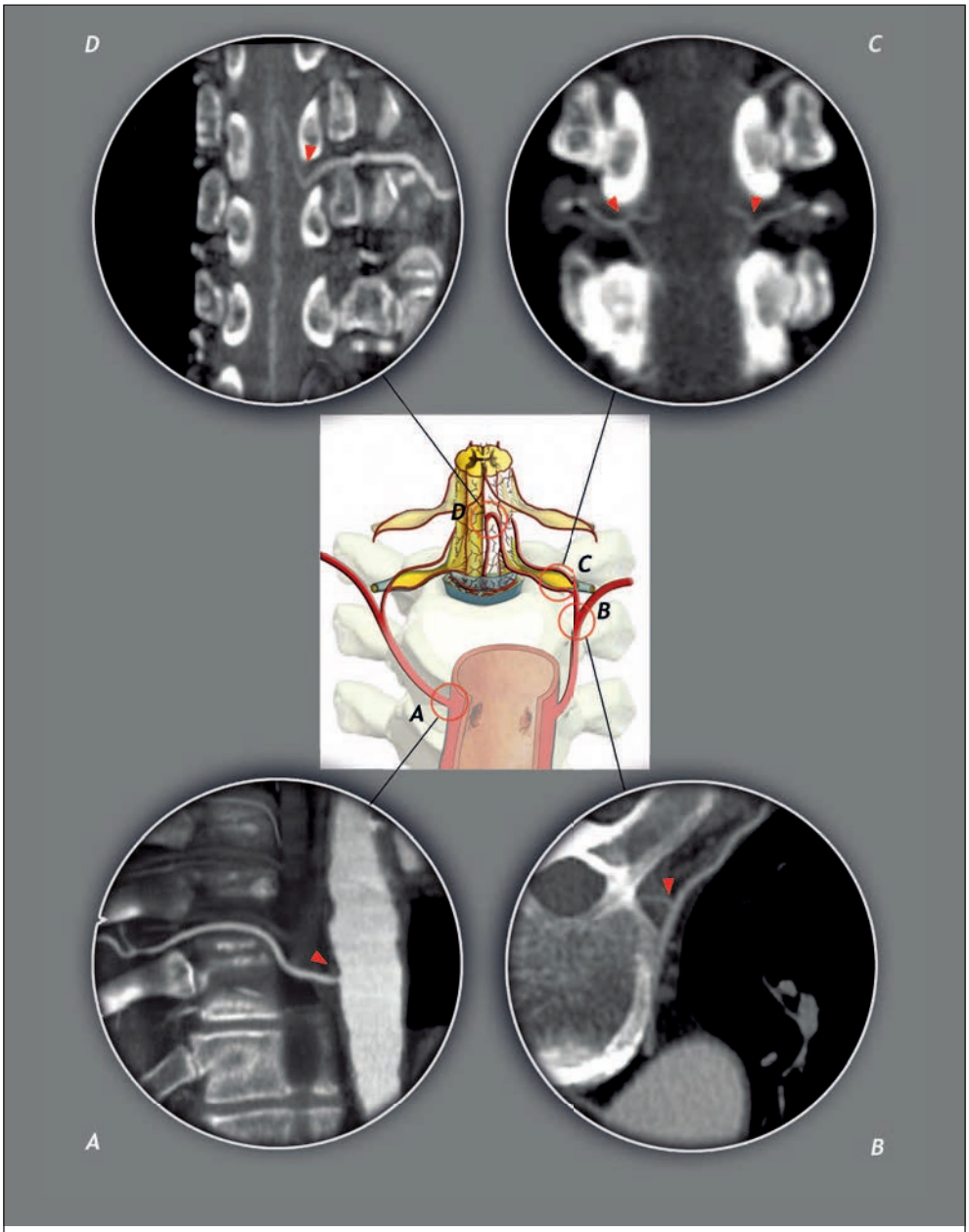

Fig.16 Schematic view of the spinal cord vascularization: **A)** intercostal artery branching from the thoracic aorta, **B)** The nervo-medullary artery divides into **(C)** an anterior and a posterior radicular artery, please note that only a few anterior radicular arteries cross the dura. In the thoraco-lumbar region one clearly dominant anterior radicular artery (the great radicular artery or artery of Adamkiewiczs) feeds directly into the anterior spinal artery **(D)**. The artery of Adamkiewiczs division has a steep cranially directed course, branching takes place lateral to the midline, a smaller ascending branch is issued before reaching the midline, the main artery continues its vertical course, and then bends sharply in a typical "hairpin" curve into the larger descending branch.

directed course in the thoraco lumbar region due to the onto-genetical "ascension" of the SC. Branching takes place lateral to the midline, with a smaller ascending branch issued before reaching the midline and the main artery continuing its vertical course and then bending sharply in a typical "hairpin" curve into the descending branch[53].

Recently, imaging methods such as MR-angiography and CT-angiography expanded the non-invasive diagnostic capabilities to include SC vasculature of individual patients and especially the presence and location of the GRA[54]. Although MR-angiography showed brilliant results in this field, we concentrated our efforts on CT-angiography, which also offers excellent imaging capabilities especially with state-of-the-art multi-detector scanners. CT is the imaging modality of choice for most patients with thoracic and thoraco-abdominal aortic disease, particularly in assessing the feasibility and planning of endovascular treatment, and the dataset needed is therefore already available for analysis. CT datasets, appropriately post-processed with the OsiriX software (which may be downloaded free of charge from the Internet and runs on regular Mac OS X computers, even laptops, thus avoiding the need for expensive dedicated radiology workstations) provided information on the SC vasculature in 76% of 67 cases in a published series[55]. Moreover, in the last three years 432 additional cases were evaluated with visualization of the spinal cord vasculature in 82% (unpublished).

Once validation and improved understanding of the information acquired with CT-based angiography of the spinal cord vasculature are realized, several important clinical benefits are possible:

1. Preoperative stratification of the risk of SCI[56,57]
2. Selective intercostal/lumbar artery re-implantation (open surgery)
3. Avoidance of unnecessary coverage of intercostal feeders of the GRA (endovascular procedure)
4. Collateral pathway preservation (i.e. selective re-vascularization of left subclavian artery or hypogastric artery)

Selective use of adjuncts (that have an intrinsic risk of complications), such as CSFD

Selective use of "rescue wire" kept in the aneurysm sac for the first 24 post-operative hours to facilitate the insertion of a stent to induce a type Ib endoleak[58]

Design of specific stent-grafts that avoid abrupt blood flow reduction to the intercostal feeders of the GRA[59,60].

In conclusion, knowledge of the SC vasculature may be obtained from the same CT dataset used for the aorta and may contribute to the understanding and prevention of spinal ischemic complications after procedures involving the thoracic and thoraco-abdominal aorta.

Summary

For DTA aneurysms and traumatic aortic injury, TEVAR is currently the gold standard of treatment; open repair is still used in selected instances, such as patients with connective tissue disorders and chronic dissecting aneurysms, with well proven safety and efficacy. Long term outcomes of TEVAR need to be carefully assessed. In acute and sub-acute complicated cases of TBD, TEVAR provides satisfactory safety and efficacy; moreover, the PETTICOAT technique promotes TL expansion and relieves malperfusion without affecting aortic side branch patency. Hybrid repair of aortic arch pathology is an alternative to open surgery in some patients; appropriate patient selection and stroke reduction strategies may improve outcomes. Open repair remains the gold standard for TAA aneurysms, and produces excellent early survival and acceptable morbidity; hybrid repair is offered only to truly unfit patients, who would otherwise me relegated to simple observation. Total endovascular techniques for the arch and thoraco-abdominal aorta are not discussed in this overview. Modern noninvasive imaging modalities allow for much improved visualization of the SC vasculature which may play a role in stratification and prevention of SCI related to aortic procedures.

Acknowledgements

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Innovative technologies for Patient Safety in Aortic Surgery:
Surgical Robotics and Automation

The experience of SAFROS and ISUR project

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The introduction of surgical robotics and innovative technologies marks a turning point for the surgical practice with significant performance improvements, bringing forward the benefits introduced by minimally invasive technologies and solving some of their limitations. For instance, surgeons can now perform extremely precise and dexterous movements by surgical robotics [1]. For this reasons it has been said that "Surgical Robotics is rooted in the strengths and weaknesses of its predecessors" [2]. Robotic devices continue to evolve and – as they become less expensive and more widely disseminated – are likely to become more frequently utilized in surgical procedures. About 234 million of major operations are executed worldwide every year and surgical robotics is used in an ever increasing number of them. Robot-assisted surgical process exploits computer technology and enhanced devices for the surgeon-patient interaction during a surgical operation and assumes some degree of control heretofore completely reserved to the surgeon. Current surgical robots are continuously controlled by the surgeon and do not move autonomously. They possess neither artificial intelligence nor independent functioning, but remain a high level, sophisticated tool used by the surgeon in performing an operative procedure. Robots do not actually replace humans, but rather allow to overcome human limitations and eliminate impediments associated with conventional surgical and interventional tools.

Since MIS (Minimally Invasive Surgery) first introduction in 1987, the number of procedures performed laparoscopically has definitively grown by virtue of a wide appreciation collected

	Benefits	Limitations
Mechanics	Scaled movements (conversion of large natural movements to ultraprecise micromovements)	Cumbersome systems
	Improved degrees of freedom (up to 7 degrees of freedom, i.e. the greatest possible motion around a joint)	Mechanical problems
	Elimination of tremor: stabilization of instruments within the surgical field	Augmented fragility of the tools
	Hand-eye coordination	Absence of tactile and force feedback
	Elimination of fulcrum effect	Long set-up time of robot and the operating room
	Precision Instruments: all the instruments are miniaturized and fit through operating ports, incisions in the body no larger than a dime.	High costs
	Stable and untiring	Technology in flux
	Resistant to radiation and infections	
Imaging	Superior visualization including 3-dimensional imaging of the operative field	3D vision could be more fatiguing
	Magnified imaging: The high-definition camera is designed for stereo imaging, allowing depth perception unlike any standard laparoscopic camera. Images are magnified 10 times beyond what the human eye can see. The surgeon also has complete control over the image, without having to rely on an assistant.	Monitor equipment failure

Table 1: Pros and cons of robotic surgery

both by surgeons and patients. Among the advantages of this procedure we can include shorter hospital stays, less risk of infections, smaller incisions, decreased pain; but there are also significant limitations, mainly involving the technical nature of the surgical tools. The develop of surgical robotics devices derives from the challenge to improve limitations of currently available laparoscopic technologies and to enhance benefits of minimally invasive surgery. The use of robotic devices allow surgeons to improve their ability to operate through small incisions, thus allowing laparoscopists to perform advanced procedures with greater ease.

The major benefits brought by surgical robots could be grouped as reported here below:

Table 1: Pros and cons of robotic surgery

	Benefits	Limitations
Surgeon, OR team and intervention workflow	Ergonomic position for the operating surgeon who sits comfortably in an ergonomically-designed workstation	Ergonomics: this benefit may not apply to the patient-side assistant. Such ergonomic differences will be magnified for lengthier procedures and reduced working space for the assistants and nurses.
	Telemanipulation/surgery	Training: at present there are no simulators that provide training equivalent to that obtained in a formal clinical setting.
	Shortened learning curve	Not established method in operative work-flow
		Lack of standardized method of training
		Difficult team communications
		Difficult set up and need for a dedicated surgical team
		Unable to use qualitative information
Patient	Benefits for patient: Increased surgical dexterity and better surgical results	Risks related to the surgical procedure

1) IMPROVED VISUALIZATION (3D visualization and adjustable magnification): many studies refer to these characteristics as the most appreciated by surgeons. Compare to the more traditional 2D visualization through the laparoscopic camera, the 3D view offers the dimension of depth perception and a better capability to zoom in on critical points, allowing surgeon to perform delicate operations with high precision.
2) IMPROVED MOVEMENT AND DEXTERITY (more degrees of freedom than laparoscopy, scaled motions, removal of the fulcrum effect and physiologic tremors,): traditional laparoscopic instruments have only four degrees of freedom, increment natural shivering and the presence of the fulcrum affect the surgeon to move unnaturally the clamp. The use of robotic wristed instruments allows a more fluid action ,similar to natural hand movements; motion scaling and tremor filtering contribute to increase dexterity and allow an unparalleled level of operative precision.
3) IMPROVED ERGONOMIC POSITIONING: the possibility to

operate in an ergonomic position allows a surgeon less fatigue and a greater ability to concentrate on the operation, with consequent improvement of safety for the patient.

Based on what discussed above, Table 1summarizes the main characteristics of robotic surgery [3][4], dividing them into four categories - Mechanics, Imaging, Surgeon-OR team and Patient - and highlighting its benefit and limitations.

Despite the ability of surgeons in operating surgical robots and their level of precision, the introduction of such new work technologies might potentially add unforeseen complications and procedural risks, affecting negatively the clinical outcomes. First of all, as a new robotic instrument/equipment is acquired then a selection of surgical staff members must be exposed to and perfectly trained to use and operate the new systems. The operational and functional requirements, for surgeons and physicians, to coexist, interact and coordinate with robotic technologies supporting them during the intervention can dramatically increase the complexity of the surgical scenario. Put simply, automation modifies the failure modes of the operating team, but does not eliminate them. Moreover the system may introduce complications in the interactions between surgeon and patient, or between the surgical staff members. Several other performance failures may add onto the equation: more prolonged operative time, mechanical interferences or electronic failures, opacity of the system, human machine interaction failures etc….

Overall, the robotic approach is not without disadvantages. First of all, robotic surgery is a new technology and its uses and efficacy have not been fully studied yet. Other disadvantages include maintenance and upgrading costs, complete elimination of tactile feedback, limited options for trocar placement, higher consumption of operating room resources, such as space and the availability of highly trained staff with extra-skills in operating the robot.

Risks of robotic surgery can be categorized into those pertaining directly to the use of the robotic system and the general risks of the operative procedure. Devices have the potential to be fatal if they malfunction. One of the most challenging aspects of developing devices for robot-assisted procedures is the special attention to be paid to those malfunctions or failures that are

Type of problem	Error, malfunction or failure
Mechanical failure and malfunction	Arm malfunction Camera malfunction Setup joint malfunction Ocular monitor loss Metal/fatigue break of surgeon's console handpiece
System error	Failure of backup battery Failure of instrument identification Power error On/Off failure Console failure Out of range motion Software incompatibility Optical malfunctions Master malfunction Circuit board malfunction
Instrument error	Shaft injury (curving, breaking, peeling away of coating) Cutting of wire Unnatural motion because of attaching problem to adapter Problem of instrument tip (peeling away of coating or inadequate closure) Limitation in carriage motion

Table 2: Pros and cons of robotic surgery.

naturally embedded within a robotic tool. Nevertheless technical problems and complications associated with the use of robotics in surgery are reported in several papers in literature [5][6][7][8][9]. Malfunctions include on/off failure, console malfunctions, robotic arm malfunctions, optic systems malfunctions, system errors (e.g. out of range motion) and instrument failures (e.g. curving, breaking, peeling away of coating, cutting of wire, unnatural motion because of attaching problem to adapter, inadequate closure of tip…). The causes included setup joint malfunctions, software incompatibility, arm malfunction, "power off" error, monocular monitor loss. The Table 2 reports the most frequently detected malfunctions and failures that have been identified.

Several efforts are being spent by industries to reduce these risks by developing systems that minimize these potentially deleterious effects, such as system redundancy, fault tolerance, just-in-time maintenance and system alerting. Consequences of

the failure could show low severity, such a little delay in the operation, or otherwise lead to more severe complications that surgeons have to manage in different ways: conversion to open or laparoscopic surgery, robot-asset readjustment, instrument replacement and reschedule the patient. It's still open the discussion on the actual benefit provided by robotic surgery [2] as a justification to its cost of implementation.

This intervention technique is used in a variety of fields of application: paediatric surgery, gynaecology, urology, cardiothoracic surgery and otolaryngology, and the improvement in innovative robotic technologies will make possible surgeries previously difficult or unfeasible from a technical point of view.

The number and types of surgeries being performed with robots is increasing rapidly and it becomes clearer that one of the prerequisites for robotic surgery's further and future development is "*Safety*". If robotic surgery is implemented, many procedures should be redesigned to optimize the use of robotic arms and increase efficiency. Several studies [3] were conducted to analyze how a robotic technology can be safely integrated within a surgical environment, identifying some key design requirements of an ideal device. Most of all, the meaningful requisites are an easy and essential integration into existing procedures (i.e. must augment and strengthen actual therapy techniques) and the availability of operative forces and haptic feedback.

In particular, patient safety is the most important aspect during any process in healthcare environment. Patient safety is defined by the World Health Organization (WHO) as the absence of preventable harm to a patient during the process of healthcare [10]. During the last 10 years the relevance attributed to the prevention and management of errors in surgical field is grown considerably aiming to increase safety for patient within both the medical community. The reason why it's relevant investigate patient safety in robotic surgery is that, as of today, no study has looked at all aspects of safety in robotic surgery and the analysis of the effects due to the introduction of robotic technologies has been conducted by evaluating the requirements for a proper preoperative diagnostic, for the performance of the intervention and for the training of surgeons separately (e.g. in [3]). Moreover patient safety is not a design criterion for the development of

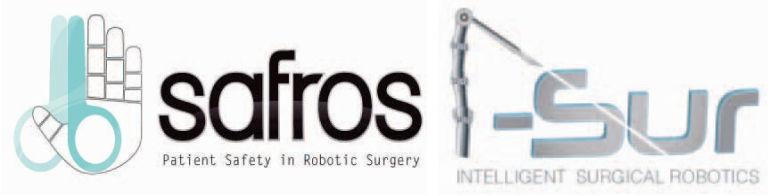

Figure 1: Logo of SAFROS and I-SUR projects

robotic devices (in addition, the evaluation of the performance quality of these phases does not involve the use of metrics that specifically address patient safety).

Following on from this, the ***eServices for Life&Health*** unit of San Raffaele Scientific Institute (http://www.eservices4life.org/) is involved in the development and application of new innovative solutions of the Information Technology to the surgical field through two research projects funded under the European Commission Seventh Framework Programme: **SAFROS - Patient safety in Robotic Surgery** (EU-FP7-ICT-2009.5.2, n° 248960) and **I-SUR -Intelligent Surgical Robotics** (EU-FP7-ICT-2009-6, n° 270396).

SAFROS - "Patient safety in Robotic Surgery" (www.safros.eu) - aims at developing technologies and methods for the enhancements of patient safety in surgical procedures extending the analysis to the whole surgical workflow. The SAFROS project addresses the complete planning-execution loop in surgical robotics, to ensure a seamless data flow and consistent accuracy in all phases of surgical processes, after having identified the most critical steps through risk analysis methodologies. Along the surgical workflow, SAFROS aims to introduce technological solutions for improve patient safety. The analysis focuses on virtual and synthetic organ models, virtual simulator for training and surgical planning, operating room monitoring system and robotic simulator, surgical interface for monitoring, and new methods for robotic surgical training.

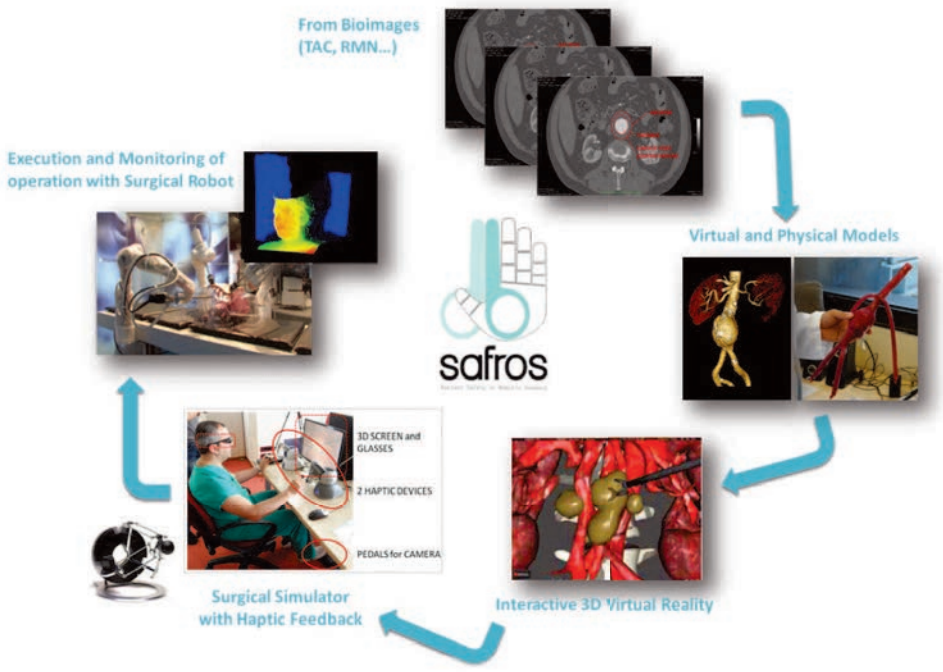

Figure 2: innovative technologies developed by SAFROS, introduced in the surgical workflow for improve patient safety.

The main objective of the project is to demonstrate that the introduction of new assistive technologies improves patient safety during the performance of surgical intervention or into training process with respect to their current way of execution. Researches have been conducted in order to identify metrics capable to assess the patient safety level achieved and methods to correctly satisfy these safety requirements.

Among the surgical procedures analyzed in the project's context, the **Abdominal Aortic Aneurysm repair** (AAA) is one of the most challenging and interesting benchmarks for the developments of this work. As for today this intervention is not routinely assisted by robots, since its high complexity of execution has hampered an extensive use of technology. Despite this, the adoption as test-beds for the SAFROS method was grounded on the belief that patient safety, as a systemic notion, could be better addressed in unexplored fields where no consolidated practices exist. In fact safety must drive the development of technological

solutions in the early design phase and not introduced when already established design constraints can impede further improvements. Considering vascular surgery, robotic technology has recently been introduced also to enhance laparoscopic vascular procedures. Although there are only few experimental studies on robotic laparoscopic aortic surgery, the results are encouraging [4][11]. The "internal" approach in the treatment of AAA include intrinsic difficulties due to the procedure such as the reaching of the retroperitoneal space, the time of clamping, the bleeding back from lumbar arteries and the suture, aspects that are crucial also in the traditional aortic surgery. Robotic technology may enhance aortic surgery by extending human capabilities: first of all, these systems can translate human movements into scale, steady and real-time micromotions inside a patient's body. Additionally these systems offer improve vision that makes possible to identify and dissect anatomic structures and perform vascular anastomosis. The adoption of robotic technology may improve surgery by increasing precision and dexterity of surgeons in performing complex tasks such as those referring to abdominal vascular surgery.

A close collaboration between *eServices for Life&Health Unit* (www.eservices4life.org) and the *Vascular Surgery operative unit of San Raffaele* (Milan) was worthwhile to understand the critical elements of this kind of intervention, that currently has prevented the introduction of robotic technologies into vascular field. Considering the intrinsic difficulties of this kind of vascular intervention (poor pre-operative visualization, reduced operating space, diffuse bleeding, etc…) risk assessment methods were exploited to outline the potential risks related to each step of the procedure in order to lay the grounds to develop technological solutions capable to reduce the risks for the safety of the patient. One of the final goals of the SAFROS research is to demonstrate that a robot-assisted procedure carried out in accordance with proper safety criteria, addressed through the introduction of innovative technologies and a widespread methodological safety culture, can improve the level of patient safety currently achievable by traditional open surgery.

Following the requirements given by vascular surgeons of San Raffaele, within SAFROS project it has been developed artificial organs models with the aim to reproduce similar anatomy and

Figure 3: Suturing test with aortic models with Vascular surgeons of San Raffaele Hospital.

tactile properties of the real abdominal aorta. Tests have been execute for assess similarity between the real and the phantom organs as well as to evaluate their general applicability to increase patient safety, as example, employing them as means for improve training for young surgeons.

Moreover requirements for the development of a simulator-based training curriculum for the education and assessment of surgical skills were studied. The innovation embedded into the SAFROS training curriculum is the inclusion of both technical skills and behavioural, environmental and human factors, called "non-technical skills". The purely technical aspect relies on the use of technological innovations such as a robotic simulator for the improving of surgical skills of the participants and physical organs models for the practice. The non-technical parts, instead, takes into account individual and teamwork attitudes, ways of communication and cooperation (the so called human factors) that are influenced and influence human behaviours and attitudes in robotic surgical scenarios. This kind of research laid its foundation in the belief that a complete training curriculum, embracing even the human aspect, is an effective means in hazards detection reduction or containment leading to better patient safety.

A more pioneering aspect of the research in robotic surgery is the development of advanced technologies for automation in minimally invasive and open surgery. Automation may thus

provide a solution to improve performance and efficiency in the operating room without increasing operating costs. Currently, automation is not used in the operating room for a number of technical and legal reasons. The anatomical environment is particularly difficult to handle by classical automation. Furthermore, the execution of a surgical intervention is not only controlled by a set of physical and geometrical set points, describing the anatomical area and its properties, but also and especially by the medical and surgical knowledge that the surgeon uses in deciding what to do and how to do it, during the intervention. These control and cognitive challenges are also coupled to a legal barrier that currently prevents the use of an automatic intervention device in the operating room.

The **I-SUR - Intelligent Surgical Robotics** (www.isur.eu) - project aims at breaking new ground in the above areas related to automation in surgical intervention, in particular design of robotic surgical instruments, task modeling and control in highly uncertain and variable environments, medical situation awareness and its interaction with task control, surgeon-robot communication, and legal barrier identification. The introduction of automation principles within a safety-critical environment such as an operating room is a very challenging issue, but can entail significant advantages from the procedural point of view, such as make some parts of the procedure faster and safer, lowering the stress for surgeons.

As a preliminary approach of the problem, I-SUR proposed to apply automation principles on three basic surgical actions, namely puncturing, cutting and suturing, to be performed on physical phantom models. Basic requirements are the identification of the critical aspects of automation in robotic surgery and the development of technological and methodological system acting from the preoperative phase to the completion of the task. More in detail, I-SUR is expected to develop the following innovative technologies:

- New methods for representing the medical knowledge relevant to soft organ surgery
- New methods for the interactive planning of surgery in deformable environments
- New designs of dexterous, sensored instruments for robotic surgery

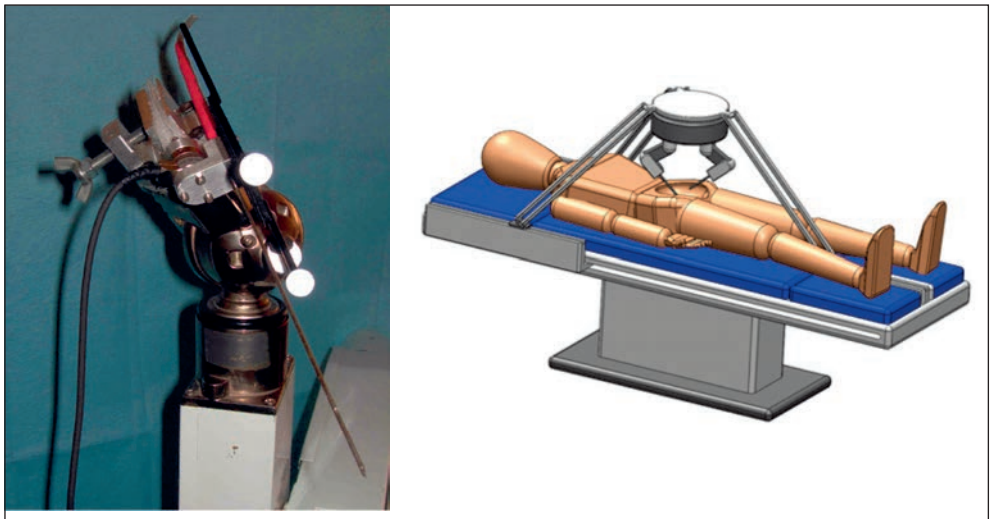

Figure 4: experimental set-up for tracking the puncturing trajectory (left); initial design of the robot for automation (right)

- New methods for intervention execution and monitoring
- New methods for real time data processing and medical situation awareness
- New communication methods between the robotic instrument and the operating surgeon

The selection of the procedures to focus on has been made considering the need to provide innovative technologies and methods that could lead to a real improvement in safety, efficacy and accuracy of the surgical interventions by addressing the needs of the surgeons. Simple cuts and sutures contribute to increase the operating time for the completion of the intervention and are not exempt from errors and adverse events, thus high accuracy is required during the execution to guarantee patient safety. The puncture of a target objective inside the human body (e.g. biopsy, tumor ablation...) is described as a very demanding task because of the current pre-operative planning methodology to provide clear indications on the trajectory to be followed from the skin surface to the target organ.

The automation of these surgical tasks involves the solution of challenging problems concerning the required imaging,

sensing and control system to be applied in order to guarantee the autonomy of the robotic system. Adverse events will be managed within the project by designing the robot for the solution of the simplest cases and allowing the switching to the teleoperated modality for the most problematic situations. The surgical interface will allow the surgeon to play an active role both during the preoperative and the intraoperative phase in addition to the already mentioned occurrence of adverse events. Given the complexity of the objectives to be reached and the need for a clear definition of the steps to be followed, the I-SUR team identified a sequence of sub-objectives for each one of the 3 surgical actions following an increasing complexity approach.

The Vascular Surgery Unit actively cooperates in the I-SUR project in close collaboration with *eServices for Life & Health Unit*, aiming to investigate the feasibility of the introduction of automation advantages within specific procedures and surgical task. The *Vascular Surgery operative unit* is offering the medical knowledge to analyze the surgical gestures for modeling specifically the suturing task and the most complex task of the vascular anastomosis.

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PEACE SUPPORT OPERATIONS

Col. ITA (A) M.D Enzo LIGUORI

State of the art and considerations on the role of Vascular Surgery

My lecture treats some new considerations related to the analysis of working group remarks and my personal opinions about "Health and Medical Policy" during Military Operations, emphasizing the differences between civilian /home and military medical treatment.

The expression "*military operations*", or, to be more precise, "*crisis response operations*", does not refer to actual combat operations against a known enemy but, rather, to "*peace support"*operations. Similarly, the term "*disaster relief"* includes humanitarian assistance, refugee care and similar missions no related to combat operations. Disaster relief operations can either be carried out within the framework of other ongoing operations, or in the form of stand-alone humanitarian operations. The latter often involve a considerable degree of logistic and military protection or support, including medical support.

The major contribution of medical support to such operations is threefold: medical support to the Armed forces, replacing or supplementing existing Host Nation assets and assisting with their regeneration or development.

This new concept determines new tasks, which require Combat Service Support Units, including medical assets, to be agile and flexible. The current environment in which NATO and EU forces operate must consider the role of the Host Nation and other entities (NGOs, other allies, etc.) working in the joint operational area.

It is important to emphasize that the ultimate role of military

medical support – supporting the troops in performing their tasks by preserving and restoring their health and fighting strength - remains unchanged.

In this context, we must consider the growing expectations for high quality medical support by the public. Public opinion and the political environment are sensitive to media coverage of health and medical support to the troops.

In all nations the military wishes to be, and to be seen as, an employer of the highest standards. While accepting the dangers involved in joining the military, public opinion does not accept avoidable risks. Consequently, there is now a requirement for the health of the forces to be assigned a very high priority before, during and after deployment. An effective and reliable military medical support system helps to improve troop's morale and maintain the trust of military personnel, the wider public and its political leadership.

On the other hand, medicine has become a highly specialised and technical field and Military Medicine has led the way in many instances. To effectively address these new challenges, the medical community constantly monitors the situation, seeking mechanisms to balance military medical capabilities and force needs. These basic mechanisms include, but are not limited to, increasing effectiveness and efficiency of existing medical capabilities, exploiting the benefits of multinational cooperation, and investing in the development of new medical capabilities and additional capacities, at a time of limited economic resources for many countries.

Management of medical shortfalls could be limited to a multinational medical support option and requires more complex co-ordination at all staff levels: NATO and EU Nations are all moving in this direction.

The first consideration arising from the lessons learned and identified during Peace Support and Humanitarian operations regards the slowness in shifting responsibility and duties from the military to the International civilian organization or to the regenerated force of the Host Nation. *(Fig. 1)*

These new challenges push the military toward seeking a multinational approach to medical support tasks. As a consequence, military medical support is frequently involved in providing care to local populations, which requires a lot of

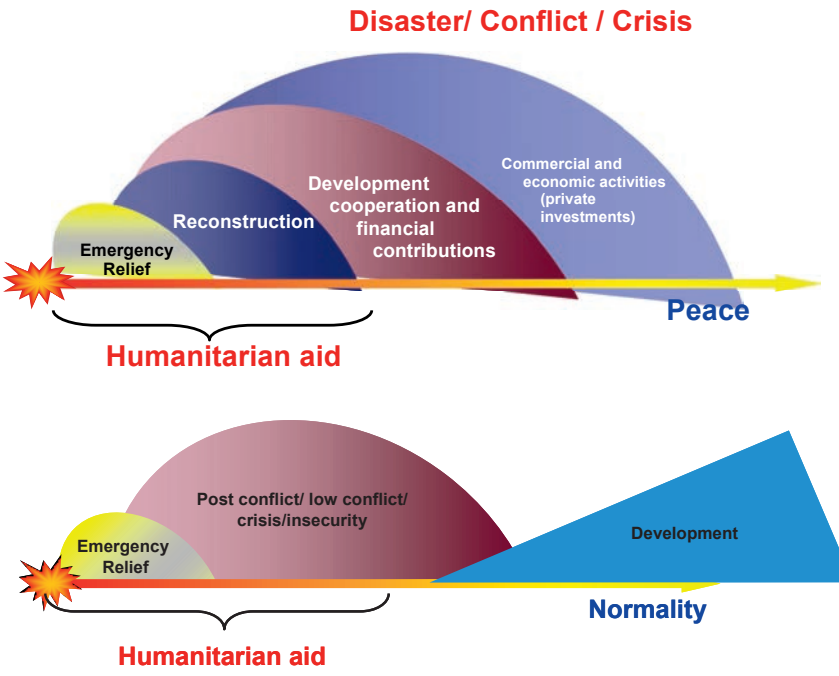

Fig. 1

resources and technical skills (obstetric and vaccinations) that are not included in routine military medical tasks.

Time is one of the peculiar aspects of military medical support. Time is a fundamental factor in the effectiveness of medical care, but we have no safety or high-speed roads during medical evacuations. The time taken until the receipt of appropriate medical intervention will affect the general outcome of medical care, including the risk of death and speed of recovery, and may affect the level of residual disability. Therefore, the allocation of medical resources must ensure the timely provision of medical care. Trained non-medical first responders, able to provide emergency life-saving procedures as soon as possible, within ten minutes of the injury, will help to improve treatment outcomes and save lives. Treatment and evacuation timelines in operations are determined by medical military doctrine, whose implementation must be ensured by clear command and control over Medical Evacuation (MedEvac) assets.

Therefore, comprehensive medical plans, a high state of medical readiness, medical intelligence and an early and continuous medical input into the force generation process are essential to provide an adequate medical support capability, coherent and effective from the onset through all the phases of any operation. Significant changes to the eligibility for military medical support (e.g. allied forces, host nation forces, civilian populations) must be taken into account in the course of deployment.

Preventive Medicine and access to Primary Health Care are fundamental aspects in maintaining the health of personnel and the sustainability of forces. Disease and non-battle injuries will be a persistent health risk to personnel.

The aim of operational medical support is to ensure that every casualty gets the right treatment, in a timely manner and at an appropriate facility.

Timeliness of treatment is a fundamental principle of medical support. The time taken to provide appropriate medical care will affect the outcome for the casualty, especially those who are seriously injured and who must be treated as soon as practicably possible. The initial response at point of injury is crucial. For the most seriously injured, provision of bleeding and airway control must be achieved within 10 minutes of wounding. It is important that a continuum of care is provided with the necessary treatment and that evacuation capabilities are available throughout the chain to meet clinical requirements. In this way, medical support will save lives, minimize the effects of injury and create the conditions for effective rehabilitation that returns personnel to active military duty.

Following are Medical procedures defined in Military doctrine:

Primary Health Care

The provision of integrated, accessible health care services by clinical personnel trained for comprehensive first contact and the continuing care of individuals experiencing signs and symptoms of ill health or having health concerns.

Explanation: Primary Health Care includes health promotion,

disease prevention, patient education and counseling, and the diagnosis and treatment of acute and chronic illness.

Damage Control Surgery (Dcs)

Emergency surgical procedures and treatment to stabilize casualties, in order to save lives, limbs or functions, including rapid initial control of hemorrhage and contamination, temporary closure, and resuscitation.

These procedures should be followed by primary surgery. Damage Control Surgery is a procedure that ensures surgical treatment at an early stage. Providing life, limb and function-saving surgery is different from primary surgery, which focuses on damage repair.

Primary Surgery

The surgical procedures directed at repairing local damages caused by wounding, rather than correcting the generalized effects, usually performed at specialized field hospitals (role 3).

Primary surgery delay allows further generalized effects to develop that may lead to an increase in mortality, morbidity and residual disability.

Focusing on vascular treatments, Primary Health Care aims at providing the use of tourniquets to stop the arterial bleeding from the limbs, which is the part of the body more frequently wounded in soldiers due to the routine use of individual protective devices. Recently, the use of new materials to stop massive bleeding like combat gauze, quick clot or hem-com (Fig. 2) can help troops to provide efficiency in auto self-care and buddy-to-buddy care, or even improve the performance of combat medics.

As mentioned earlier, operational scenarios have dramatically changed over the last few years, and the deployment of units confronting the enemy on a well-defined front line is less and less probable.

Fig. 2

In brief, the confrontation among regular armies has been replaced by low-security, low-conflict scenarios, strictly related with the impressive rise in the number of sudden, isolated attacks with a high damaging coefficient, carried out by individuals or small groups, which can be defined as terrorism or urban guerrilla acts.

On the other hand, isolated, small military unit, acting away from their deployment bases are also used by regular armies involved in response operations to control the territory. At present, Italian soldiers involved in out-of-area operations are deployed in theatres characterized by a considerable extent of the field of action and difficulties in guaranteeing the presence of healthcare personnel to provide effective first-aid to injured soldiers.

The change in the modes of employment of such units therefore requires a transformation, at least in part, of the Military Health Care Service, which should increase its mobility, flexibility and capability for forward deployment of both healthcare personnel and facilities. The latter should be smaller in size but capable to ensure high performance quality.

At international level, the analysis of recent "lessons learned" from operational theatres with high conflict situations has revealed some gaps in first-aid medical care provided by healthcare personnel, especially immediately after the occurrence of trauma injuries. In this regard, most recently the Allied Command Operations' Medical Advisor has changed the schedule of medical evacuation and emphasised the need for good medical treatment in the first ten minutes after the injury occurs, replacing the "golden hour" concept with the one of "platinum minutes".

During the last military operations it has been noted that - from the physiopathologic point of view- poorly or non-controlled hemorrhage was the main cause of mortality. These cases, which involve injuries to the lower limbs, are, from the technical point of view, easily treated by appropriate and simple first-aid manoeuvres provided by specialised personnel.

Such casualties fall among the "avoidable casualties" and represent approximately 20% of total cases. Such a high percentage makes it necessary to take every possible measure to counteract this phenomenon.

Furthermore, about 90% of total casualties resulting from wounds received in action take place in the vicinity of the site of wounding and, quite often, death occurs before the wounded soldier can be treated by healthcare personnel or transferred to a health facility.

As a consequence, it is mandatory to enable units involved in out-of-area operations to be self-sufficient in terms of medical equipment and technical ability in pre-hospitalisation emergency medical care. All these procedures must be improved in order to ensure first-aid treatment immediately after the wounding and continuing care until the arrival of medical personnel.

On this basis, the Military Health Care Service started a project aimed at creating the "Combat Medic" profile, referring to members of the operational units who are appropriately trained to provide life-saving first aid in operational theatres abroad.

Combat medics - that have been operational for a long time in countries such as the U.S.A., UK, Israel and, more recently, the Czech Republic - will increase the capability for immediate healthcare response in assisting the wounded.

As a result of this lengthy planning activity a Memorandum of Understanding was signed on 17 November, 2008 by the Defence General Staff for the Ministry of Defence and by the Quality Department- General Directorate for Human Resources and Healthcare Professionals for the Ministry of Labour, Health and Social Policy.

A provision on the training protocol and the role of combat medics could therefore be added to Decree no 209, 30 December 2008 (published in the Gazetta Ufficiale no 304, 31 December 2008), converted into Law no 12, 24 February 2009 (published in the Gazzetta Ufficiale no 47, 26 February 2009).

We will soon start selecting and preparing military personnel. At the same time - in order to guarantee the highest efficiency and safety level in the treatment of casualties, in compliance with medical evidence criteria and international models and guidelines established by scientific associations - practical training programs for both combat medics and military healthcare personnel will be enhanced.

As regards Damage Control Surgery, the general plan for vascular treatments provides for the extensive use of temporary

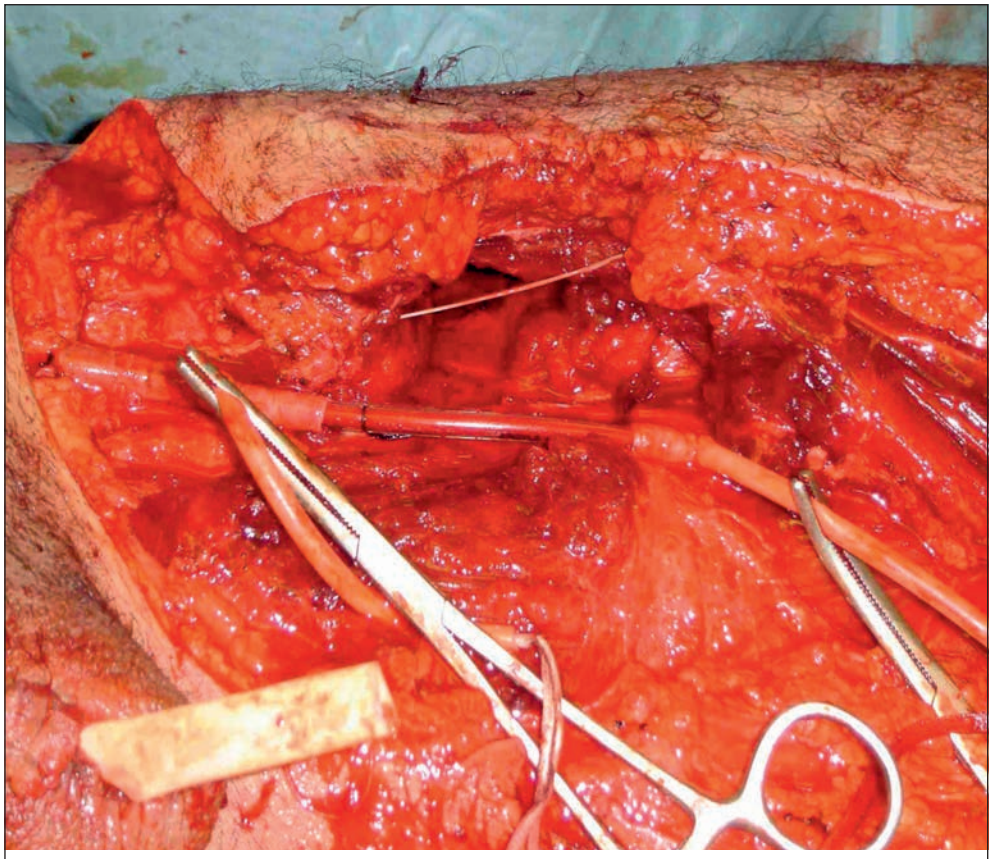

Fig. 3

plastic tube shunts or bypass using synthetic graft even if in infective environments. (Fig. 3)

Patients with extremity vascular traumas are a daily occurrence in emergency departments (EDs) and trauma centers worldwide. While much of the current state-of-the-art information is the result of wartime observations, the incidence of civilian extremity vascular trauma is significant. A basic understanding of both blunt and penetrating injuries to the extremities and the resulting vascular abnormalities that occur with these injuries helps minimize mortality and morbidity in these patients

Using data from the Joint Theater Trauma Registry, one study evaluated the epidemiology of vascular injury in the wars of Iraq and Afghanistan by identifying the categorization of anatomic patterns, management of casualties, and mechanisms of injury,

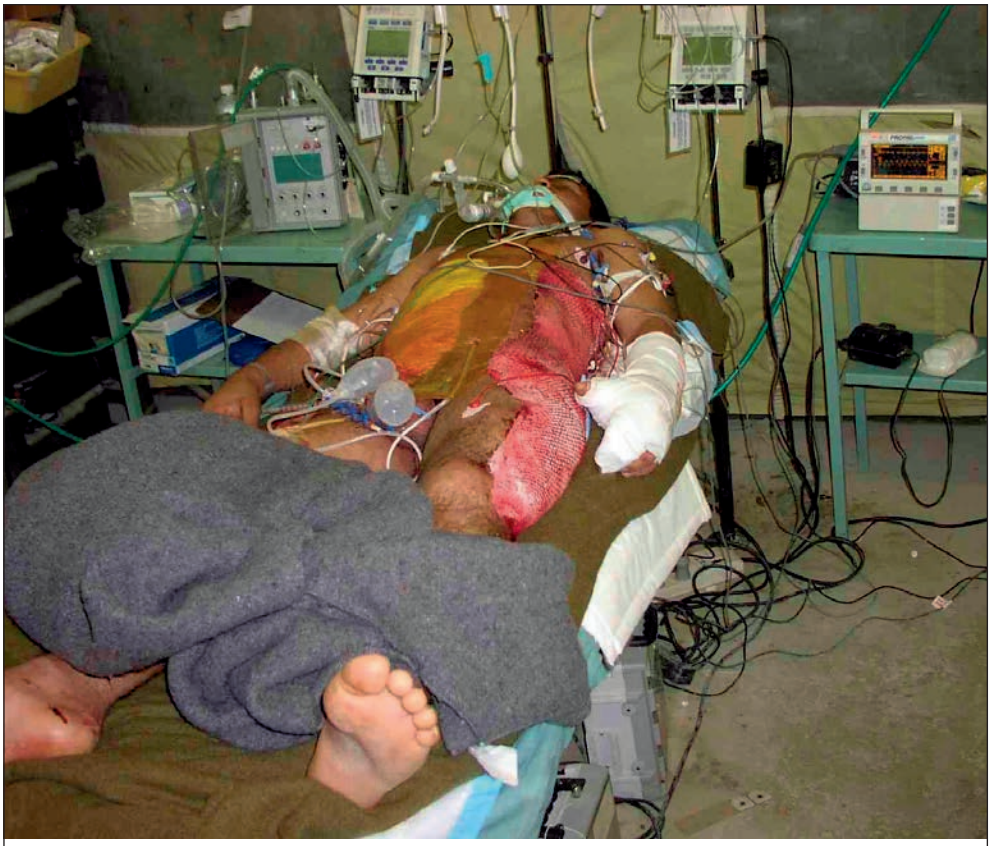

Fig. 4

including explosive, gunshot, and other injuries. The study found vascular injury rates in modern combat to be 5 times higher than in previous wars, and vary according to operational tempo, mechanisms of injury and theater of war. Newer methods of reconstruction, including endovascular surgery, are now applied to nearly halve vascular injuries and should be a focus of training for combat surgery

As noted by the preponderance of penetrating injury in the published medical literature, the vascular tree, both arterial and venous, appears to have some limited natural protection from stretching and bending, which results in fewer blunt injuries to the extremity vasculature following trauma. The smooth muscle of the arterial media protects the patient from both stretch-type injuries and minor puncture wounds, which heal spontaneously

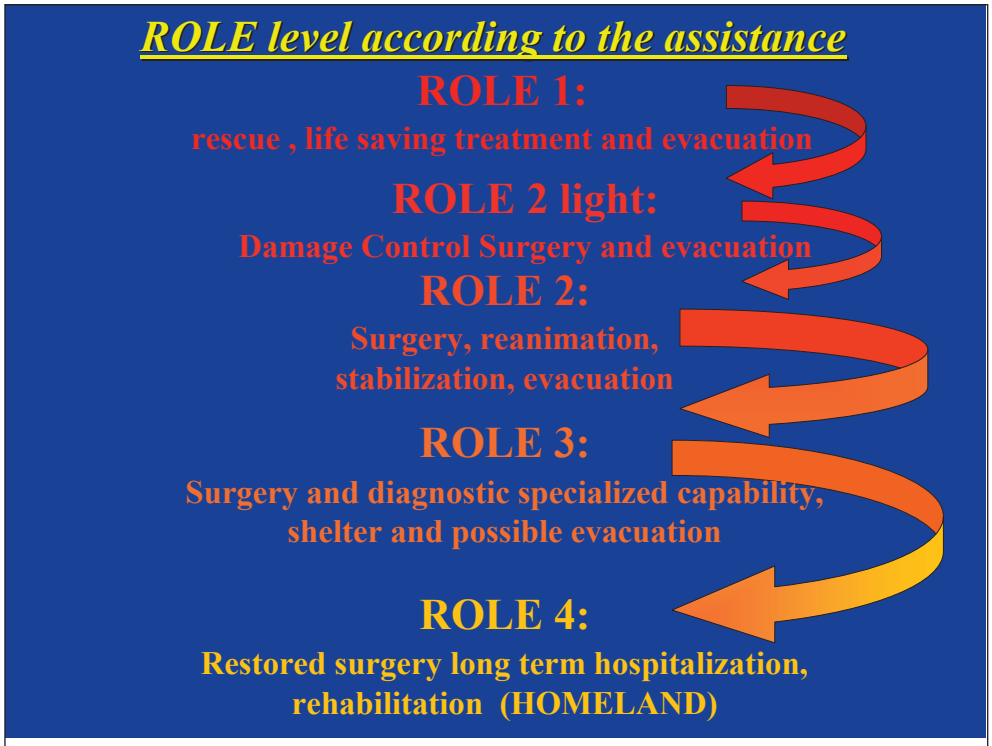

Fig. 5

in most cases. The smooth muscle layer also offers mild protection from death due to ongoing hemorrhage.

When the arterial vessel is transected, vascular spasm coupled with low systemic blood pressure appears to promote clotting at the site of injury and to preserve vital organ perfusion better than that which occurs with ongoing uncontrolled hemorrhage. This partially explains the prehospital finding that, in the subset of penetrating trauma, limited or no fluid resuscitation until arrival at the hospital may improve patient survival and outcome.

As we all know, all arterial lesions -due to the contamination during wounding- are potentially infective, in particular in gunshot casualties, when a lot of debris come in contact with damaged skin.

Usually, the use of the autologous veins bypass is the goal standard for the contaminated wound, but in a combat environment and in the DCS concept this operation is too long to be performed on patients with multiorgans failure or in

mass casualties (Fig. 4). In short lesions, direct arterial repair is mandatory while the use of synthetic patch is not correct. The vein ligature is the choice treatment in combat zones or in field hospitals, even when reconstruction or repair are needed for the haemodinamics. The non medical treatment due to its lower requirements less resources in terms of time and materials. Reaching a good skill level is not easy for military medical surgeon, because civilian medical training does not use similar treatments and due to the necessity of continuous regular training in operational military theaters (Fig. 5).

As regards the endovascular treatment, we would like to emphasize the requirement for a prompt diagnosis and treatment of penetrating and blunt vascular traumas, to avoid the late sequelae that may occur when important injuries are not treated. Sometimes traumatic pseudoaneurysms involving non essential vessels, such as branches of the hypogastric or deep femoral arteries, have been effectively treated by catheter directed arterial embolization.

Endovascular methods are rapidly evolving to treat a variety of vascular diseases, including arterial trauma, not only in the lot of applications for occlusive and expanding arterial diseases. Stent grafts can be safe and effective in vascular trauma management of short lesions, but they are not suitable in combat zones.

Despite potential disadvantages involved in using a thrombogenic stented graft device that might stimulate intimal hyperplasia to treat traumatic lesions of the femoral arteries, the advantages of minimally invasive deployment, decreased blood loss, and the ability to insert endovascular devices and stented grafts through remote sites with the patient receiving a local anaesthetic, make this endoluminal technique for repair of penetrating and blunt injuries a potentially important tool for more widespread use. This is already true for patients with multiple trauma and critically ill patients with central artery injuries. Long-term follow-up of these repairs will be necessary to fully evaluate the safety and efficacy of these devices in extremity arteries and in other less critical circumstances.

Aortic Surgery in France

Yves S. Alimi

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On the 21st to 24th of June 2013, the 28th Congress of the French Society of Vascular Surgery will take place in Nice, under the presidency of Pr. Roberto Chiesa (Milano, Italy). This event is an opportunity to celebrate the long tradition of exchange between French and Italian vascular surgeons, and to share experiences from both countries. In order to introduce the debate, this article will present different aspects of French centres in aortic surgery. Although aortic surgery was born in France with the first AAA surgical treatment performed by Charles Dubost in 1951, more than twenty years passed before the French Society of Vascular Surgery was created in December 1972. Aortic surgery is currently performed in numerous centres in France, and as in other countries, several developments have been made in order to decrease the invasiveness and peri-operative mortality of both regular and emergent aortic reconstructions. The most recent aspects of these innovative surgical techniques are presented here by some of the most renowned French vascular surgeons.

I - Research in aortic surgery in France

by Pr. Réda Hassen-Khodja (University Hospital Saint-Roch, Nice)

Research in aortic surgery includes basic research and experimental research (in this chapter, clinical research is excluded).

A - Basic Research in aortic disease

Pathogenesis of abdominal aortic aneurysm is the main area of basic research in aortic surgery. Basic research leads to a better understanding of

aneurysm disease and fundamental knowledge about the process of aneurysmal degeneration. There are many areas of this basic research: proteolytic degradation of aortic wall connective tissue, inflammation and immune responses, biomechanical wall stress, and molecular genetics.

These studies are led by physicians specialized in vascular surgery and vascular medicine, as well as basic scientists focused on various aspects of connective tissue biology, inflammation and immunology, biomechanics, and molecular genetics. Strong collaborations between basic and clinical investigators are therefore needed to better understand the etiology and pathophysiology of aortic aneurysms.

A variety of animal models and experimental techniques have been described in the investigation of the pathophysiology of aortic aneurysm. In France, two vascular surgeons are particularly specialized in basic research on aortic diseases: Jean-Baptiste Michel and Eric Allaire.

Doctor Jean-Baptiste Michel is a research director at INSERM, in the unit 698 (Hôpital Bichat, University Paris Diderot). One of the concepts of his team is that the mural thrombus is a driving force in the evolution of aortic aneurysm by convicting blood-borne serine protease towards the arterial wall, including proteases of the fibrinolytic system and proteases contained in polymorphonuclear leukocytes (PMNs).

Professor Eric Allaire is the director of the unit CNRS UMR 7054 (Hôpital Henri Mondor, Créteil). One strategy of his team consists in restoring the solidity of the aortic wall and in stabilizing the diameter of aortic aneurysms by infusing genes or cells, by means of a catheter placed in the aorta of rats.

These two teams welcome young vascular surgeons interested in basic research, students in Master 1 and 2, and PhD students.

Some colleagues are referral medical advisors in some areas of research that can affect aortic surgery, such as vascular graft infection (Pr. Olivier Goéau-Brissonnière, Amboise Paré University Hospital, Paris), or durability of the vascular grafts or stent-grafts (Pr. Nabil Chakfe, research center on biomaterials: GEPROVAS, Strasbourg).

Many French academic vascular surgeons stayed in foreign research centers to complete their training in basic research (research fellowship). We cannot all quote them. For example,

Professor Eric Steinmetz (Dijon) and Doctor Michel Bartoli (Marseille) stayed in the research center of the department of vascular surgery in Saint Louis (Professor Robert W. Thompson, Washington University School of medicine, Saint Louis, USA). Doctor Michel Bartoli continued his work in the University of Marseille by using the animal model of aortic aneurysm of RW Thompson (elastase perfusion model), and continue collaborations with the team in St. Louis. There are many other examples of collaborations with foreign centers: Stanford University (Pr. CK Zarins and Pr. M Dake), Seattle (Pr. A Clowes, Pr. Wright), Nottingham (Pr. BR Hopkinson), St George's Vascular Institute of London (Pr. M Thompson), Cleveland Clinic (Dr. RK Greenberg), University of Laval - Quebec (Pr. Y Dion)…

B - Experimental research in aortic surgery

There are many experimental research projects on the treatment of aortic disease, in different academic centers of vascular surgery. A variety of experimental techniques have been described in the development of improved endovascular and surgical techniques: in vitro tests, benchtop flow models, experimental studies on animals (pigs, mice), studies on cadavers. It is not possible to report all these studies, but we can give four examples:

– Dr. Ludovic Canaud and Pr. Pierre Alric (Montpellier) devised a benchtop pulsatile flow model was by to test stent-graft anchorage. This benchtop pulsatile flow model simulates an aortic isthmus, with human cadaveric aortas inserted in the circuit.
– Ischemic preconditioning for spinal cord protection in thoraco-abdominal aneurysm repair: an experimental study on pigs with embolization of lumbar arteries before deployment of the stent-graft in the aorta (Marseille).
– Evaluation of new suture systems for aortic laparoscopic surgery (automated anastomotic system, sutureless anastomotic device): an experimental study on pigs and cadavers (Toulouse and Marseille).
– Experimental studies to create a model of aortic dissection on a benchtop flow model with cadaveric aortas (Montpellier), or on pigs (Dr. M Boufi, Marseille).

For young vascular surgeons who want to take up an

academic career, experimental and basic research studies are generally required (PhD). These activities are supported by grants from foundations, the European Union, industrial partners, and last but not least the French Society for Vascular Surgery.

II - Aortic surgery in France: How to choose between open and endovascular surgery?

by Pr. Fabien KOSKAS (University Hospital Pitié Salpêtrière, Paris)

Open repair of aortic lesions and especially aneurysms has continuously developed from the fifties, when it was invented, to the present day. The level of experience of French vascular surgeons in open surgery has remained high since then, explaining rates of morbidity among the lowest in the world, even when dealing with high-risk patients. The number of well trained vascular surgeons and high volume centers, full access of almost all patients to a healthcare of high standard and progress in taking comorbidities into account are the main reasons behind a very low rate of patients with denied open repair already in the late nineteen eighties.

Endovascular repair of aortic lesions was universally welcomed in the nineteens nineties as the last therapeutic revolution. French surgeons were so enthusiastic that they were among the first to push stent-grafts into the market of medical devices. Those first generation devices blazed the rail to present days "star wars" endovascular technology but at the price of failures that prompted mistrust from regulatory and reimbursement authorities. Moreover, this situation in the late nineties cleaved the vascular community into subgroups from endo-fanatics to endo-sceptics. Those subgroups battled endlessly for almost two decades. With the growth of experience, improvement of technology and new generations of surgeons "born with a catheter in hand", indications evolved from a regulatory blockade, where stent-grafts were strictly reserved for high-risk patients, to a more nuanced consensus where patient were

divided into four categories. These four categories are based on the limitations of open surgery on one side and those of endovascular techniques on the other:

- The first category consists of extremely high-risk patients that can benefit from . open surgery nor from endovascular techniques. Although this category is shrinking into a small percentage of cases, there are still a few unfortunate cases that remain beyond the reach of therapy.
- The second category consists of cases fit for open surgery where endovascular solutions are technically impossible or considered overkill. These patients are proposed for open surgery and experience the best long-term results.
- The third category is comprised of high-risk patients who are not eligible for open surgery but whose anatomical conditions are amenable to endovascular techniques. Endovascular surgery is the only choice.
- The fourth category is growing fast: the patient is eligible for an open surgery and the anatomical characteristics of the patient's lesion render it amenable to endovascular techniques. In these situations, it is crucial that the patient is given quality information before offered a choice between open surgery and endovascular repair. Open surgery has the best long term results but there is low but definite risk of immediate complications. Endovascular repair has an unbeatable immediate result but there is a need for a long-term surveillance and there is a low but definite risk of long term failure. Informed choice of the patient is respected even if reasonably oriented by the surgeon.

The lessons taken from this story are that vascular surgery has proven successful at keeping the lead in aortic therapeutics regardless of which technologies are used, marking thus a noticeable difference with other surgical disciplines.

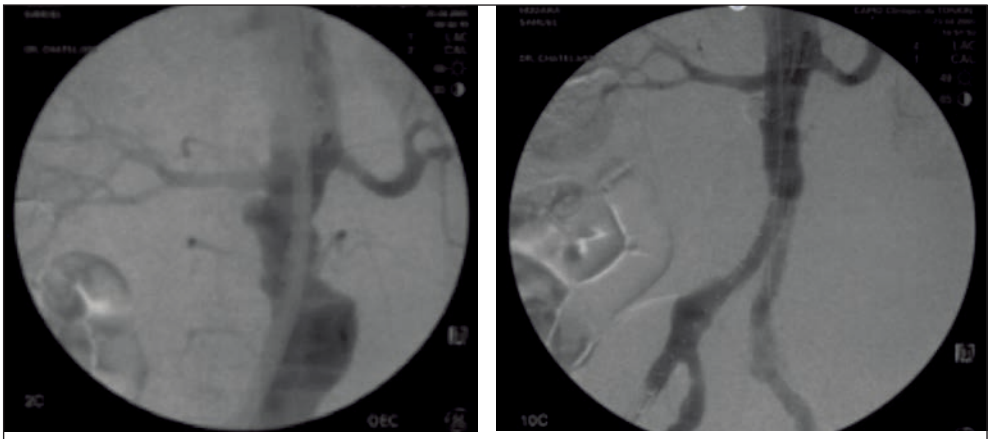
III - Aortic surgery in private centres

By Dr. Philippe Chatelard (Clinique du Tonkin, Lyon)

Every French vascular surgeon receives the same training. After six years of study, a residency (5 years) and a fellowship (3 years) allow to obtain the specialization in vascular surgery, certified by the diploma called the DESC (Diploma of Complementary Specialized Studies) in vascular surgery. Examination by the French College of Vascular Surgery (CLFC) validates the 3 years post internship training in a vascular surgery department.

In France, vascular surgeons can either work in the public sector in a university hospital Centre (CHU) or a regional hospital centrel (CHR) or in the private sector (clinic or private hospital). Of the 480 vascular surgeons practising in France , approximately two-thirds work in the private sector. Aortic surgery is practiced in both sectors with differences depending on the aortic segment.

The conventional treatment (Open repair - OR) of infra-renal abdominal aortic aneurysm (AAA) is routinely performed in private centres. The activity reports of the French College of Vascular Surgery (years 2010 and 2011) show that over 50% of AAA, OR and EVAR are performed in private centers. Due to the advent and rapid development of endovascular surgery for AAA (EVAR) and the addition of stents to the list of reimbursable products and services, today in the private sector about 70% of infra-renal AAA are treated by endovascular treatment (Source: Association for Research in Vascular Surgery Private (ARCHIV). Conventional surgery or endovascular abdominal aorta surgery can be performed in any private hospital structure with a regular activity of vascular surgery, however this is not true for more complex aneurysms. Indeed, aneurysms of the descending thoracic aorta, aneurysms of the abdominal aorta involving the visceral aorta (ATA I, II, III, IV), or isolated aneurysms of the thoracic aorta reaching the segments 0, 1 or 2 require combining gestures associating cardiac and vascular surgeons, and anesthesiologists with experience in the management of these serious illnesses with the need to maintain a stable hemodynamic and drainage of cerebrospinal fluid. In France,



A B

Fig. 1: Intra-operative angiograms showing a proximal complex AAA neck (A), and the final control after embolization (arrow) of the proximal neck aneurysm and EVAR implantation (B).

this activity is mostly performed in the public sector, and in only a dozen of private centers equipped with a cardiovascular intensive care unit and with the ability to treat a large volume of patients. These private centers may receive patients with ruptured aortic aneurysms directly from the emergency medical services (EMS), to be treated according to preoperative imaging results (angio-CT) by conventional or endovascular treatment.

The endovascular treatment of aortic aneurysm (like that of any arterial occlusive disease) is dependent on adapted imagery and materials which are expensive and that all private health structures can afford. For this reason, there are now teams of vascular practitioners in private centers oriented in cardiovascular pathology with heavy technical equipment. Most often these centers are organized in large groups with one owner (Générale de Santé, Capio Santé, Vitalia, etc. , ...). Generally, one center within the group is a referent private cardiovascular centre where vascular surgeons, cardiac surgeons, interventional cardiologists and anesthesiologists experienced in cardiovascular disease are gathered. This combination allows the creation of hybrid rooms associating advanced radiological imaging facilities (angio-CT) within the operating theatre that meet the specifications

for endovascular treatment (fenestrated or branched EVAR) of aneurysms in any location.

Moreover, these groups of private institutions can purchase robotic equipment that allows to perform the laparoscopic AAA conventional treatment (Creech technique) with the easier technical surgical robot acquisition and with 3D vision.

Since surgery of the abdominal aorta (conventional or EVAR) is equally divided between the public and private sectors, aortic surgery in France is routinely performed in private centers. On the other hand, surgery of the thoracic aorta and TAAA (conventional or endovascular) is only performed in a few private centers of excellence in cardiovascular pathology, the public sector having a dominant share of activity in this segment of the aorta.

IV - Thoraco-abdominal aneurysms

by Pr. Stéphan Haulon (Univeristy Hospital, Lille)

The extent of the diseased aorta in patients with thoraco-abdominal aortic aneurysms (TAAA) is described using the Crawford classification. The treatment of the most extensive TAAA (type II) is associated with the highest risk of complications, including paraplegia and visceral ischemia. The indication for treatment of TAAA is generally accepted at a diameter of 6 cm or greater in patients with degenerative or atherosclerotic aneurysms; or at a diameter of 5cm in patients suffering from connective tissue diseases (Marfan, Ehlers-Danlos and Loeys-Dietz syndromes). Patients planned for open or endovascular TAAA repair require a thorough pre-operative cardio-pulmonary and renal evaluation to assess surgical risks.

Surgical procedures (open, hybrid or endovascular) for TAAA are best performed by highly experienced dedicated multidisciplinary teams in high volume centres. Open TAAA surgery often requires extra-corporeal support for distal aorta and organ perfusion to reduce ischemic complications when prolonged cross-

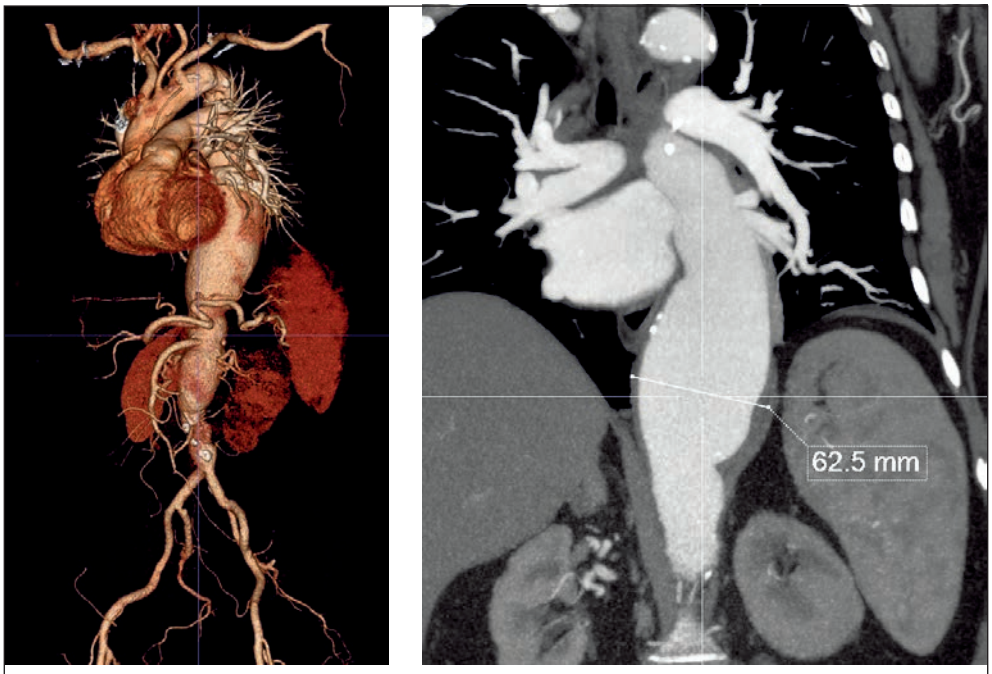


Fig. 2: pre operative CT scan 3dVR (a) and MIP (b) reconstructions of a type 3 TAAA.

clamping is required. Cerebrospinal fluid drainage, optimization of mean aortic arterial pressure, moderate hypothermia, neuro-monitoring and reimplantation of segmental arteries is recommended to prevent spinal cord ischemia. Despite advances in surgical technique and perioperative care, the morbidity and mortality associated with open repair of TAAA remains high (up to 19% and 60% respectively). The hybrid technique (consisting of an open laparotomy and debranching of all of the visceral vessels with reperfusion from a remote inflow site, followed by exclusion of the aneurysm using a tube endograft) and the totally endovascular approach have been advocated as less invasive options. The morbidity and mortality reported with both of these more recent techniques are disappointing, comparable to open surgical repair. However, it should be borne in mind that all of the patients treated with the hybrid and/or the totally endovascular approach were considered high risk and deemed unfit for open surgery. The relatively greater risk of in-hospital death with advancing age and chronic renal failure underlines the importance of not treating patients with a poor physiologic status and limited life expectancy (elderly patients

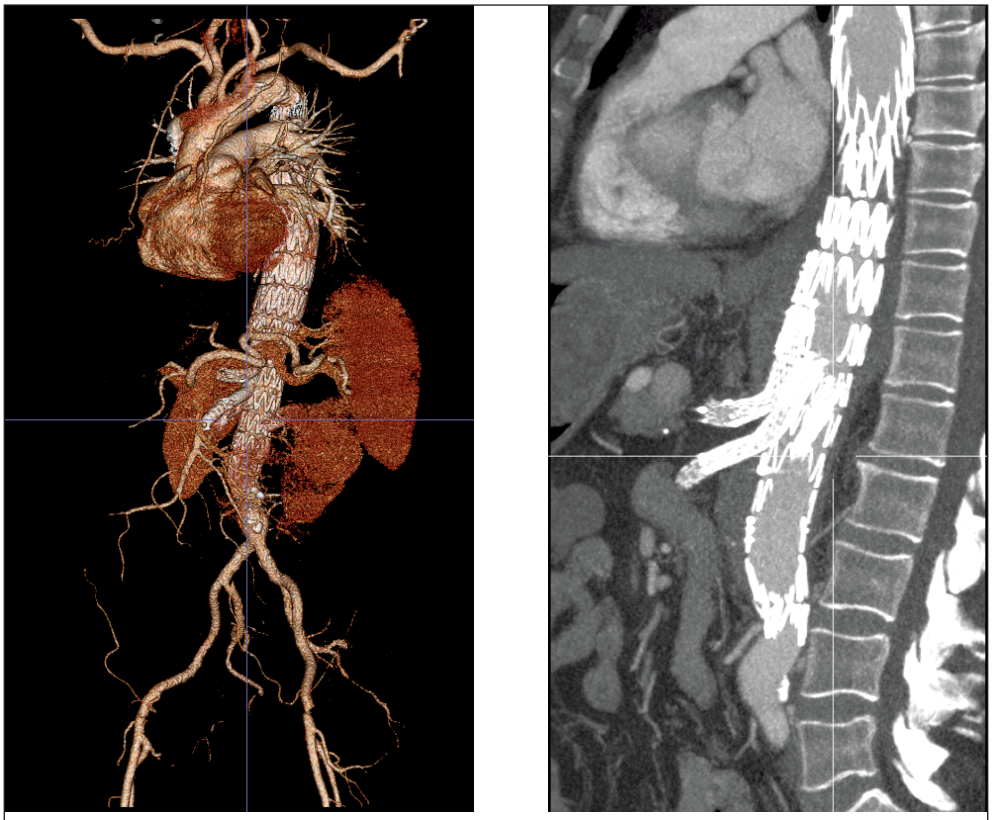


Fig. 3: post operative CT scan 3dVR (a) and MIP (b) reconstructions after implantation of a 4-branch endograft.

with renal, pulmonary, or cardiac comorbidities). In contrast, the encouraging midterm results of the endovascular approach suggest that this technique may have a role with (relatively) unfit patients and could also prove a reasonable alternative to open surgery in fitter patients (Fig. 2 & 3).

Endovascular treatment of TAAA is evolving rapidly and has now reached a degree of maturity in high-volume aortic and endovascular centres. The aortic anatomy is still a limiting factor, but the progress in imaging and device conception has begun to overcome this challenge. Long-term results are awaited to identify the group of patients that will benefit from an endovascular approach. It is mandatory to perform TAAA treatment in high volume centres with expertise in both open and endovascular repair.

VI - Results of prospective studies

by Pr. Jean Pierre Becquemin (University Hospital, Créteil)

Among many aspects of vascular surgery, our group has always had a special interest in aortic aneurisms. AAA remains a major cause of death in industrialized countries and surgical treatment is so far the only option to prevent rupture. Since the introduction of stent grafting, the treatment shifted from open surgery to EVAR. We actively participated in the very first steps of this technology. We published the first French multicenter report of the early Stentor device showing an acceptable mortality rate in a group of high risk patients (1). These results were confirmed by the report of the Vanguard study, with a first generation stent graft (2) We then compared the results of EVAR with open surgery in a retrospective series showing an early lower mortality rate with EVAR, the same midterm results and more reinterventions in the EVAR group. (3;4) We contributed to the creation of the Eurostar database which aimed to determine the main cause of failure after EVAR (5) in order to identify which patients may best benefit from EVAR. Rupture and surgical conversion were mostly seen in patients with large aneurysms and /or endoleaks. Among the causes of endoleak material fatigue was identified as a frequent event which helped companies to improve the devices (6,7). We also investigated the predictive factors of death after open surgery in an attempt to select patients for operation and choice of techniques. We found that renal insufficiency ,age, cardiac past history and chronic obstructive pulmonary disease (COPD) were significantly associated with poorer outcomes (8). We then evaluated second generation stent grafts such as the Zenith Cook graft which showed excellent mid to long term results (9). We also looked at the causes of limb graft occlusions (10) and limb kink (11), the consequences of covering the hypogastric arteries (12), the late impact of EVAR on renal function according to supra or infra renal fixation (13), the risks of colonic ischemia following EVAR or open AAA repair (14) and the respective merits of Duplex and CT scan for EVAR follow-up. Following the early investigations we were confident in the principles of EVAR

and we conducted a national prospective randomized study comparing EVAR and open surgery in good risk patients (ACE Trial). The ACE trial was founded by a grant from the national Programme Hopitalier de Recherche Clinique (PHRC). We found no difference in early and late mortality at the cost of more reinterventions and late ruptures in the EVAR group (15, 16) . We showed however that reinterventions were not associated with an excess of mortality (17). These findings somewhat tempered the enthusiasm of many who advocated EVAR as a first choice in almost all patients with AAA.

Ruptured AAA remains a devastating event with a high mortality rate. Since there are clues that EVAR may lower peri-operative mortality(18,19), we have organized a randomized study (ECAR) again with a PHRC grant, Currently, ecruitment is almost complete and results are awaited (23) .

Thanks to the advancing technology, short neck aneurysms are no longer a contra indication for EVAR. In the case of short neck aneurysms, fenestrated and branched grafts are promising options (20, 21). We organized a prospective multicenter study with an independent assessment of events, thanks to a grant obtained from the STIC (a fund dedicated to innovative and costly technology (18, 20, 21). Compared to the results of open surgery recorded at the national level in the mandatory data base of the Social Security we found little advantage in term of early mortality and complications including paraplegia. However patients treated by fenestrated and branched EVAR were a higher risk groups. We are currently collecting the long-term data to evaluate the results of the technique over a long period of time and to better define which patients could benefit most from this technology. the Chimney technique which is the use of parallel stents in the renal or superior mesenteric artery in combination with EVAR, was also a step forward and is a minimally invasive technique for difficult anatomy(22) with positive results in high-risk patients.

Finally our group launched a national study devoted to small aneurysms comparing best medical treatment (BMT) and BMT plus EVAR. If proved effective this treatment may lower or even stop the growth of AAA .

It is our strong belief that vascular surgeons, especially those working in university hospitals have the duty to comply with the

IDEAL principles: no innovation without evaluation. For the last 25 years, we have worked hard to anticipate and then follow these recommendations and to enlarge the boundaries of our knowledge for the sake of our patients.

VII - Emergent aortic surgery,

by Pr. Yves S. Alimi (University Hospital Nord, Marseille),

Is it possible to use endovascular techniques to treat emergent aortic lesions in order to obtain the same decrease of peri-operative morbidity and mortality as in elective endovascular aortic restorations? Because of the multiplicity of actors involved in the management of patients with aortic rupture or dissection (emergency home and hospital medical care, team of surgeons, radiologists, anaesthesiologists, radiographers, nurses and technicians available at all times , technical means implemented in a very short time), it is clear that the introduction of an endovascular ruptured abdominal aortic aneurysm repair (EVRAR) service has substantial cost implications, in terms of staff, fixed resources and procedure-associated equipment (24). During the last 10 years, 72 patients have been treated by endovascular means for emergent aortic lesions in our department: 53 for thoracic aortic lesions (TAL) and 19 for AAA rupture (RAAA). Endovascular techniques were used in all TAL except one, but only in 36 % of RAAA, due to severe hemodynamic instability making it impossible to achieve a preoperative CT angiography (33 %), anatomical unsuitability (aortic neck too short, too large and/or very angulated, …) (25 %) or unavailable equipment or surgical team (6 %).

Early death rates were 23% for TAL endovascular treatment and 37% for EVRAR, and early re-intervention rates were respectively 13 % and 46 %. As has been seen with elective EVAR practice, advancements in stent-graft design and endovascular techniques have lead to improved outcomes. In our experience, all except one of the last 10 patients were treated under local anaesthesia and bifurcated endografts are now implanted instead of aorto-uniiliac device associated with a fem-fem

bypass. These new improvements lead to a decrease in the early mortality from 50 % in the 8 first patients, to 20 % in the last 10 patients. From our experience of EVRAR and of endovascular TAL treatment, we notice that the majority of patient can be treated with a small range of devices made available by a satisfactory arrangement with a commercial partner. Furthermore, in our centre without cardiac surgery, after the endovascular treatment of TAL, no severe early postoperative complication justifying an emergent transfer to a cardiac department was necessary.

EVRAR is less invasive, reduces surgical stress, reduces hemodynamic instability, and can be achieved with a local or loco-regional anaesthesia. However, evidence from several studies including ours has shown that the aneurysm morphology is significantly more challenging for endovascular techniques in those assessed for RAAA compared with those undergoing elective EVAR. In the literature, reported studies reveal substantial variation in the anatomical inclusion and exclusion criteria employed, with anatomical suitability rates ranging from 34% to100% (25, 26, 27, 28). In particular many groups accept inferior proximal neck anatomy which would preclude patients from elective EVAR, suggesting a trend to be more inclusive in these high risk patients (64). Whilst there is no long term follow-up data available for patients undergoing EVRAR, evidence from elective EVAR would suggest that relaxation of the criteria for anatomical suitability may lead to future problems, such as increased rates of endoleak, graft displacement, complications, re-interventions or the need for open conversion (29,30).

Accumulating published data suggests that endovascular treatment of emergent aortic lesions is feasible in selected patients in institutions with experience with endovascular techniques. Furthermore, in those selected centres, EVRAR and endovascular TAL treatment may also be accompanied by reductions in blood loss, intensive care unit (ICU) stay, and mortality. However, a significant proportion of patients especially with ruptured abdominal aortic aneurysm remain anatomically unsuitable for contemporary endovascular repair, and whilst relaxation of exclusion criteria may make EVRAR feasible, this is likely to increase device and aneurysm related complications. This is the reason why advanced research is necessary to develop new devices specially adapted to emergent aortic implantations

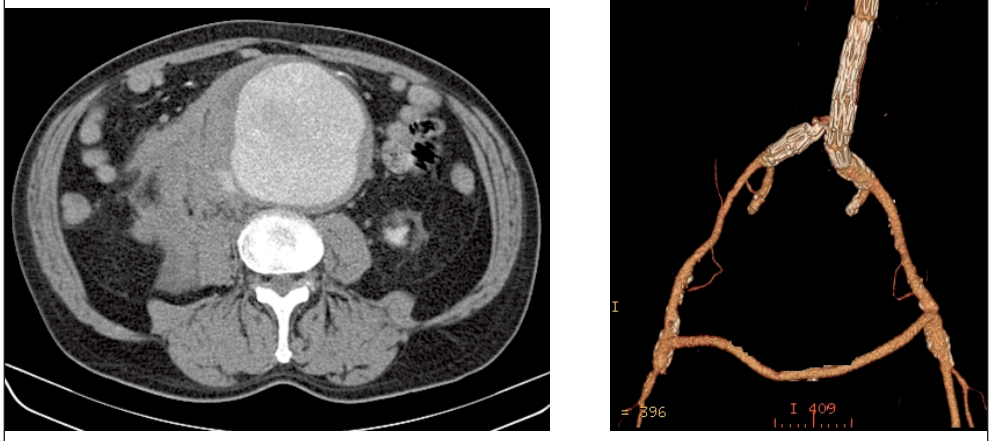


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Fig. 4: A - Pre-operative angiogram performed in emergency for a ruptured AAA, **B -** postoperative Angio-CT after implantation of an aorto-uniiliac EVAR and fem-fem crossover performed under local anaesthesia.

in order to simplify the surgical procedure and to allow a larger inclusion rate of patients.

In conclusion, this article, constructed with 6 different chapters, provides a current overview of different aspects of aortic surgery in France. Beside the six large centres that were asked to present a specific area of their activity here, numerous other French and foreign vascular surgery departments will present a large selection of communications about the modern treatment of aortic disease, during our next meeting (21-24 June, 2013). Our 2013 President, Pr. Roberto Chiesa (Milan) and all the Administration Council of the French Society of Vascular Surgery will be honoured to welcome you, during this scientific and friendly event in Nice, the most Italian French city...

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BICYCLE UNIVERSITY

Alberto Sanna, Sauro Vicini, Dario Colombo, Vittorio Chiesa.
I.R.I.S. Research Unit (e-Services for Life and Health)
Scientific Institute San Raffaele

2012 has been a great year for the bicycle in Italy: it has been confirmed as the new means of transportation for urban mobility and leisure. Bicycle's great potential makes it an ideal instrument for the development of a healthy, ecological and sustainable lifestyle where physical activity and mobility can become essential triggers both for individuals' and society's greater care and attention towards health and the environment.

The Bicycle University has been ideated by IRIS (e-Services for Life and Health), a department of the San Raffaele Hospital of Milan. It's main objective is to promote the correct and safe use of this revolutionary (as well as entertaining) means of transport and to promote users' knowledge and awareness of every aspect of the bicycle's ecosystem, through an interdisciplinary and hands-on approach.

The Bicycle University strives to address the world of the bicycle in a multilayered manner so as to involve the individual in a process of growth - be he/she a cyclist (either beginner or expert, commuter or tourist), the owner of a business (from the bicycle store owner, to the manager of a B&B specialized in housing cyclists), or a public administrator.

The aim of the Bicycle University's hands-on approach is to provide all the tools necessary to widen and deepen cyclists' personal motivation, and general knowledge on bicycles and their conscientious use. At the same time, the Bicycle University also strives to provide professionals with useful suggestions

regarding urban planning, the integration and the supply of technological services, the development of an educational and awareness support system, and technology innovation by providing a meeting-place for end-users and business actors.

The main sections that compose the experimental program of the Bicycle University are as follows:

History of the bicycle

This section will analyze the bicycle's evolution over history, focusing specifically on its role and its use over time. Some of the topics that will be covered include:

- Leonardo Da Vinci and the bicycle.
- The bicycle in the modern age.
- Technology's evolution up to now.
- Sociology and the Social nature of the bicycle.

Man

This section will address the bicycle as instrument for man's wellbeing, from a physical, emotional and social point of view. Some items of this unit will include:

- The bicycle: an instrument for health promotion, recreation and sports, discovery and knowledge.
- Physiology and biomechanical aspects of the bicycle.
- The bicycle and children.
- Cyclist's behavior.
- Cyclist's safety.

The medium

This unit will focus more in depth on the physical and mechanical aspects of the bicycle, as well as the technological evolutions that have changed the medium as well as the accessories. Some topics include:

- Safety through certification.
- Bicycle kinematics.
- E-bikes, technology and bikes.
- HANDS-ON workshops for efficient bicycle management.

The environment

All the aspects related to the interrelations between the cyclist and the external environment as well as other road users will be addressed in this section. This part of the course will also tackle topics such as public administration's planning activities, services (commercial and non) that can be offered to cyclists, especially technological infrastructures and integrated ones. Some items include:

- Road rules and codes.
- Infrastructures for bicycles and cyclists.
- Bicycle insurance and business opportunities and strengths.
- Social networking and the sharing of well-being.

The educational program offered by the Bicycle University is extremely wide but can be directed in such a way so that it can be replicated over time and scaled according to the resources available and the target audience.

The first Bicycle University will be launched during the 5th "Aortic Surgery and Anesthesia - How to do it" International Congress. Such an event was chosen in order to highlight the importance of adopting a more healthy lifestyle through correct physical activity.

Since this first edition of the University will address only a few of the themes previously mentioned, and will focus on forming the cyclist. The topics will be presented through a series of seminars and will focus on the road code, the standards for safety and quality in cycling activity, the potentials of new technologies, the biomechanics of both man and the bicycle, the relationship between the cyclists and the urban environment, cyclist safety and comfort and the use of the bicycle as instrument for man's wellbeing, from a physical, emotional and social point of view. Concurrently, a great deal of time will be dedicated to prepare cyclists from a practical point of view through a series of hands-on labs where they will be taught the foundations for the correct maintenance for their two-wheeled vehicle.

Another feature of the Bicycle University is to exploit the force of Co-Creation. A collaborative approach with the end user will be useful in order to generate improvements of the training process for the following editions. Participants will be able to influence the structure and running of the course with

their feedbacks, as well as have the opportunity of becoming speakers of a personal experience involving the bicycle.

The University could also evolved and develop into a on-line version also suitable for children ("Bicycle University – *for kids!*"). A playful and engaging approach can help children appreciate and understand important and useful messages related to "health literacy" and to motivate them into adopting correctly executed physical activity.

It is with great pleasure that we offer our sincere thanks to the corporate sponsors which have contributed to the organization of the 5th International Congress Aortic Surgery and Anesthesia "How to do it".
Apart from the economic contribution, which is clearly indispensable for the organization of such an event, we thank these companies for their profound and dedicated commitment to developing and continuously improving products without which our daily work would in fact be inconceivable.

We also thank the non-medical companies that have honoured us with their partnership; they offer great examples of Italian excellence in the world.

ab medica spa, founded in 1984 by Aldo Cerruti, President of the Society, works in the sector of medical and electromedical products.

ab medica develops and distributes innovative medical products in the fields of robotics, vascular surgery, anesthesia and reanimation, heart surgery, cardiac interventions, pediatric cardiac interventions, interventional vascular radiology, minimally invasive surgery, dialysis, electrophysiology, gynecology, neuroradiology, neurosurgery, radiology, radiosurgery and urology.

With reference to Anesthesia and Vascular fields, ab medica operates on the market with innovative products like the new generation central venous catheters and new catheters for mini-invasive treatment of the vascular disease.

The mission of ab medica is to make minimally invasive and non-invasive technologies available to the greatest number of people, thus enabling more precise interventions, faster and less painful post-operative recovery. The aim of ab medica has always been the research of advanced medical technologies able to reduce risks, operative trauma and recovery times, thus significantly improving both the quality of care and the quality of life of patients. For these reasons, and thanks to the expertise of its staff, ab medica is considered the best partner for any company introducing innovative products into the Italian hospital system.

ab medica provides solutions to more than 400 hospitals throughout Italy. Furthermore, the company is now committed to broadening its horizons, working outside Italy with branches in some European countries such as Switzerland, Croatia, France and Germany. ab medica also operates in others sectors thanks to partnerships with AETHRA (A TLC srl), a leader in the field of telecommunications, and Telbios spa, a leading company in the field of telemedicine technology and services.

Moreover, since 2004, ab medica is a production Centre and Research & Development scientific park, engaged in the design and realization of a vast range of products and projects ranging from disposable kits for procedures to a broad range of instruments for minimally invasive surgery and committed to ambitious achievements in the fields of stem cells and genomics.

ab medica has its own facilities and laboratories for training, where it regularly organizes seminars to train staff. Each year, ab medica participates in numerous conferences, both in Italy and abroad, to spread knowledge about new technologies, promoting their use through the organization of workshops, seminars and meetings with clients.

Abbott Vascular, a division of Abbott, is a global leader in cardiac and vascular care with market-leading products and an industry-leading pipeline. Headquartered in Northern California, we are committed to advancing patient care by transforming the treatment of vascular disease through medical device innovations, investments in research and development, and physician training and education.
We offer cutting-edge devices for coronary artery disease, peripheral vascular disease, carotid artery disease and structural heart disease. Our flagship product is the market-leading XIENCE V Everolimus Eluting Coronary Stent System a drug eluting stent for the treatment of coronary artery disease. In addition, our comprehensive product portfolio includes bare metal stents, balloon catheters, guide wires and vessel closure devices.

Abbott Vascular: Endovascular Division

Carotid Intervention
First to market with an FDA approved carotid stent and embolic protection system, Abbott Vascular now offers two distinct carotid stents and embolic protection systems, offering physicians a choice in systems to best meet their patients' needs:

- Embolic Protection devices: Emboshield Nav 6 and Accunet
- Stents: Acculink and Accunet

Peripheral Intervention
Abbott Vascular offers a full range of products designed for peripheral intervention including peripheral guide wires, dilatation catheters, guiding catheters and stent grafts.
Advanced technologies are now offered for treating BTK lesions with Armada 14 and Armada 14 XT(PTA Catheter); and the family of guidewires HT Connect (0.018"), HT Command and HT Winn (0.014")

Vessel Closure
A pioneer in closure technologies, Abbott Vascular offers suture-mediated and clip-based vessel closure products designed to facilitate secure closure of the vascular access site after coronary and peripheral catheterizations.

- Starclose SE
- Proglide
- PRostar XL for large holes until 24 Fr

The Company Amnol Chimica Biologica srl operates in the pharmaceutical area and is registered as Pharmaceutical Industry with the Italian Ministry of Health to the Code Number SIS 0821.

AMNOL is associated with Farmindustria, Associazione Industriali Novara and, through its associated Concerns and Controlled Companies, with Federsalus and Associazione Piccola Industria.

AMNOL is certified UNI EN ISO 9001:2008 (registration No. 6860-A).
Range of activities: manufacturing and marketing, import and export of chemical, pharmaceutical, biological products, medical devices, patents, formulas and trademarks concerning the biochemical, biotechnological, pharmaceutical and cosmetic areas.

The Company, established in 1978, had, at the origin, the aim of forming and training staff members in biochemical, biotechnological and pharmaceutical areas. In addition to this activity, during its first twenty-year period the Company developed intense research activities on new biotechnological products, up to realize in partnership with some of the major Pharmaceutical European Companies a number of patents having biochemical, biotechnological and nanotechnological matrices, which are, as of today, extended and utilized in many European Countries and outside Europe.

The year 1998 marked a turning point for AMNOL. The Company underwent restructuring at all levels, involving a new management. Their action, for the period in complete contrast to the logic of the pharmaceutical market, which envisaged exclusive use of synthesis molecules, has concerned all areas of the Company, converting them, and brought to focus its activity on the production and marketing in Italy and abroad of chemical and pharmaceutical products, having strictly biological extractive origin (nutraceuticals), as well as of patents, formulas and trademarks concerning biochemical, biotechnological, nanotechnological areas and dermocosmetics.

In the year 2001, the intense activity of AMNOL in the field of nutraceuticals was crowned with the important international recognition of affiliation as Permanent Member of the prestigious scientific American Organization "American Nutraceutical Association". This Organization sits for its prestigious in the Council of Food and Drug Administration, American government body, worldwide recognized, which chairs the activity of checking and admitting into the flow of commerce of all pharmaceutical, medicinal products and food supplements.

Through a newly acquired Logistic Company, certified HACCP and UNI EN ISO 9001:2000, AMNOL is part of a process of logistics and qualitative-quantitative optimization system. As a consequence of this company transaction, AMNOL can distribute its products using the "cold chain", monitoring at the same time stocks and distribution steps and making sure of the traceability of goods.

APTUS ENDOSYSTEMS

Headquartered in Sunnyvale, California, **Aptus Endosystems** is a privately held medical device company engaged in developing and manufacturing advanced technology for endovascular aneurysm repair (EVAR).

Abdominal aortic aneurysms (AAA) can be life-threatening if left untreated. Open surgical repair of aortic aneurysms, a treatment option that has been practiced for decades, has high procedure related mortality rates and long patient recovery times. However, open surgical repair provides patients with a very durable treatment that requires little to no follow-up or need for secondary interventions. EVAR, which has been in practice since the 1990's, is a minimally invasive catheter based AAA treatment that has significantly reduced procedure related mortality and patient recovery time—but requires annual monitoring and may need additional interventions in the years after treatment.

Aptus Endosystems is focused on developing innovative technologies to transform EVAR, empowering physicians to perform minimally invasive aneurysm repair while still providing the control and potential **long term durability** of open surgical repair. The company's initial product offering to accomplish this includes a unique endograft – **the Fortevo™ AAA Endograft System**, and innovative **helical anchor technology** – **the HeliFX™ Aortic Securement System**. The advent of the HeliFX System pioneers a new endovascular capability that has potential applications beyond AAA repair as the company undertakes further product development initiatives.
The **HeliFX** System is the world's first available endovascular anchoring system and is indicated for patients whose AAA endografts are at risk of, or already experienced device migration or Type 1 endoleak. The HeliFX System implant is a helical EndoAnchor that's designed to replicate the fixation and sealing of a surgical anastomosis through an endovascular method, and therefore has the potential to improve the long term durability and effectiveness of EVAR.

HeliFX is the only product that has demonstrated compatibility with the leading AAA endografts – the Cook Zenith, Gore Excluder, and Medtronic Endurant, Talent, and AneuRx. HeliFX can be used in both, primary endograft implantation procedures and revision procedures.

B. Braun, a globally operating family owned company with more than 29.000 employees, offers hospitals and practitioners all over the world a wide range of products and services.

With a large network of subsidiaries in more than 50 countries in the world, the company has tradition and competence in fields such as Surgery, Cardiology, Anesthesiology, Intensive Care Medicine. More than 45.000 selling Products can cover all needs regarding the Hospital, Private Practice and Home care.

Setting knowledge as the core value, B. Braun is worldwide devoted to the Scientific updating of its clients through the Global Network of the Aesculap Academy.

As one of the world's leading cardiovascular medical device companies, with several million implanted devices, BIOTRONIK is represented in over 100 countries with its global workforce of more than 5600 employees.

Known for having its fingers on the pulse of the medical community, BIOTRONIK assesses the challenges physicians face and provides the best solution for all phases of patient care, ranging from diagnosis and treatment to patient management.

Quality, innovation and clinical excellence define BIOTRONIK and its growing success – and deliver confidence and peace of mind to physicians and their patients worldwide since 1963.

Our motto is "Excellence for Life" BIOTRONIK Italia was born on 2007 distributing the Cardiovascular Intervention and Electrophysiology products and on 2010 extended his activities to CRM products, with a sale network covering the whole national territory.

Werfen Group | Bolton Medical Italy

Bolton Medical is a subsidiary of the giant international health care corporation: **Werfen Group**, which is comprised of a number of leading manufacturing and distribution companies in the field of medicine. The Werfen Group is active worldwide in several medical areas such as: in-vitro diagnostics, medical devices and scientific instruments for industry and research.

Bolton Medical was founded in 1999 specifically for the distribution of cardio vascular products in Europe, U.S. and Singapore. Since 2005 Bolton Medical has focused solely on **endovascular devices**.

The company has developed a wide experience and is respected as a reliable supplier of high quality medical products with innovative design features in endovascular therapies.

Bolton Medical is dedicated to bring the best endovascular devices to the market with a commitment to develop future technologies to help physicians provide the best medical treatment possible.

www.boltonmedical.it

Boston Scientific

Boston Scientific (NYSE: BSX) is a worldwide developer, manufacturer and marketer of medical devices with approximately 25,000 employees and revenue of $7.622 billion in 2011. For more than 30 years, Boston Scientific has advanced the practice of less-invasive medicine by providing a broad and deep portfolio of innovative products, technologies and services across a wide range of medical specialties. The Company's products help physicians and other medical professionals improve their patients' quality of life by providing alternatives to surgery. Boston Scientific's mission is to improve the quality of patient care and the productivity of health care delivery through the development and advocacy of less-invasive medical devices and procedures. This is accomplished through the continuing refinement of existing products and procedures and the investigation and development of new technologies which can reduce risk, trauma, cost, procedure time and the need for aftercare.

CA-MI was founded from Mr. Mario Attolini in the 1984.

Since the beginning, CA-MI has been manufacturing in Italy and distributing world-wide electro medical equipment for Hospital and Home-Care as nebulizer and surgical suction units.

We present our line of products: Kamila, graduated compression stockings, support and medical, a complete and full line of compression stockings made in Italy according to the highest parameters of technology and quality, manufactured from more the 50 years of experienced technicians.

This supreme quality and wide range of products has recently achieved the RAL certificate.

This line of products has a good successful on the Italian market and have recently been presented at the international market of "Reha Technique" in Leipzig and "Medica" in Düsseldorf, to follow our best customers.

Cardiatis S.A., headquartered in Isnes, Belgium, is an innovative medical technology company with a focus on the research and development of a new endoluminal **"flow modulating device"** for endovascular repair of arterial aneurysms.

Primary purpose of endovascular aneurysm repair is to prevent death from aneurysm rupture. An aneurysm ruptures when the forces acting on its wall become greater than the wall's tensile strength. These forces are directly connected to the presence of vortex inside aneurysm sac.
Current endovascular approach to treat aortic and peripheral aneurysm relies on the use of covered stents that mechanically blocks the aneurysm in an effort to eliminate it from circulation.
Despite going through several generational improvements covered stents, or stent grafts, are prone to leaks which tend to increase pressure within the aneurismal sac. Over 35% of aneurysms treated with covered stents continue to enlarge. Moreover the presence of collateral vessels represent a big technical issue.

The Cardiatis Multilyer Stent is a bare, self-expanding, braided wire tube of metallic cobalt alloy (Phynox) wire constructed in multiple interconnected layers.
Cardiatis 3-dimensional layers modulate the flow inside aneurysm sac.
The device does not allow the vortex to be formed, redirecting the flow along the wall in the same direction as the systemic pressure flow. The aneurysm wall is therefore protected from rupture.
Flow modulation is independent from aneurysm anatomy and dimension and it is not affected by the presence of collateral vessels.
In an aneurysm without collaterals flow velocity is reduced up to 88%, this allowing physiological organized thrombus to form.
In saccular/fusiform aneurysm with collateral, the flow is channeled to the branch owing to the Venturi effect, wich induces the aneurysm wall retraction.

The Cardiatis Multilayer Stent is intended for the treatment of aortic aneurysms (from sublclavian up to carrefour) and peripheral aneurysms (lower limbs arteries, visceral arteries, subclavian and carotid arteries).

CEA S.p.A.
PRESIDI MEDICO-CHIRURGICI

CEA is a dynamic Company who is working in a competitive and professional way in distributing in the hospital areas medical devices, surgical instruments and apparatus of the most prestigious Companies.

The aim of CEA is to improve constantly the co-operation with the utilizers using new technologies at the lowest costs.

Our company, on the market since 1967, has a network of specialized promoters and product's salers supported by our commercial team in order to offer an efficient and professional service.

The registered office is in Milan where there is the Administrative Dept. along with a show room.
The head office is in Segrate (Milano Oltre 2) where there is a warehouse specifically conceived for the stock, logistic and distribution of medical devices.

CEA is a certified company UNI EN ISO 9001:2008 and UNI EN ISO 13485:2004.

CID (Carbostent & Implantable Devices) is an independent company with a wealth of background and expertise gained in over a decade of research, development and proven clinical experience in the treatment of vascular disease. CID is dedicated to contributing to human welfare by improving the quality of patient care and after-care through the development of innovative, minimally invasive implantable devices, procedures and therapies.

The renewed portfolio includes PTA balloons and a wide range of stent (balloon and self-expandable) covered with the innovative Bio Inducer Surface (iCarbofilm).

Patients need better, safer treatment and doctors need simpler, more effective options. Since 1963, Cook Medical has been working with physicians to create simple solutions to hard problems.

Cook is a family-owned company with more than 10,000 employees who work to do what's best for patients.

What started with three products has grown into a global company serving 135 countries across the Americas, Europe, Asia, Africa and Australia, and offering 16,000+ products. Today, we manufacture and combine medical devices, drugs, biologic grafts and cell therapies to serve more than 41 medical specialties.

Covidien is part of the local fabric of the communities in which we operate around the world. Our success is made possible through the dedication of our 41,000 employees, nearly two-thirds of whom work in 53 manufacturing facilities located in 16 countries. Every day, over 5,000 Covidien sales representatives meet the needs of our customers in more than 65 countries. In all, our Company derives over 45% of its sales from outside the United States.

At Covidien, we're passionate about making doctors, nurses, pharmacists and other medical professionals as effective as they can be. Through ongoing collaboration with these medical professionals and healthcare organizations, we identify clinical needs and translate them into proven products and procedures. Our industry-leading brands – including Kendall, Mallinckrodt, Nellcor, Puritan-Bennett and Valleylab – are known and respected worldwide for uncompromising quality.

Edwards Lifesciences is the global leader in the science of heart valves and hemodynamic monitoring. Driven by a passion to help patients, the company partners with clinicians to develop innovative technologies in the areas of structural heart disease and critical care monitoring that enable them to save and enhance lives.

Edwards Lifesciences' roots date to 1958, when Miles "Lowell" Edwards set out to build the first artificial heart.

Our spirit of innovation remains central to Edwards today as the number of patients requiring treatment for cardiovascular disease and critical illnesses is increasing dramatically, and further growth is expected in the future. Several factors are feeding this dynamic: an aging population, high incidences of rheumatic fever in developing nations, and improved diagnostic techniques that allow physicians to detect problems sooner.

Today, we continue to lead the field of tissue replacement heart valves and repair products, which help treat the approximately 300,000 patients worldwide each year who undergo heart valve procedures.

With more than 50 years of experience, we have grown into a global company, with a presence in approximately 100 countries and approximately 7,000 employees around the world. Each one of them is dedicated to furthering Lowell's original vision to help clinicians, patients and their families work together as a united community fighting cardiovascular disease and critical illnesses.

Our board of directors and executive leadership team are guided by Our Credo and are passionate about helping patients and meeting the needs of all of our stakeholders. These executives serve as leaders not only for our employees, but also for the medical device industry and our global communities.

Edwards Lifesciences partners with physicians to innovate products designed to help patients live longer, healthier and more productive lives. We focus on medical technologies that address large and growing patient populations in which there are significant unmet clinical needs, such as structural heart disease and critical care monitoring.

As part of Edwards Lifesciences' commitment to improving the quality of life around the world, we provide philanthropic assistance to important health-related and community causes. In 2004, we established The Edwards Lifesciences Fund to support advancements in knowledge and improvements in quality of life, focusing primarily upon cardiovascular disease, education and the communities where our employees live and work. The Fund's mission is fulfilled by making grants to qualified charitable organizations.

ENDOLOGIX

Endologix develops minimally invasive treatments for aortic disorders including the AFX™ Endovascular AAA System in the U.S. and Europe, and IntuiTrak™ Endovascular AAA System in other regions. Future technologies include the Ventana™ Fenestrated Stent Graft System, designed to treat juxtarenal and pararenal aneurysms, and the Nellix™ EndoVascular Aneurysm Sealing System, a novel treatment using biostable polymer to seal the aneurysm.

Website: www.endologix.com

Email: customerservice@endologix.com

The W. L. Gore & Associates Medical Products Division has provided creative therapeutic solutions to complex medical problems for more than three decades. During that time, more than 25 million innovative Gore Medical Devices have been implanted, saving and improving the quality of lives worldwide. The extensive Gore Medical family of products includes vascular grafts, endovascular and interventional devices, surgical meshes for hernia repair and sutures for use in vascular, cardiac and general surgery.

The company's technical agility makes it a leader in diverse consumer, industrial, electronic, medical and surgical markets. At Gore, innovation is fostered by a unique corporate culture that encourages problem solving and inventiveness—relying on teamwork and direct communication rather than chains of command. The culture is a key factor in the creation of Gore's innovative and reliable products. It's also a reason Gore has ranked repeatedly among the "Best Companies to Work For."

We take our reputation for product leadership seriously, continually delivering new products and better solutions to the marketplaces of the world.

Italfarmaco is a European pharmaceutical group focused on R&D, manufacturing and commercialization of ethical products. In early 90s, the company has started a process of international expansion, that led to the creation of fully owned subsidiaries such as Spain, Portugal, Greece, Nordic Countries, Turkey, Russia, Morocco, Chile and Peru. Since 2003, Italfarmaco has entered the French market through Effik, a Company specialised in Women Health which is now part of the Group. The total turnover in 2011 was over €470 million. The Group has developed over the years a marketing expertise in a broad range of therapeutic areas, such as cardiovascular, immuno-oncology/supportive care, dermatology, gynaecology, orthopedics and CNS. Italfarmaco has several Partnerships and agreements in place with primary pharmaceutical companies, such as Chugai/Sanofi-Aventis, Astellas, Otsuka, Bayer AG, GSK, Helsinn, Janssen, Novartis, Pfizer and Servier.

Italfarmaco is active in R&D and specifically in immuno-oncology (givinostat/ ITF 2357), infectious diseases (ITF 2534), women health projects and new liquid formulations of CNS products (paroxetine, venlafaxine, zolpidem, etc.).

Johnson & Johnson
MEDICAL S.P.A.

Johnson & Johnson Medical Spa, market leader company, distributes and markets medical devices and technologies intended to improve individuals' quality of life.

It is organized into several business segments comprised of franchises and therapeutic categories.

The Medical Devices and Diagnostics segment produces a broad range of innovative products used primarily by health care professionals in the fields of orthopaedics, neurovascular, surgery, vision care, diabetes care, infection prevention, diagnostics, cardiovascular disease, sports medicine, and aesthetics. This segment is comprised of our Global Medical Solutions, Global Orthopaedics and Global Surgery Groups.

JOTEC®
SOLUTIONS FOR VASCULAR DISEASE

JOTEC – German specialist for treatment of peripheral and aortic vascular disease

JOTEC a German medical device company provides Vascular and Cardiac Surgeons, Interventional Radiologists and Cardiologists with *SOLUTIONS FOR VASCULAR DISEASE*. According to the highest standards of innovation and quality JOTEC develops, manufactures and markets medical devices for peripheral and aortic vascular disease. The product portfolio comprises surgical grafts, endovascular implants and accessories. The company's headquarters are based in Hechingen, Germany. JOTEC employs about 160 people.

The company's core competence incorporates ePTFE (e.g. extrusion, expansion) and Polyester (e.g. weaving, knitting) processing as well as coating techniques (collagen, heparin) for the vascular graft lines: **FlowLine Bipore** / **FlowLine Bipore Heparin** ePTFE grafts and **FlowWeave** / **FlowNit** polyester grafts. Extensive Nitinol know-how as well as catheter technology for delivery systems constitute the strength for the interventional product line. The whole production facility has been established in Hechingen, Germany, and is based on cutting edge technology.

Following the market trends towards minimal invasive treatments JOTEC launched its first endovascular product in May 2004: **E-vita** – a thoracic stentgraft system. Subsequently the product portfolio has steadily extended by the **E-vita abdominal** stentgraft system, the **E-XL** aortic stent and **E-vita open** – a unique hybrid stentgraft for optimized Elephant Trunk procedure. Interventional accessories such as the **E-wire** extra stiff guide wire, the **E-asy plus** introducer sheath and the **E-xpand** balloon catheter round off the picture.

In the recent years JOTEC has built up direct sales channel in Germany, Italy, Poland, Spain, and Switzerland and has reacted to the superior business growth in these countries. In addition, JOTEC has installed a strong partnership to distribution partners located at the entire world. Physicians can rely on a direct communication to JOTEC and can expect best service from highly dedicated employees to support their individual needs.
By continuous product improvements and new developments JOTEC aims to offer best possible solutions for both – patient and physician.

www.jotec.com

Levi BioTech is leader in the cardiovascular field, dedicated, wide-ranging, specialized, and professional. We excel in the cardiovascular field selling specialty products such heart valves, TAVI Trans apical Heart valves, Injectable pulmonary valve, Mitral repair system, heart failure devices, open heart cannula, cardioplegia products, pediatric products, pericardial, patches, beating heart products, biological glue, hemostatic systems and more including new technologies and techniques.

Our target is to carry on focusing and growing in cardiovascular field with extra efforts given by our newfound and higher potentials. We provide national coverage on the field with direct agents, and independent agents and sub-distributors. All these people have extensive experience, good relationships, and good introduction in all the most highly specialized departments. Our sales force is backed up with a recently reorganized staff, which includes, Product Specialists, Medical Advisor, Sales Manager. This has shown extremely encouraging results, reinforcing our commitment to reinvest every Euro of profit to strengthen the company. Our product lines reflect the aim of our company, Quality & Service.

We remain committed to additional investments in time, efforts and capital with the goal of becoming the utmost top service to our existing and future customers as well as the cardiac surgeon's top choice.

MAQUET
GETINGE GROUP

As a trusted partner for hospitals and clinicians since 1838, Maquet is a global leader in medical systems that advance surgical interventions, cardiovascular procedures and critical care. Maquet develops and designs innovative products and therapeutic applications for the operating room, hybrid OR/cathlab, intensive care unit, and patient transport within acute care hospitals, improving outcomes and quality of life for patients.

Maquet is a subsidiary of the publicly listed Swedish Getinge Group. In 2011, Maquet generated more than half of the company's annual revenue of 2.4 billion Euros. The company has 13,000 employees worldwide, including 6,000 Maquet employees in 50 international sales and service organizations, as well as a network of 280 sales representatives. For more information please visit www.maquet.com and www.getingegroup.com.

MAQUET – The Gold Standard.

MAQUET has three specialty Divisions**:**

- Surgical Workplaces - Equipment for surgical workplaces
- Critical Care - Anesthesia system and workstations for intensive care
- Cardiovascular - Medical devices, equipment and instruments for counterpulsation therapy, cardiac and vascular surgery

As a result of the acquisition of Datascope by Getinge AB, the MAQUET Cardiovascular product portfolio now includes the market leading intra-aortic balloon pump systems as well as the vascular prosthetic business from Datascope. This combination allows us to provide a more complete product offering that improves clinical outcomes and make a difference in the lives of the patients.

Medcomp Srl, was founded by many years' experience people few years ago, works in the medical field and distributes the following prestige and quality brands in Italy:

- "Avitene™" (CR Bard brand) - Microfibrillar Collagen Hemostat and Ultrafoam™ Collagen Sponge for all specialized surgical procedures;
- "Bard Medical" - Silicone Channel Drain, and Closed Wound Suction System;
- "Lina Medical" - Danish Company producer of innovative single use laparoscopy products and surgical Smoke Evacuation System.

The Medcomp sales team is specialized in promoting and supporting innovative products in order to match the surgical needs.
Medcomp is mainly focused on Gynecology, Surgery, Urology and Vascular.

medi. I feel better.

Tradition and innovation
The family company with almost 100 years' tradition doesn't see itself as just a manufacturer: medi's aim is to make a major contribution to improving and maintaining the quality of life for people.

Key figures
medi consists of different divisions and departments.
medi has 320 product brands and patents.
medi owns 17 branch offices, (Germany and USA have their own production sites).
medi exports to 90 countries.

Corporate Division Lifestyle
CEP: the sports brand from medi
Every athlete profits from compression sportswear with the patented compression "made by medi". These garments help athletes to a measurable increase in performance and a more rapid regeneration.

Corporate Division Medical
medi produces medical aids for different clinical pictures and life situations. Medical compression stockings for patients with venous and oedematous disorders have made medi one of the world leaders in this field.
Modern leg prostheses, the well-known white hospital "bed stockings", which are donned as a precaution against thromboses, and the compression garments worn after plastic and aesthetic surgery as much a part of the product range.
medi Phlebology: products for treating venous and lymphatic diseases, travel and active socks.
medi Orthopaedics: supports and braces for treating joints.
medi Prosthetics: provision of leg prostheses.
medi Hospital: thrombosis prophylaxis stockings, interdepartmental integration of products for hospital treatment and provision of services for hospitals.

medi Phlebology - Venous diseases are widespread diseases
Medical compression stockings is the basic therapy for venous disease.
People with unusual anatomic proportions, e.g. with **lymphoedema**, are also in the best of hands with medi.

medi Hospital - Thrombosis prophylaxis in hospital
For over three million bed-ridden patients every year, medi's medical thrombosis prophylaxis stockings present an effective measure for preventing a blood clot or even a life-threatening pulmonary embolism Thrombosis prophylaxis in hospital.

medi Prosthetics - Modern leg prostheses
People who have lost their legs by amputation can also count on medi:
In the process, medi relies on high-tech materials such as carbon, on an ingenious, robust mechanism and on the exclusive range of shoes.
According to a nationwide survey, approx. 75% of all amputees suffer from phantom pain. Powerful drugs are the usual treatment. However, they provide no lasting treatment success and have marked side effects.
The solution: the medi silicon liners.

www.medi-italia.it

At Medtronic, we're changing the face of chronic disease. By working closely with physicians around the world, we create therapies to help patients do things they never thought possible.

Our medical technologies help make it possible for millions of people to resume everyday activities, return to work, and live better, longer. We're able to do this with the help of some very special people around the world: 38,000 dedicated employees who share a passionate purpose to improve lives, thousands of medical professionals who share their insights and ideas, and hundreds of advocacy associations that help us share information so people with debilitating diseases know relief is possible.

CardioVascular is Medtronic's third-largest business. As hospitals increasingly encourage collaboration between cardiovascular specialties, Medtronic continues to serve as a key resource. Our therapies span the major specialties of vascular surgery, cardiac surgery and interventional cardiology and radiology.

Our products, developed in collaboration with leading physicians, are used to reduce the potentially debilitating effects of coronary, aortic, peripheral and structural heart disease. These products include:

Stent grafts to treat aortic aneurysms. Their rupture leads to more than 15,000 deaths in the United States alone. Through our collaboration with the scientific societies all across the world, we helped to develop abdominal aortic aneurysm (AAA) screenings to help detect this potentially life-threatening condition, which can be treated with our minimally invasive therapies.

Heart valves and valve repair technology to treat congenital heart defects and valve disease. We also continually work to develop minimally invasive approaches to traditional full open-chest heart surgery for valve replacement and repair.

Open-heart and coronary bypass graft products to restore blood flow to the heart.

We're continually making our products simpler for surgeons to use and easier on patients. For example, we're now on the 10th generation of our Octopus® Stabilizer, which holds arteries in place so a surgeon can operate on a beating heart.

Renal denervation technology. Medtronic offers a novel and innovative therapy for treatment-resistant hypertension. The SymplicityTM renal denervation system is a new, safe, and effective tool for healthcare professionals to use for patients who have been unable to achieve target blood pressure levels despite multiple prescription medications, and are considered treatment-resistant.

Angioplasty technologies to treat arteries that are blocked by atherosclerotic plaque and restore blood flow. Our highest-profile products in this area are the In.Pact Drug Eluting Balloons and the Resolute Integrity Zotarolimus-Eluting Coronary Stent System.

Nutricia is a specialised healthcare division of the food company Danone, focussed exclusively on research-based scientifically-proven nutrition, developed to meet the needs of patients and individuals for whom a normal diet is not sufficient or possible.

Nutricia's mission is to lead the use of advanced medical nutrition in disease management, and in this way to extend and complete Danone's mission to bring health through food to the greatest number of people. Nutricia has been a specialised division of the international food company Danone since 2007.

Nutricia has been the pioneer of Advanced Medical Nutrition in Europe, and is rapidly expanding its services for patients across the world. We have developed a broad and unique portfolio of products for many classes of patients, and we seek to provide solutions and services wherever nutritional intervention can be shown to improve clinical outcomes. In partnership with doctors, healthcare professionals and caregivers, we work to make a real difference in people's lives by speeding recovery and encouraging independence.

Products developed by our ground-breaking science teams have long been used to help people who cannot eat, who lack specific nutrients or who have special nutritional needs. The specialised nutrition of today can also help manage certain diseases, or even delay the progression of disease in patients. Our ambition is to deliver only proven benefits through nutrition, as an integral part of disease management.

Serom Medical Technology S.r.l. is a very dynamic company in the medical devices field. It distributes a wide range of medical products in the whole Italian territory concentrating its attention to specific sectors of surgery and medicine such as vascular surgery and endosurgery, cardiosurgery, interventional radiology and cardiology.

Its primary objective is to offer innovative solutions with advanced technology and high quality products to the medical community, supporting its sale activity with a very professional service.

The Product Specialists are very well trained people and the sale force is very active and present in order to guarantee the daily contact with the clients. In the office, based in Rome, there are people working to support the sale activity on the field offering answers and solutions in a very quick, serious and efficient way.

www.serom.com

S.I.D.EM. S.p.A. – Prodotti Elettromedicali

Sidem is on the medical market for 30 years as a distributor of medical products.

Reliability and efficiency have made S.I.D.E.M. a certified Philips's distributor. SIDEM technical area provides customer support both on site and bench site on Philips products. It consists of expert engineer, well trained and equipped with appropriate tools to maintain the products in the optimal working conditions.

SIMAD
X-RAY MEDICAL TECHNOLOGY

A Sago Medica Company

SIMAD S.r.l. X-ray Medical Technology was born in Italy in 1989 to design and create, exclusively mobile X-Ray Systems for interventional radiology.

YOUR NEED IS OUR SPECIALITY

Simad products provide avant-garde under technological point of view and distinguish themselves for innovation, upgradeability and safety. Simad makes concrete your ideas and the best of technology, realizing mobile radiological equipments which improve activities in operating rooms. The major specialization, passion and results challenge Simad to dare in the direction of new targets and customer fulfillment.

REDUCED X-RAY DOSE, CARING FOR YOUR OWN SAFETY

Simad research is oriented to reduce and restrain x-ray dose. Earlier than our competitors, SIMAD has provided concrete evidences of the possibilities and advantages of working by using seven times less dose and providing the major image quality and diagnostic results. This dose cutback is an immeasurably valuable achievement and provide added value in terms of safety to the patient and operators. Moreover it extends the lifespan of the equipment and reduces overheating risks of rx tube and monobloc.

APPLYING TECHNOLOGY TO ALL CONCRETE NEEDS OF THE END-USER.

Research and Development of SIMAD products is oriented to the real need of the user and patient. The product is developed day by day in radio-surgical theatres from where we receive systematic feedbacks which provide SIMAD of the right experience to develop operative solutions to operative necessities.

UPGRADABLE SOLUTIONS

Clinical evolution requires upgradeable systems able to adequate, match and fullfill multiple needs of the Customer. SIMAD manufacturing is totally focused in realizing products which can do this.

THE SIMAD EDUCATION CENTER

The Training courses arranged by Simad and also developed in collaboration with the most scientifically accredited Italian Associations, are studied to develop the right competences useful to operators.

Such as the "Training course for radiology-protection in operating theatres". This course explains in a manual the right positioning of mobile c-arm x-ray imaging systems in adherence to principles of radiation protection. This project underline the target of Simad: being specialized not only in C-Arm manufacturing but also in Surgery Team Care in daily activities. Particular attention is given to the Patient Safety which is becoming more and more important in onward oriented hospitals and clinics.

SORIN GROUP (www.sorin.com) is a global medical device company and a leader in the treatment of cardiovascular diseases.
The Company develops, manufactures and markets medical technologies for cardiac surgery and for the treatment of cardiac rhythm disorders.

With over 3,750 employees worldwide, the company focuses on three major therapeutic areas:

- Cardiopulmonary bypass
- Cardiac rhythm management (CRM)
- Heart valve repair and replacement

While headquartered in Milan, Italy and listed on the Milan Stock Exchange, SORIN GROUP is a global company. Each year, more than one million patients are treated with SORIN GROUP devices in more than 80 countries. Our life-saving products are in more than 5,000 hospitals worldwide.

SORIN GROUP's success is built around its cardiovascular products and related therapeutic services. Through continued expansion and development, SORIN GROUP has established itself as a market leader within cardiovascular device technology. The Company is the world leader in cardiopulmonary bypass (extracorporeal circulation and autotransfusion), holds a strong market position in heart valves and is a growing player in the cardiac rhythm management market. Despite challenging market conditions, SORIN GROUP strengthened its global leadership position, especially in the cardiopulmonary arena. Bolstered by the drive to continuously improve patient care, SORIN GROUP is committed to sustaining its longer-term growth strategy with further geographic expansion initiatives and additional investments in innovation.
SORIN GROUP's devices are built to save lives. Across the globe we strive for the highest levels of performance and quality while maintaining rigorous standards of ethics in our business practices.

TEKMED
INSTRUMENTS FOR LIFE

"OUR COMMITMENT IS THE SEARCH FOR GLOBAL TECHNOLOGICAL INNOVATION IN THE MEDICAL AND SURGICAL FIELDS IN ORDER TO OFFER IDEAS AND INSTRUMENTS FOR IMPROVED QUALITY OF LIFE."
- FULVIO ALBANO -

Founded in 1977 and based on quality, innovation and customer satisfaction, Tekmed Instruments S.p.A. has been operating in the medical devices sector for over thirty-five years providing, as exclusive distributor over the Italian territory, for innovative and technologically advanced products.
Based on a thorough careful market analysis and international technological developments, Tekmed has gradually focused its activities on specific reference sectors and found its own targets in the following ones:

- neurosurgery
- neurotraumatology
- intensive care
- general surgery
- neurology & neurophisiology
- image guided surgery
- orthopedics
- radiotherapy

This choice has led Tekmed to improve its structure along the years, by investments in sales & marketing as well as in the service area, through the collaboration of bioengineers and highly qualified personnel.
Strategically located in Milan, where top management is headquartered, Tekmed operates throughout Italy via widespread commercial network covering entire country.
Tekmed Instruments S.p.A. applies IT procedures to manage orders, invoicing, administration and its warehouse, that is specialized in the management of items and equipment destined to the hospital sector.
Maintenance of the equipment distributed on the Italian market is made by Tekmed Instruments' post-sales service assistance.
Tekmed Instruments S.p.A. is certified ISO 9001:2008.

Teleflex

Teleflex is a leading global provider of specialty medical devices used for diagnostic and therapeutic procedures in critical care, urology and surgery.

Our mission is to provide solutions that enable healthcare providers to improve outcomes and enhance patient and provider safety.

Every day, hospitals, clinicians and patients rely on our high quality medical devices. Dedicated to meet the challenges of a changing healthcare landscape, our products are designed to cost effectively provide clinical benefits.

But good is not enough.

Committed to partnering with healthcare providers, we continuously reinforce our product development. With a strong customer focus, it is our aim to provide optimal solutions with every single product we manufacture.

The problem of hospital acquired infections is a challenging issue healthcare professionals currently address. That's why Teleflex has launched an initiative to meet the associated requirements by providing innovative products and services that enhance the safety, efficacy, and quality of healthcare.

More often than not, it's the small details, that create the base for great improvements.

This is especially true of Teleflex products, nearly all of which feature some innovation that may be small but is often ground-breaking.

Terumo
Contributing to society through healthcare
The physicians, led by Dr. Shibasaburo Kitasato, that founded Terumo in 1921 to design and make superior thermometers had a larger goal: healthier living abetted by superior medical technology. The will to contribute to society through better health care still drives every Terumo employee. In the 21st century, Terumo is rising to the challenge of making health care more accessible and suitable to a range of needs, wherever in the world we possibly can.

Terumo Angiographic & Endovascular Interventional Systems offers minimally invasive therapies for patients suffering from vascular disease. With our leading edge access and delivery systems, interventional and angiographic procedures can be performed in a safer, faster and more comfortable way.

Pioneering the hydrophilic concept for high performance medical devices, we offer a wide range of products for interventional procedures including stents, balloon angioplasty catheters, diagnostic catheters, microcatheters, drug-eluting beads, coils, guidewires and accessories.

TRIVASCULAR™

TriVascular has pioneered numerous design and manufacturing technologies in pursuit of our commitment to providing optimal solutions for endovascular aortic repair (EVAR).

TriVascular's initial product offerings are novel endovascular grafts focused on significantly advancing EVAR. Building upon partnerships with thought leading clinicians worldwide, TriVascular's products are designed to address unmet clinical needs and expand the pool of patients who are candidates for EVAR.
Based in Santa Rosa, California, TriVascular offers highly talented, motivated individuals the opportunity to positively impact global healthcare.

TRIVASCULAR COMPANY HISTORY

1998	January: TriVascular founded. - novel approach and platform - 79 patients treated with first generation device
1999	Raised $6 million Series B led by Delphi Ventures.
2001	ABS Ventures led a $13 million Series C round.
2002	Boston Scientific signs licensing agreements with TriVascular, including equity stake purchased through a Series D financing and Option to Buy. TriVascular starts Phase I trial.
2004	Phase I trial completed.
2005	Boston Scientific buys the remainder of TriVascular for $65 million upfront payment; with earns-out transaction can potentially total close to $1 billion. TriVascular first discovers presence of fractures in some implanted abdominal grafts, implanted in Phase I trial.
2006	Boston Scientific purchases Guidant. TriVascular completes redesign of fractured stent. Boston Scientific decides to shut down TriVascular program, citing cost of continuing the project. Negotiated spinout from Boston Scientific.
2008	TriVascular re-launched - over $200 million raised through a series of financings - strong IP portfolio - next generation device developed
2010	Ovation CE Mark approval. TriVascular beginning CE mark Trials in Europe and pivotal trials in US.
2011	Pivotal Study enrollment completed. First patient enrolled in PMR.
2012	Currently enrolling in Phase 3 (Continued Access). Currently enrolling 500 patients for European Post market Registry. TriVascular receives US FDA Approval for the Ovation Abdominal Stent graft system: First-ever HDE for EVAR. Ovation Prime CE Mark Approval: the Ovation Prime Abdominal Stent Graft System optimizes the two most important requirements for EVAR, access and Seal. Its 14F OD system is the lowest profile commercially available device, and expand the patient population suitable for EVAR. With over 1000 Ovation patients treated worldwide, Ovation Prime represents next generation EVAR technology – **today**.

UNIVET
OPTICAL TECHNOLOGIES

Univet is a modern and reactive Company, specialized in the design and manufacture of magnification systems and industrial, medical and laser safety eyewear (PPE).

From its own production site in Northern Italy, Univet exports in more than fifty Countries all over the world, with a share up to 50% of the global turnover: 10.4 million euro in 2011, with an increase of 18% compared to 2010. Extraordinary results rewarding Italian design, research, products' quality and company's loyalty to its primary aim: effectively support surgical, dental and aesthetic performances, allowing the user to observe very tiny details in the operating field, increasing the precision during both diagnosis and operation.

Expertise and passion are at the base of each product from design to production; extensive experience in optical technologies becomes tangible through care and innovative devices. An 100% Italian touch that shines through from the design and it is developed through constant attention to detail throughout the production chain. The in-depth study of materials and forms is reflected in the sophisticated and functional models that combine the perfect fit with typical elegance Made in Italy.

Technology takes form in optical designs designed and developed exclusively by Univet. Achromatic lenses and a special high-tech anti-reflective treatment offer crisp, clear pictures without distortion. A constant and superior quality due to qualified personnel and technologically advanced equipment for the in-line control of binocular devices' assembly. The Galilean and Prismatic systems are available in TTL or Flip-Up version, making a complete array of solutions to implement the best performance in every job.

Univet TTL system is a customized product which highly improves comfort and performances. The Galilean TTL devices support the new optical design PRO that combines improved image quality with efficient product engineering. Superior performance and unparalleled visual comfort: the eye adapts easily to the view through the magnifying system due to enhanced optical properties.

Thanks to the quick and intuitive adjustment and the possibility to adjust the declination angle, Univet Flip-up products allow ease of use by multiple users and offer total stability of the binocular system.
Magnification system of new generation, Flip-Up Air-X helps to reduce eye strain, improve posture and greater precision. These devices are equipped with high definition optics and over-moulded temples to relieve pressure on sensitive areas and are available with magnification up to 6x.

Arti Grafiche Colombo is a printing company that has offered high quality services and value added products since 1959. Our management philosophy drives our belief that our main objective is to meet the needs of the client and their line of business.

AGC uses the most recent and advanced methods of communication which add innovative services and proposals to our business: graphic design, point-of-sale consultancy, coordinated imaging, marketing communication, personalisation and finishing of printed matter, maintaining complete flexibility for production time – a characteristic we have always prided ourselves on.

We also use a digital colour management programme which allows us to differentiate our proposals and services from those of our competitors, and also to choose more precisely between the traditional offset and the advanced digital print.

AGC has obtained ISO 9001:2008 certificate for quality and FSC chain of custody which guarantee the use of environmentally-friendly paper products, assuming responsibility for rigid qualitative and ecological standards and working actively towards an eco-friendly future.

"The world of communication is evolving and communication helps towards a change in the world".

AGC has followed the evolution path of printing techniques from Gutenberg's block printing, to high quality offset printing, and on to the newest digital technology and use of materials and innovative works on large scale plotters.

Arti Grafiche Colombo is taking new steps as a global company in the field of communication, progressively gaining experience from new multimedia technology.

CeMEF – Center of Exercise and sport Medicine

The CeMEF, in line with the recommendations of the World Health Organization and the European Union and several scientific societies, as well as ministerial guidelines that correlate exercise and the national health system, is an advanced example of this issue and specifically pursues the goal to use exercise as a "medicine" by customizing the requirements of physical activity:

- Support for traditional treatment protocols in several clinical areas (sensitive exercise)
- Increase levels of functional efficiency
- Provide a strong preventive action to the risk factors in many diseases

The CeMEF is classified as a second level center under the "Prescription of exercise as a means of prevention and treatment in the Lombardy Region" project and to this Center are addressed subjects whom it's prescribed exercise as a factor of the diagnostic-therapeutic-preventive process in relation to the clinical problem.

In this context, the CeMEF is the educational and cultural reference point for its territorial. In fact, enabled, for teaching and training, a collaboration with the Faculty of Medicine, University Vita-Salute in Milan, with the Faculty of Sport Sciences, University of Verona and The FMSI (Italian Federation of Sports Medicine).

The most significant aspects that characterize the CeMEF are the instrumental and technological solutions available, from protocols adopted operational and organizational model represented by the various integrated services: Sports Medicine, Cardiology, Nutrition, Psychology and Traumatology related to Sport, Functional Assessment and Biomechanics laboratory, GymLab.

The operating characteristics of the CeMEF provide integrated pathways of clinical and functional evaluation for all problems related to sports activities, combining clinical approach to the use of specific tests to define fully the features and functional levels of each subject.

It's then possible to offer to any person interested in physical activity a custom path defined at every stage: evaluation, prescription, administration, monitoring, verification. Specifically, the various stages of this route are well delineated:

- definition, after the results of clinical and instrumental analysis, of a complete personal profile (clinical, biological and psychological) of the subject
- identification of the specific objectives for each user
- determination of the personality profile of the user for the selection of tools and intervention strategies appropriate
- formulate an individual treatment plan (integrated in a poli-specialized support)
- coordination of administration / implementation of treatment plan
- monitoring the response to treatment proposed
- possible adjustment of the program
- definition of the maintenance plan of the proposed program.

The CeMEF staff (doctors specialized in sport medicine, cardiologists, nutritionists, endocrinologists and experts in metabolism, of graduates in physical education adapted, bioengineers, psychologists, nursing staff with specific skills in this sector) works closely with specialists from relevant clinical areas (cardiovascular, metabolic, oncology, pulmonary, hypertension, osteoporosis, mood disorders, etc..) and leads the user to achieve his objectives, assessing and recording the progress.

SCHOOL BACKGROUND

Established in 1869 Collegio San Carlo is located in the heart of historic downtown Milan.

Christian truth, freedom and solidarity are the ethos of school activities and academics. The didactic and extracurricular activities aim at preparing students to be responsible, creative and mature adults.

At Collegio San Carlo students from 16 different nationalities are represented. The school welcomes students from a variety of backgrounds, ethnicities and religions. Collegio San Carlo offers all levels of education starting from preschool to the Italian high school diploma.

THE INTERCULTURAL PROGRAM

The Intercultural Program is a peculiar dual-language educational program that allows students to experience a mix of different cultural areas, as well as religions, in order to promote a unique life in common, established on mutual humanity.

Approximately 30% of the contents are delivered in English representing a major breakthrough within the Italian school system. The areas of the curriculum delivered in English by qualified mother tongue teachers are the following: History, Geography, Art, Science, Music, P.E.

The Intercultural Program constantly makes reference to two or more different worlds; offers different perspectives on the same contents, stimulating comparisons and underlining the relative nature of knowledge; indirectly works on different curricula; merges different disciplines on the common grounds of cognitive processes.

ACTIVITIES

Collegio San Carlo offers a variety of curricular and extra-curricular activities for students of all ages. Each student is required to take physical education and is encouraged to take advantage of the numerous sports facilities the school has to offer, such as soccer and basketball courts, a fully equipped gym and swimming pools.

The Collegio also offers a variety of community service programs and excursions for students of all ages, as well as didactic intercultural and study abroad programs with schools all around the world. Numerous foreign language classes that can be both mandatory as well as extracurricular back up these programs. English, French, Spanish are all foreign languages offered at an advanced level at Collegio San Carlo. Chinese is offered as an extra-curricular course starting from pre-school.

Collegio San Carlo - C.so Magenta 71 - 20123 Milano, Italy
Tel +39 02 430631 - csc@collegiosancarlo.it - www.collegiosancarlo.it

Director: Aldo Geranzani

COLNAGO

Colnago is a manufacturer of high-end bicycles founded by Ernesto Colnago in 1954. Instead of following his family's farming business, Ernesto Colnago chose to work in the cycle trade, apprenticing first with Gloria Bicycles, subsequently taking up road racing. After a bad crash ended his racing career, he opened his own shop. He was then mechanic on the Nivea team Giro d'Italia in 1955.

The company first became known for high quality steel frames, and later as one of the more creative cycling manufacturers responsible for innovations in design and experimentation with new materials including carbon fiber.

Colnago is regarded as one of the builders of the world's best custom road race frames. In 1960, Colnago saw fame as Arienti rode to victory at the Rome Olympics on a Colnago bicycle. Later, Colnago joined the Molteni team as head mechanic. A win on a Colnago in the 1970 Milan-San Remo race inspired Colnago to change his logo to the famous 'Ace of Clubs'.
Eddy Merckx then joined the Molteni team, and what ensured was mutual innovation: "Merckx was an up and coming champion, and I was an up and coming bike builder. It helped us to grow." Merckx used a super-light Colnago bicycle in 1972 to break the world hour record.

With a growing reputation from their racing wins, Colnago plunged into the market for production bikes. The mainstay of the Colnago line in the 1970s were the Super and the Mexico. They were great bikes and developed a cult-like following.
In the 1980s, Colnago experimented with various crimped-tube frames which became production models as their top of the range frames, beginning with the "Master."

Since the 1980s, while Colnago continued to produce high-end steel bikes and began to produce bike frames using titanium, aluminum and carbon. Subsequently, Colnago worked with Ferrari in developing new carbon fiber technology.
Colnago's early attempts at carbon fiber frames led to their flagship frames, the C40 and its successor, the C50, that set new standards of excellence.
Colnago has sponsored professional teams every year since 1974. In the early 1970s, the Molteni team which included Merckx rode on Colnago bikes. Saronni rode Colnago bikes throughout his career. Colnago was well known as the sponsor of the Mapei Team throughout the 1990s.
In the last Tour de France, Team Europcar rode Colnago bikes, winning several stages and the King of the Mountain jersey with Voeckler.

Established in 1856, Riso Gallo is an Italian family business spanning 6 generations and 155 years specialising in risotto rice. Riso Gallo is one of the oldest rice-growing companies in Italy and one of the greatest European rice mill based in the Northern Po Valley, the authentic risotto rice growing region in Europe.

Last century, since illiteracy was still widespread, the company decided to opt for animal symbols to identify the different rice varieties: a giraffe, a tiger, an eagle, an elephant and a cockerel stood out on all the packets. Soon, the cockerel – the animal associated with best-quality rice - became the symbol of the company itself.

Generations of families have dedicated their working lives to Riso Gallo to ensure the production of rice of the highest quality – making us the experts in risotto rice.

Riso Gallo has grown to become the Brand Leader in Italy with 22% value share, and exports to 74 countries around the world.

With over 150 years of history, Riso Gallo has built its' strength on a passion for goodness and quality. From this extensive know-how and continuous innovation from its team of expert researchers, the product 'Chicchi Piu Ricchi' was born, the first functional product from Riso Gallo with beta-glucans. The beta-glucans help to maintain normal cholesterol levels without sacrificing the pleasure at the table.

'Chicchi Piu Ricchi' is a mix of three cereals: Rice, Oats, and a special Barley naturally rich in beta-glucans: dietary fibres that naturally reduce the absorption of cholesterol, thus lowering the concentration of LDL.

As part of an active lifestyle and a balanced and varied diet, 3 grams per day of beta-glucans are the optimal amount to help control cholesterol. One single portion of 80 grams of Chicci Piu Ricchi will give you approximately 1.9 grams of beta-glucans, which is over 50% of the daily recommended intake.

With the launch of the new product 'Chicchi Piu Ricchi', Riso Gallo has a new dedicated web site (www.controllocolesterolo.it) where you will find information on nutrition and fitness. In our new web site, there you will find a calculator to work out the amount of cholesterol taken daily and monthly, based on your diet. There is also a selection of recipes to help you appreciate, not only the product, but also the taste of "Chicchi Piu Ricchi".

eServices for Life and Health is a department of the San Raffaele Hospital of Milan, which since 1997 is specialized in discovering ways of merging Information Technology to the realm of health with the aim of developing and delivering services within the hospital environment as well as fostering innovation across numerous different domains and disciplines.
The mission of this research unit is to demonstrate the ethical, scientific, economical and technological feasibility of innovative services, that intend to deliver personalized and context-specific information, so as to improve individuals' motivation towards healthier, more environmentally friendly and socially responsible lifestyles. In order design and engineer technology-based systems in line with WHO holistic vision of *Health*, in the past years the e-Services for Life and Health research unit has developed a unique Service Design model, the Engineering Awareness™, that sync three drivers: **Emotion** (a trigger to an Individual's psychological reaction in context with his/her preferences) and **Relation** (a trigger for a social interaction with other Individuals physically present or not, and/or with a proximity or remote Environment in context with his/her preferences) to each and every **Function** (an Individual's practical need addressed by the service) delivered. The essential Service Design requirement is to provide an unbiased understanding of the impact that a given decision/action implies, to empower the making of informed choices, to provide Individuals' with proper skills that will be used to manage alternative lifestyles (abilities) and equal access to them in their life environments (choice architectures).

The main research area covered by eService for Life and Health expertise are:
1. SMART HOSPITAL: the researches focus on Hospital's Process Engineering and Robotics for Surgery.
2. SMART LIFE: covers researches on PHS (Personal Health System) for Well-Being and Healthier Lifestyle and Cognitive Robotics and Edutainment.
3. SMART CITY: involves researches on Trust, Security and Privacy Management, Ambient Intelligence and Sensor Network, Energy, Environment and Sustainability, Traceability and Supply Chain Management and Ontologies, Knowledge Management and Semantic Web.
The unit is involved in the development of research projects funded by the European Commission within the 5th, 6th and 7th Framework Programme, projects funded by the Italian Ministry of Economic Development, and funded projects in the region and from private foundations.

Website: http://www.eservices4life.org/
Email: contacts@eservices4life.org

The company was founded in 1981 and acquired by TILI GROUP in 1991.

Istituto Finanziario S.p.A. is based in Rome, near Piazza Navona, and operates as a Financial Intermediary under the authorization and control of the Bank of Italy.

It provides consulting services for the acquisition and reorganization of companies internationally. Not only does it offer financial instruments, but it also provides its clients with advice, analyses and leadership skills, assisting in defining strategies, providing support in the implementation of their development plans, and participating also in the risk involved in such plans.

It has over the years widened the scope and significance of its services, developing a growing know-how in the performance of existing activities and enhancing them with new activities related to consulting in M&A operations. It has increased its client base and strengthened its position in the market as a merchant bank and a financial advisor with a specialization in deals with multinational players.

The services offered to date by Istituto Finanziario both to its subsidiaries and to external companies can be summarized as follows:
- Financial instruments (loans, leasing, factoring, etc.);
- Assets management;
- Business reorganization;
- Shares purchase valuation, negotiation and closing.

In the area of its specialization as a merchant bank, the company has recently supported one of its subsidiary in the sale of the majority share in Ansaldo T&D S.p.A. to the Japanese multinational company Toshiba Corporation. Istituto Finanziario supported the selling party throughout the whole transaction, from negotiation of the terms to finalization of the contracts and closing of the sale, which occurred in March 2011.

Istituto Finanziario, through its subsidiaries, currently participates as a shareholder in the management of each of its businesses, together with highly respected international partners, namely: Parsons Transportation Group Inc. (world leader in transportation and infrastructures) in the business of engineering; Toshiba Corporation (world leader in electronic and electric technology) in the business of energy; Enel S.p.A., the first Italian power company, and Terna S.p.A., the first grid operator for electricity transmission in Europe, through CESI S.p.A.

The La Scolca estate is still run by the founding Soldati family. **Gavi** is a wine made from the Cortese grape. Gavi wine was made popular by La Scolca more than 90 years ago. The philosophy of La Scolca: To obtain an **excellent wine from excellent grapes**. It is arduous work to make wine "in the vineyard" rather than "in the winery", that is, to grow the best grapes possible and make wine out of top-quality primary material, rather than counting on manipulations in the winery.

The results of our way of working is evident when tasting: not only is the wine more complex and elegant, with distinct *terroir* personality, but is is also more healthy. Gone are the days of unpleasant "illnesses" too often attributed to white wine, such as headaches, slight dozing and more. It is not a coincidence that many of our fans are doctors. All fruit is hand harvested in small crates.After no more than 30 minutes, the fruit is taken to winery where it is immediately cooled (when needed). The fruit is undergoes a soft pressing with modern pneumatic presses.

Cryo-maceration and cold fermentation (13-14C) in temperature-controlled stainless-steel preserves the Cortese's freshness, subtle fruit aromas, and flinty acidity.Complex and concentrated age-worthy wines now found on the world's finest wine lists. A glass of wine is a pleasure and should be a souvenir of the time at which it was enjoyed: an everyday or special occasion and the company with which it was shared. Wine must recall emotion.

Wine is passion and for this reason, when a producer talks about their wine they also speak about themselves, like a chef describing their food, they are proud of their products. Behind important wines there are great passions. The global world now allows us to taste white wines from all countries, even if they comes from the most remote and unthinkable places, with explosions of flavors, aromas, and with great power, but **the quality of Gavi La Scolca manages to overcome its fashions and trends with a strong personality and with great character: gentle but firm and persistent. It is very difficult to not to remember Gavi La Scolca after having tasted it. We can truly say that "Gavi dei Gavi™" is a "timeless passion".**

MASI®
AGRICOLA

Masi Agricola is a leading producer of Amarone and proposes high class wines of the Venetian area, using native grapes and traditional production methods, with constant technological updates. Recognized for its expertise in the technique of Appassimento (drying of the grapes), Masi produces five Amarones and some modern Supervenetian wines.

momoDESIGN

Technology, innovation, research and style are the values that have been inspiring MOMODESIGN for over thirty years, setting the company in the international survey as a point of reference for all the style and design enthusiasts.
MOMODESIGN was founded in 1981 from an idea of Marco Cattaneo, Managing Director of MOMO Group, world leader in car accessorie , in order to offer to the company a Style Centre specialized in research and design development.
Since the very first years, MOMODESIGN has alternated research activity in car design and development of ideas and innovative projects in lifestyle accessories, creating a product line that helped in building the image of a dynamic company, always abreast of times and up-to-date on new trends.

At the end of the Nineties, when the MOMO Group was sold to an American company, Marco Cattaneo took over MOMODESIGN to engage, with the fundamental help of his children Paolo and Eleonora, in a new and exciting challenge: transforming MOMODESIGN in an international brand with its own identity and philosophy, a modern and innovative brand, synonymous of lifestyle at 360 degrees.

Today, MOMODESIGN is organized in three departments:
- *The Style Centre*. Its activity is industrial design at an international level and the study of the design of all the collection branded MOMODESIGN;
- *Licensing*. The licensee division provides support of the own design study centre to all the selected partners providing the style and the design of the products;
- *Franchising*. The franchising division was born to the need to be able to exhibit all the products designed by MOMO DESIGN in a unique and special space in the most famous cities in the world. In Italy we are present in Milan, in Galleria San Babila 4/a. Next openings in Abu Dhabi and Dubai.

MOMODESIGN follows accurately the process of its creations: from concept to design development, from pre-industrialization to quality check until the formulation of strategies for brand image, positioning in the market and distribution.
All the products branded MOMODESIGN synthetize and express the research of the Style Centre and are thought to be objects characterized by elegant design and strong personality, creations with high added value that can rouse emotions in a careful and demanding public.

This point of view is the source of all the products, which stand out for their modern and innovative design, the use of technological materials and the extreme attention to details.

Creativity and versatility of the Style Centre create a wide and heterogeneous collection of items such as helmets, watches, eyewear, leather goods, shoes, snowboards, citybikes, IPhone, iPod, iPad and mp3 cases, appareal, ceramics…
Latest creations: a new fragrance for man, a high tech collection of carbon fiber pens, a new line of agendas and copybooks.

The choice to collaborate during these years with some of the most prestigious multinational companies has contributed with the evolution of the brand: with 3 (Tre.it) in the communication sector with a latest generation telephone and modem line; with YAMAHA NL for the personalization of XMAX scooter for the European market; with Logitech for the creation of a game console for playstation and pc, up to the latest and consolidated cooperation with Lancia of FIAT Group for the launch of the new Ypsilon Sport MOMODESIGN, a car characterized by a series of chromatic and aesthetical interventions directly linkable to MOMODESIGN style values.

WWW.MOMODESIGN.COM

Rocca di Castagnoli

THE HISTORY OF ROCCA DI CASTAGNOLI

The earliest documentary evidence known concerning Castagnoli dates back to the X Century: it consists of an account book of Coltibuono that refers to the sale of an estate called Stielle, today one of the superior vineyards belonging to the wine-producing firm Rocca di Castagnoli.

The Rocca, a stern-looking stronghold that towers above the village, dates back to the XI Century, at least.

Distinguished families, such as the Piccolominis, the Tempis and the Ricasolis, held Castagnoli with its villa, built in 1700 with the spur of extremely flourishing viticulture that renewed the wine-making reputation acquired in the Middle Ages. The estate became one of the most well-known ones in the area, so greatly looked upon to deserve the worthy consideration of Pietro Leopoldo di Lorena, who visited the Chianti region in July 1773. He noted that "the villa and the estate of the Tempis of Castagnoli are maintained in excellent conditions and the peasants are well lodged".

Significant restructuring works have been carried out in recent years by the current owners, the family Calì, bringing back bygone magnificence to both the villa and the Rocca, which hosts the estate's oak ageing cellars under its stone columns beautiful brick vaulting and fascinating age-old wooden ceilings.

THE PRESENT

In a simple and functional cellar, Rocca di Castagnoli produces nowadays top-class wines, based mainly on local grape varieties, exclusively harvested and selected in the estate's own vineyards: Sangiovese, Canaiolo, Colorino. Our flagship wines, the Chanti Classico and the Riserva, have been produced in full respect to the Tuscan winemaking traditions, and their style and taste, elegant, rich, pleasant, have been awarded worldwide.
In addition, the estate also offers a range of the so-called *Supertuscans*, proving that also international grape varieties can give excellent wines in the Chianti area.

75 years ago, Mr. Francesco Vitaloni opened a food store in Milan - Via Lecco No. 18 – and decided to call it "La Rosticceria San Carlo" because of the proximity of the small church of "San Carlo al Lazzaretto". The store soon stood out for a revolutionary food specialty: "crunchy potato chips", which were distributed daily in bakeries and snack bars in the surroundings. A limited production (20 kilos per day) that turned quickly into considerable quantities. In 1940, Mr. Vitaloni moved to "Greco", another town district, to start up the industrial production with the company changing its name into "San Carlo... le patatine". In 1955 Mr. Alberto Vitaloni, the actual owner and President, took over from his father and in 1970 founded the Milan-based multinational with the headquarter in Via Turati that got the name of "San Carlo Gruppo Alimentare S.p.A.". In the following years the company experienced a consistent growth. At present, the production is around 100 tons of chips a day (plus a wide range of savoury snacks, sweets and bakery) with 11 factories, 2200 employees, 170 warehouses, 1300 salesmen and vans that guarantee a tough distribution all over the country. Year 2011 was a special one for San Carlo, that celebrated its 75th anniversary as undisputed market leader, with its constant focus on consumer needs, development and products innovation, and reached the third generation with Mrs. Susanna Vitaloni.

www.sancarlo.it

SeRist
SERVIZI RISTORAZIONE S.r.l.
I Ristoratori Italiani

SeRist combines organizational and managemrnt techniques with high quality. Italian catering, offering top class service. The versatility of its organization allows to resolve all company catering requirements in the best possible way.

SeRist is synonymous with certified quality, attention to the customer's needs, commitment to high quality raw material standards, respect of the environment, professionalism and expertise of its staff.

Our Company was founded in Arcore (MB) in 1983.

Although the public catering market was close tomaturity, consumers immediately acknowledged the uniqueness of our proposal allowing us a constant growth rate.

The entire chain of activities and sidelines necessary for the supplyng of public catering services in the brosdest sense is carried out using our resources:

- the administering of meals to all types of users
- food supplies to comunities
- dietary and nutritional consulting
- the obtaining of business licenses and health authorizations
- the planning and supervision of works in large kitchens and restaurants of various types (bars, cafeterias, free flow restaurants, food courts)
- staff training
- direction and management of food chains for third parties

Today we provide approximately 80,000 meals per day with the work of our 2200 employees operating with users nationwide.

Our Values
We are Italian restaurateurs who deeply believe in the wealth of local customs and traditions available in our region.
We strongly believe in the supremacy of the Italian history and culture of food. We intend to continue working with enthusisam and passion to defend and promote these core values of our profession.

Our Mission
We want to serve as a reference for all the authorities that guarantee an impeccable catering service to the community that thry protect from the health and hygiene and organoleptic points of view, and care for all the boundary conditions thath transform the mere fulfilment of the need for nutrition into a full dining experience for the individual's body and spirit.
We believe in growth inspired by respect and by the enhancement of our human capital.
We impose full compliance with our *"Code of Ethics"* on all our employees, collaborators and suppliers.

HISTORY

HULKA srl was set up in 1996 with the vision to create innovative cosmetic products, safe, effective and of the highest quality. The company was founded by Dr Giorgio Panin MD, PHD and Dr Franca Astolfi an industrial economist, thanks to their determination to develop patented cosmetic products which were safe and effective especially for children. Their goal was to design formulas as simple as possible, containing no fragrances, preservatives, colourants and mostly without water. This has now led to the creation of 24 cosmetic products focusing on bringing health benefits to people with certain skin problems. 7 Skin care range, 3 Lip care range, 5 Cleansing Bath care & Detergent range, 3 Sun care range and an oral hygiene product.

We have also extended our lines and developed two outstanding medical devices FILME® OPHT for the well being of the eye and FILME® GYNO a vaginal suppository.

Our principle activity is the production and distribution of high quality cosmetic products which are all nickel and gluten tested, through the network of medical representatives, pharmacies, distributors and agents, sold under the brand name VEA®.

Delivering our products via pharmaceutical warehouses > pharmaceutical wholesalers > pharmacies. The secret of our success lies in our research centres, the high quality raw materials we use and through the collaboration with the medical community to deepen our understanding of skin.

We have experts working with us who are professional in innovating and developing products in respond to either problematic or normal skin.

Over 120 of our medical representatives regularly visit Hospitals, Private Clinics, Surgeries, Paramedical staff, Medical staff and are in constant communication with the medical world through participation at national and international congress to provide the best product to our customers.

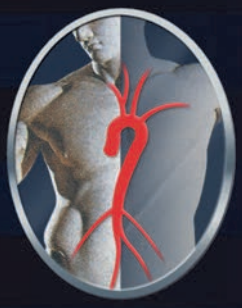
MISSION

Our mission is to contribute to the satisfaction and the enrichment of the lives of our customers and employees by drawing on our creative and innovative strengths.

To continue to develop products of excellence and outstanding performance and to win the loyalty and trust of our customers.

6TH INTERNATIONAL CONGRESS

AORTIC SURGERY AND ANESTHESIA



"HOW TO DO IT"

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