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<thead>
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</tr>
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<tbody>
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<tr>
<td>Simona Zannetti</td>
<td>Medtronic Cardio Vascular (Santa Rosa, CA)</td>
</tr>
</tbody>
</table>
HISTORICAL PERSPECTIVE

89 From Ebers to EVARs: A Historical Perspective on Aortic Surgery
   Joseph L. Bobadilla

ORIGINAL RESEARCH ARTICLES

96 Painless Type B Aortic Dissection: Insights From the International Registry of Acute Aortic Dissection

102 Outcomes of Aortic Arch Replacement Performed Without Circulatory Arrest or Deep Hypothermia
   Nisal K. Perera, William Y. Shi, Rhiannon S. Koirala, Sean D. Galvin, Peter R. McCall, George Matalanis

110 Urgent Carotid Endarterectomy in Patients with Acute Neurological Symptoms: The Results of a Single Center Prospective Nonrandomized Study
   Samuel Bruls, Philippe Desfontaines, Jean-Olivier Defraigne, Natzi Sakalihasan

STATE-OF-THE-ART REVIEWS

117 Acute Traumatic Thoracic Aortic Injury: Considerations and Reflections on the Endovascular Aneurysm Repair
   Luca Di Marco, Davide Pacini, Roberto Di Bartolomeo

CASE REPORTS

123 Dissection of Iliac Artery in a Patient With Autosomal Dominant Polycystic Kidney Disease: A Case Report
   Audrey Courtois, Betty V. Nusgens, Philippe Delvenne, Michel Meurisse, Jean-Olivier Defraigne, Alain C. Colige, Natzi Sakalihasan
126 Simultaneous Surgical Treatment of Type B Dissection Complicated With Visceral Malperfusion and Abdominal Aortic Aneurysm: Role of Aortic Fenestration
Gianfranco Filippone, Gabriele Ferro, Cristiana Duranti, Gaetano La Barbera, Francesco Talarico

131 An Unusual Complication of Surgery for Type A Dissection Treated by Thoracic Endovascular Aortic Repair (TEVAR)
Giuseppe Petrilli, Giovanni Puppini, Salvo Torre, Daniele Calzaferri, Antonella Bugana, Giuseppe Faggian

BASIC SCIENCE FOR THE CLINICIAN

135 Genes in Thoracic Aortic Aneurysms and Dissections – Do they Matter?: Translation and Integration of Research and Modern Genetic Techniques into Daily Clinical Practice
Julie De Backer, Marjolijn Renard, Laurence Campens, Katrien François, Bert Callewaert, Paul Coucke, Anne De Paepe

IMAGES IN AORTIC DISEASE

146 Imaging Assessment of Periaortic Inflammation in Erdheim-Chester Disease
Thierry Couvreur, Györgyi Lipcsei, Alain Nchimi

POLL THE EDITORIAL BOARD

149 How Would You Correct an Aberrant Right Subclavian Artery?
Bulat A. Ziganshin

UPCOMING MEETINGS

152 List of Upcoming Meetings
From Ebers to EVARs
A Historical Perspective on Aortic Surgery

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Department of Surgery, Vascular & Endovascular Surgery, University of Kentucky, Lexington, Kentucky

Abstract
Pathology of the aorta has been recognized for nearly three and a half millennia, dating back to the first recorded description in the scrolls of Ebers, circa 1550 BC. Since that time, treatment has evolved from magical medicinal remedies and incantations to nearly outpatient percutaneous interventions. From the first attempts at open surgical reconstruction in the 1700s and 1800s, to the latest generations of endovascular devices, innovative pioneers have pushed the envelope of surgical technique in developing unique and novel strategies to treat the ever complex pathology of the aorta. We are just now beginning to understand these pathologies at the molecular and genetic levels, and with that expansive extent of investigation enters a journal, dedicated solely to the aorta. With this article, we hope to illuminate the rich and deep history of aortic pathology, and the innovations leading to the technology of today. A firm understanding of our past provides a strong foundation for further growth into the future.
Advancements in aortic surgery over three and a half millennia. Anatomic, open surgical, and endovascular advancements are all illustrated. The first rudimentary description of the cardiovascular system and aneurysms dates back to 1550 BC.

Excerpt from the Ebers Papyrus. Thought to have been based on even more ancient texts, the Ebers Papyrus contains the first documented description of the human heart, aorta, and aneurysms in general. Courtesy of the online catalogue of the research archives of the Oriental Institute, University of Chicago. Located at: http://oilib.uchicago.edu/books/bryan_the_papyrus_ebers_1930.pdf. Originally appears in: [2].
nal dedicated to the multidisciplinary approach to treatment and research in diseases of the aorta and its first-order branches. A journal dedicated to the future of this increasing complex field. However, as Alexis de Tocqueville, a French political thinker and historian once stated: “when the past no longer illuminates the future, the spirit walks in darkness.” In the following pages, we hope to illuminate the history of aortic surgery.

Ancient Anatomic History

The term aorta was first applied by Aristotle in the 4th century BC, used to describe the great vessel of the heart. Prior to this description, the term had been used by Hippocrates to describe the bronchial tree, consistent with the belief that the vital “pneuma” derived from respiration was delivered to the body by these vessels. The respiratory and circulatory systems were seen as one continuous circuit until the early 1600s when separate blood circulation was described by Harvey. Since Aristotle’s time however, the term aorta has continued to define the primary arterial outflow of the left ventricle. Pathology of the great vessel, however, had been recognized for nearly a millennium before the times of Hippocrates and Aristotle. The first preserved written account of the aorta dates back to 1550BC. The Ebers Papyrus (Fig. 2) was a hieratic script of Pharaonic Egypt, thought to be a transcription of an even earlier text. It consisted of a 110 page long papyrus scroll containing more than 700 magical and medicinal remedies for ailments of all organ systems [1,2]. The book of hearts was the largest and most highly regarded of these scrolls. It described the heart and great vessels as the center of all being and existence. Within this script lies the first recorded mention of aortic aneurysms, quoted as “…only magic can cure tumors of the major arteries.” [2] The scrolls go on to describe other conditions of the cardiovascular system, including peripheral arterial aneurysms:

“When thou meetest a tumor of the vessels in any part of the body of a person and thou findest it round in form, growing under thy finger … . Treat it with the Knife and burn it with Fire so that it bleeds not too much. Heal it like the Cautery heals.” [2]

This script likely references the development of traumatic pseudoaneurysms but remains the earliest
recorded description of major vascular pathology. Nearly 1,000 years pass before the next mention of these vessels again. Galen, a Greek physician practicing in Rome, served as the physician to the gladiators. Galen holds the reputation as the first trauma surgeon, caring for those injured in combat. He developed rudimentary anatomic charts which were based on canine vivisection [3]. While the only anatomic reference of his time, and for hundreds of years later, they were somewhat incomplete and inaccurate in their representation of human anatomy. In his writings, he describes aneurysms on physical examination as “localized pulsatile swellings.” Furthermore, he goes on to describe the first documented ruptured aneurysm as when “an aneurysm is wounded, the blood is spouted out with so much violence that it can scarcely be arrested.” [4,5] A contemporary to Galen was Antyllus, another Greek surgeon practicing in Rome. He is considered the true father of vascular surgery. He described both true and false aneurysms in his writings and documented the first attempted aneurysm repair in the year 200AD [6]. The “Antyllus method” consisted of proximal and distal ligation, central incision of the aneurysm, and evacuation of the thrombotic materials [1]. This remained the standard treatment of aneurysms for over 1,000 years to follow.

A few hundred years later, Aetius of Amida, a 7th century Byzantine physician and medical writer authored the manuscript *De Vasorum Dilatatione*, loosely translated “on the dilation of the vessels.” This was a detailed manuscript on the development and repair of abdominal aortic aneurysms utilizing a technique similar to the Antyllus method [6]. Unfortunately, as many of the time did, Aetius of Amida believed no wound heals properly without the formation of pus, and to encourage this, the aneurysm sac was packed with incense.

Andreas Vesalius lived from 1514–1564 AD, a Flemish physician, who traveled to Paris to study anatomy, medicine, and surgery. In 1554, he authored a seven-volume text of anatomic plates, *De humani corporis fabrica* (*On the Structure of the Human Body*, Fig. 3). These were the first human anatomic charts of their time, based on actual human anatomic dissections [4]. He taught his students by direct observation of dissection, and thus, he became known as the founding father of modern human anatomy. His seven-volume anatomic text provided new, detailed descriptions of the heart, great vessels, and vascular system. These volumes provided a level of detail never before seen and helped lay the foundation for future surgical pioneers that would follow in the centuries to come.

**Early Operative History**

John Hunter is perhaps best known for his famed ligation of the popliteal artery; however, his older brother, William, also studied aneurysms throughout the vascular system [1]. In 1757, William published the manuscript “The History of an Aneurysm of the Aorta with Some Remarks on Aneurysms in General.” He described these aneurysms as dilated and pulsatile vessels. He was also one of the first to describe arteriovenous fistulae, along with the hissing noise heard on
auscultation [6]. One of Hunter’s pupils, Sir Astley Cooper, went on to further the field of aortic surgery. He experimented with and developed a retroperitoneal exposure of the aorta in a cadaveric model. In 1817, he was summoned urgently to care for a 38-year-old porter with a large external iliac artery aneurysm that had eroded the overlying skin and freely ruptured [1]. He explored the patient transperitoneally and ligated the distal aorta with a single heavy silk tie. The patient survived 48 hours postoperatively. The post mortem specimen remains on display in the Gordon Museum of Pathology at King’s College London (Fig. 4) [6]. Around the same period, Jean-Nicolas Corvisart, personal physician to Emperor Napoleon I, published his essay on disease of the heart and great vessels (1806, translated to English by Jacob Gates 1812) [7]. He is now known as the father of cardiology, with the first detailed description of dilative cardiomyopathy, congestive failure, and other valvular heart disorders. In addition to these diseases, he also provided a detailed evolution of aneurysms of the aorta [7].

In 1865, the first attempts at percutaneous endovascular aneurysm repairs were made (Fig. 5). Moore and Murchison attempted aneurysm sac thrombosis by direct needle cannulation and wire packing. Via direct aneurysm puncture, 26 yards of wire coils were introduced into a large thoracic aneurysm [8]. The patient ultimately expired, but the aneurysm had partially thrombosed. Sepsis and distal embolism were obvious complication. In 1879, the addition of electricity was included, and the Moore–Corradi Method was born. This electrothrombosis entailed the coiling with silver and copper wire, and before complete packing, the passage of current through this wire to encourage thrombosis [8,9].

Rudolf Matas (1860–1957) attempted to use electrothrombosis in 1900 for the treatment of a large abdominal aneurysm. Prior to this, he had described the use of endoaneurysmorraphy in the treatment of peripheral aneurysms (Fig. 6) [10]. He described three forms of aneurysmorraphy: obliterative, restorative, and reconstructive [6]. In 1923, he used these techniques to successfully treat an infrarenal AAA [11]. The patient survived for 18 months postoperatively, eventually succumbing to pulmonary tuberculosis complications [1].

Rea suggested an alternative form of plication, utilizing cellophane wrapping around abdominal aneurysms [12]. This technique gained wide exposure after Rudolf Nissen used it to wrap an abdominal
aneurysm of Albert Einstein in 1949. He survived for more than 5 years after this intervention but ultimately succumb to a ruptured aneurysm April 18, 1955. Frustrated by the poor results with wraps, coiling, and ligation, Charles Dubost performed the first successful aneurysm resection and interposition graft using cadaveric aortic allograft on March 29, 1951 [1,13]. This technique included the complete resection of the aneurysm sac, an often bloody, morbid, and dangerous procedure. The next major advancement in aortic surgery came with the combination of Dubost’s interposition grafting and Matas’s endoaneursymorraphy. In 1966, Oscar Creech described this combined procedure that remains the operation of choice nearly 50 years later [14]. This simple synthesis greatly simplified open aortic operations and removed much of the associated morbidity from complete aneurysm sac resection.

Contemporary Surgical History
The use of cadaveric allografts was, however, of limited wide-scale utility. These conduits were of obvious limited supply and were also wrought with the complications of alloimmunity and late aneurysmal degeneration. Because of this, the search for a more stable, long-term, synthetic conduit material was undertaken. Through an intense combined effort of investigation, including surgeons, textile engineers, and mechanical engineers, the Dacron vascular graft was born, including a completely new manufacturing process and knitting machine that allowed for the seamless construction of these novel branching vascular grafts. This new arterial substitute was officially announced to the medical community in 1958 with the landmark paper authored by our contemporary cardiovascular surgical giants: Michael E. DeBakey and colleagues [15]. DeBakey and Cooley, however, had
been developing techniques for complex aneurysm repair and spinal cord protection during thoracic aortic surgery for some years prior, with their first successful resection of a fusiform thoracic aneurysm on January 5, 1953. They went on to expand their experience, with a series of 245 successful aneurysm repairs by July 1955. Now, with the addition of a stable and suitable synthetic conduit, the Dacron interposition graft became the mainstay of modern vascular surgery, allowing complex operations for thoracic, abdominal, and thoracoabdominal aortic aneurysms. In 1974, Stanley Crawford reported his experience of thoracoabdominal aneurysm repairs [16]. Initially involving side arm branches to the renovisceral vessels, and ultimately evolving to incorporate small visceral patches sewn directly to the graft, these open techniques have only recently been challenged by the newest generation of endovascular technologies.

While others had dabbled in “endovascular techniques” in aortic surgery for nearly 125 years prior, including attempts at wire coiling and electrothrombosis, the true breakthrough came with the work of Parodi and Palmaz. They initially experimented with stainless steel stents hand sewn to thin-walled Dacron tube grafts (Fig. 7). Their handmade endografts were used in canine models before initial human trials. On September 6, 1990, the first successful human endovascular aneurysm repair was performed. They went on to describe their first five patients in the landmark paper “Transfemoral intraluminal graft implantation for abdominal aortic aneurysms.” [17] Since then, endovascular devices have progressed to be more readily available, lower profile, and more complex in configuration.

Conclusions

From the Ebers Papyrus to endografts, over three and a half millennia, pathology of the aorta has plagued mankind and been an area for bold and progressive innovations. From a disease once treated with magical medicinal remedies to a pathology that can now be treated percutaneously, pathology of the aorta continues to provide challenging opportunities for innovative and landmark research. It is with this understanding that the journal AORTA has come to fruition. A forum dedicated solely to advancing the knowledge in this specific niche. We hope that this article has helped to illuminate the deep, rich history of this field and that this journal will help to elucidate the future of it.

References

11. Matas R. Ligation of the abdominal aorta: report of the ultimate result, one year, five months and nine days after ligation of the abdominal aorta for aneurism at the bifurcation. Ann Surg. 1925;81:457–464. 10.1097/00000658-192502010-00004

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Painless Type B Aortic Dissection
Insights From the International Registry of Acute Aortic Dissection

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Abstract

Introduction: The classical presentation of a patient with Type B acute aortic dissection (TBAAD) is characterized by severe chest, back, or abdominal pain, ripping or tearing in nature. However, some patients present with painless acute aortic dissection, which can lead to a delay in diagnosis and treatment. We utilized the International Registry on Acute Aortic Dissections (IRAD) database to study these patients. Methods: We analyzed 43 painless TBAAD patients enrolled in the database between January 1996 and July 2012. The differences in presentation, diagnostics, management, and outcome were compared with patients presenting with painful TBAAD. Results: Among the 1162 TBAAD patients enrolled in IRAD, 43 patients presented with painless TBAAD (3.7%). The mean age of patients with painless TBAAD was significantly higher than normal TBAAD patients (69.2 versus 63.3 years, P = 0.020). The presence of atherosclerosis (46.4% versus 30.1%, P = 0.022), diabetes (17.9% versus 7.5%; P = 0.018), and other aortic diseases (8.6% versus 2.3%, P = 0.051), such as prior aortic aneurysm (31% versus 18.8% P = 0.049) was more common in these patients. Median delay time between presentation and diagnosis was longer in painless patients (median 34.0 versus 19.0 hours; P = 0.006). Dissection of iatrogenic origin (19.5% versus 1.3%; P < 0.001) was significantly more frequent in the painless group. The in-hospital mortality was 18.6% in the painless group, compared with an in-hospital mortality of 9.9% in the control group (P = 0.063). Conclusion: Painless TBAAD is a relatively rare presentation (3.7%) of aortic dissection, and is often associated with a history of atherosclerosis, diabetes, prior aortic disease including aortic aneurysm, and an iatrogenic origin. We observed a trend for increased in-hospital mortality in painless TBAAD patients, which may be the result of a delay in diagnosis and management. Therefore, physicians should be aware of this relative rare presentation of TBAAD.

Key Words
Aortic dissection · Painless

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Introduction

The classical presentation of a patient with acute aortic dissection (AAD) is characterized by severe chest, back, or abdominal pain. However, previous reports showed that between 5 and 17% of all dissection patients present with painless acute aortic dissections [1,2]. As expected, atypical presentation can lead to a delay in diagnosis, which is associated with higher mortality [3,4]. Painless Type B acute aortic dissection (TBAAD) does not mean that these patients have uncomplicated dissections, as they still can develop malperfusion and aortic rupture [1,2]. Immediate adequate medical treatment is essential and has to include optimal blood pressure control in order to reduce shear stress and limit the propagation of the dissection. Therefore, it is important to recognize these patients at the earliest possible stage. The aim of the current study was to assess the clinical characteristics, diagnostics, treatment, and outcomes of patients with painless TBAAD.

Methods

Patient Selection

The International Registry of Acute Aortic Dissection (IRAD) is an ongoing multinational registry designed to provide a representative population of patients with acute aortic dissection. The rationale, design, and methods of IRAD have been previously published [5]. The diagnosis of TBAAD was based on clinical symptoms, diagnostic imaging, direct visualization during surgery, and/or postmortem examination. Patients were enrolled at diagnosis or retrospectively. We analyzed all TBAAD patients enrolled in IRAD from January 1996 to July 2012 and selected those patients presenting without any pain symptoms. Demographics, medical history, presenting symptoms, management, and outcomes were compared between patients presenting with and without pain.

Statistical Analysis

Categorical variables were compared for both groups utilizing the chi-squared tests and Fisher’s exact tests. Student’s t-test was used to analyze continuous variables and the non-parametric test of medians to analyze non-normally distributed variables. A p-value ≤0.05 was considered significant. Kaplan-Meier survival curves were plotted to estimate survival. Data analysis was performed with the use of SPSS statistical analysis software (SPSS Inc, Chicago, Ill).
Among the 1162 TBAAD patients enrolled in IRAD, 43 patients presented with painless TBAAD (3.7%). The mean age of patients with painless TBAAD was significantly higher than normal TBAAD patients (69.2 versus 63.3 y; \( p \)-value \( \leq 0.020 \), Tables 1–3). Painless patients presented more often with a history of diabetes, (17.9% versus 7.5%; \( p \)-value \( < 0.018 \)), atherosclerosis (46.4% versus 30.1%; \( p \)-value \( < 0.022 \)), and were more often diagnosed with a known prior aortic aneurysm (31% versus 18.8%; \( p \)-value \( < 0.049 \)) Painless patients presented less frequently with hypertension (45.9% versus 68.8%; \( p \)-value \( < 0.003 \)) and with a lower mean systolic blood pressure (mean 147.28 mm/Hg versus 166.8.2 mm/Hg; \( p \)-value \( < 0.003 \)). Syncope was more represented in the painless group (10.3% versus 2.5%; \( p \)-value \( < 0.020 \)).

### Diagnostics

As might be expected, the mean time interval between admission and diagnosis of aortic dissection was 34.0 hours among painless patients, as compared to 19.0 hours in the control group (\( p \)-value \( < 0.006 \)). Computed Tomographic Angiography (CTA) was more often used as the primary diagnostic modality in the painful group (96.2 versus 82.9% \( p \)-value \( < 0.001 \)). Previous angiography was more frequently performed in the painless group and these patients also had significantly more iatrogenic dissections (19.5 versus 1.3%; \( p \)-value \( < 0.001 \)). The iatrogenic cause in the painless group was: Percutaneous transluminal coronary angioplasty (PCTA) in three patients (37.5%), cardiac surgery in three patients (37.5%), and unknown cause in two patients (25%).

### Management and Outcome

Almost two-thirds of the patients were treated medically, which did not differ between groups. (65.2 versus 65.1%; \( p \)-value \( = 0.988 \); Table 4.) Surgical and endovascular therapies were equally used in approximately 35% of each group. In-hospital mortality was 18.6% in the painless group, compared with an in-hospital mortality of 9.9% in the control group (\( p \)-value \( = 0.063 \)). There were no statistically significant differences in complications between both groups. Kaplan-Meier survival curves did not demonstrate a significant difference in mortality during five-year follow-up (\( p \)-value \( = 0.960 \); Fig. 1).

### Discussion

The most common characteristic of TBAAD presentation is acute pain localized to the chest, abdomen,
and back. Previous IRAD reports showed that 95.5% of all AAD patients presented with pain [5]. However, in rare instances the presentation of dissection can be atypical and our study showed that 3.7% of all TBAAD patients were painless, in contrast with previous experiences which reported an incidence up to 17% in AAD [1,2]. The lower incidence that we observed could be explained by the fact that, while this study focused only on TBAAD, previous studies focused on painless dissections in general, including a majority of patients with ascending aorta involvement (Type A acute aortic dissection), which makes up for more than 75% of the patient population [1,2]. In addition, IRAD consists of cardiovascular referral centers, specialized in the treatment of aortic dissection, where patients are referred for surgical/endovascular treatment, whereas patients who are thought to be unfit for invasive management will not be transferred to these centers. Typically, transferred patients have more complications, resulting in a relative low incidence in the IRAD database. The true incidence in the population is probably even higher, as an atypical presentation will likely result in a higher risk of death prior to the diagnosis.

The clinical presentation of dissection patients may be diverse, and sudden collapse or an altered state of consciousness have been reported to be the presenting symptom in up to 30% of all patients [6]. This report also included TAAAD patients, which are more prone to develop complications like syncope or alteration in consciousness [7]. Painless AAD, especially concerning the ascending aorta, presents more often with neurological deficits, syncope, and disturbances in consciousness. These complications influence the perception of pain, resulting in a relative high prevalence of Type A dissection in this patient category. As expected, painless Type B dissection patients did not show this clinical pattern since involvement of the head and neck vessels did not occur.

Our study showed that TBAAD painless patients are older at presentation and more often had a history of atherosclerosis. With increasing age, the incidence of painless dissections might rise, as previously reported [1]. In that study, patients who presented at significantly older age, more frequently had a history of cerebrovascular accidents, and some patients had only atypical symptoms such as dyspnea, nausea, and
abdominal fullness. These three atypical clinical signs were not recorded within the IRAD registry, so we can’t make any comparison.

The pathological mechanism of painless TBAAD is not well understood and multiple explanations for this phenomenon have been proposed. Our study showed that painless patients present with less hypertension. Due to low blood pressure, the propagation of the dissection might develop relatively slow, thereby reducing the wall stress, which could result in reduction of pain. Alternatively, pain will act as an acute stressor, determining an increased blood pressure. Furthermore, the perception of pain can be modulated as the adventitial layer, the site for aortic innervation, is involved by the dissection or affected by previous interventions. In addition, it is thought that other pathologies, like aneurysmatic enlargement, may influence the ability to sense pain. This possibility is supported by the higher incidence of other aortic disease and previous aortic aneurysms in our study population. Most interestingly, significantly more painless patients had a dissection of iatrogenic origin. Iatrogenic dissections are thought to occur very rarely, with Type A dissections reported in 0.04% of the patients during percutaneous coronary interventions and in 0.12 to 0.16% after cardiac surgery procedures [8–11]. The incidence of TBAAD in these patients is thought to be even lower. During such procedures, analgesics and sedation may alter the patient’s perception of pain, increasing the incidence of painless TBAAD in this subset of patients [12].

The in-hospital mortality was 18.9% in the painless group, compared with an in-hospital mortality of 10.3% in the control group ($P = 0.096$). The explanation for this trend is probably 2-fold. First, the painless group tended to present at older age, which is a condition associated with a higher mortality [13]. Second, the extended delay to diagnosis and treatment, due to the difficulty in diagnosis, may have resulted in a higher mortality.

Although this study represents the first report focusing specifically on TBAAD with absence of pain at presentation, it has some limitations. Previous studies reported a higher incidence and registry data might not reflect the true incidence, since the centers are specialized in aortic dissection and therefore receive many referred patients. Furthermore, many patients may have died from a painless dissection before they were diagnosed and therefore are not registered.

**Conclusion**

Painless TBAAD is a relatively rare presentation of aortic dissection and is associated with a history of atherosclerosis, diabetes, iatrogenic origin, and aortic disease like aneurysm. We observed a trend in increased in-hospital mortality rate among painless TBAAD patients, which may be the result of a delay in diagnosis and any type of management due to the absence of classical symptoms. Therefore, physicians should be aware of this relatively rare presentation of TBAAD.

**Conflict of Interest**

Possible Conflict of Interest: IRAD is supported by grants from the University of Michigan Health System, Varbedian Fund for Aortic Research, Mardigian Foundation, and Gore Medical Inc (Flagstaff, Ariz).

**References**


Outcomes of Aortic Arch Replacement Performed Without Circulatory Arrest or Deep Hypothermia

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Abstract

Background: Aortic arch replacement using standard techniques, including deep hypothermic circulatory arrest and selective antegrade cerebral perfusion, is still associated with significant mortality and cerebral morbidity. We have previously described the “branch-first” technique that avoids circulatory arrest or profound hypothermia with excellent outcomes. We now describe our clinical experience with a larger cohort of patients as well as follow-up of our earlier results. We also describe a further technical simplification to this technique. Methods: From 2005 to 2010, 43 patients underwent a “branch-first continuous perfusion” technique for aortic arch replacement. In this technique, arterial perfusion is peripheral, usually by femoral inflow. Disconnection of each arch branch and anastomosis to a perfused trifurcation graft proceeds sequentially from the innominate to the left subclavian artery, with uninterrupted perfusion of the heart and viscera by the peripheral cannula. In the first cohort perfusion to the trifurcation graft was by right axillary cannulation. Since 2009, a modification was introduced such that perfusion is supplied directly by a sidearm on the trifurcation graft. This was used in the last 18 patients of this series. After reconstruction of the debranched arch and ascending aorta, the common stem of the trifurcation graft is anastomosed to the arch graft. In this series, there were 27 males, and mean age was 63 ± 13 years. Fifteen cases (35%) were performed with urgent/emergent priority. Nineteen patients (44%) were operated for aortic dissection, and the remainder for aneurysms. Seven patients (16%) had previously undergone a cardiac surgical procedure. Results: There were two (4.7%) early mortalities while one patient (2.3%) experienced a permanent stroke. One patient (2%) required mechanical support while three (7%) required hemofiltration for renal support. Extubation was achieved within 24 hours in 21 patients (49%) while 19 (42%) were discharged from the Intensive Care Unit (ICU) within two days. Eight patients (19%) did not require any transfusion of red cells or platelets. Mean follow-up duration was 21 ± 19 months and was 100% complete. At three years, survival was 95 ± 3.2%. No patients required subsequent aortic reoperation during this early follow-up period. Conclusions: This modified branch-first continuous perfusion technique brings us closer to the goal of arch surgery without cerebral or visceral circulatory arrest and the morbidity of deep hypothermia. Our early experience is encouraging although greater numbers and longer follow-up will reveal the full potential of this approach. Copyright © 2013 Science International Corp.

Key Words

Aortic arch · Aortic surgery · Cerebral protection

Introduction

Deep hypothermic circulatory arrest with or without selective antegrade cerebral perfusion is currently...
widely utilized for cerebral protection during aortic arch surgery. Nonetheless this technique is still associated with significant risks. Even short periods of cerebral circulatory arrest have been shown to be deleterious for higher cognitive function [1]. While deep hypothermia is frequently used to compensate for the unpredictable duration of cerebral circulatory arrest, its associated morbidities such as prolonged bypass times for cooling/rewarming and coagulopathy are well documented. Selective antegrade cerebral perfusion while providing nutritive cerebral flow introduces the risk of atheromatous and/or air embolism from direct manipulation of the arch branches. It also relies on deep hypothermia alone to provide distal organ protection.

Since 2005, in an attempt to minimize the risks and morbidity associated with aortic arch replacement, our center has adopted a branch-first continuous perfusion technique, in which there are no periods of global cerebral circulatory arrest or deep hypothermia, with encouraging early results [2]. More recently, modifications of this technique have been made to enhance applicability and reduce technical complexity.

We hereby describe our technical modifications and report our early experience with this branch first continuous perfusion technique for replacement of the aortic arch in both elective and emergent settings.

Methods

Patients and Methods

Between, 2005 and 2010, 43 patients have undergone this technique, selectively in the first year and as a routine from 2006 onwards. Of these, 27 were male and 16 were female. The average age was 64 years (range 29–85 years). Preoperative demographic data are shown in Table 1. Of note, 15 were operated as urgent/emergent cases for aortic dissection.

Eighteen patients underwent reimplantation of all three arch branches. Twenty-three patients did not require reimplantation of the left subclavian. Two patients underwent reimplantation of only the innominate. Arch branch reconstruction ceased at the point where the aorta became free of disease.

Concomitant aortic root surgery was performed in 19 patients in whom six patients underwent root replacement via the David reimplantation technique, while other valve-sparing techniques (Yacoub remodeling or reconstruction of the non-coronary sinus and sino-tubular junction) were applied in four patients. Nine patients underwent a Bentall’s procedure, with three and six patients receiving mechanical and tissue valves, respectively. Six patients underwent concomitant coronary artery bypass grafting.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Patients (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 (55–74)</td>
</tr>
<tr>
<td>Male</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Nonelective cases</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Previous Type A dissection</td>
<td>3 (7)</td>
</tr>
<tr>
<td>AVR/ASD</td>
<td>1 (2)</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Coarctation</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Bentall’s</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type A aortic dissection</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Acute dissection</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Chronic</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Operative

Arch branches reimplemented

Trifurcation 18 (42)
Bifurcation 23 (53)
Innominate only 2 (5)

Side-arm inflow modification 18 (42)
Coronary artery bypass grafting 6 (14)
Bentall’s 9 (21)
Mechanical valve 3 (7)
Bioprosthesis 6 (14)
David reimplantation 6 (14)
Other valve-sparing 4 (9)
Elephant trunk 6 (14)
Frozen 4 (9)
Regular 2 (5)
Miscellaneous 1 (2)

Cardiopulmonary bypass time (min) 285 (219–329)
Minimum temperature (degrees C) 27 (22–31)
Cerebral exclusion time 165 (133–222)
Cerebral perfusion flow rate (L/min) 1.0 (0.8–1.4)
Distil circulatory arrest 20 (47)

Continuous variables expressed as median (interquartile range).
Categorical values expressed as absolute values (percentages). AVR/ASD indicates aortic valve replacement, atrial septal defect; CABG, coronary artery bypass grafting.

Operative Technique

Preoperative investigations include axial computerized tomographic angiography (CTA) of the thoracic and abdominal aorta and transesophageal echocardiography (TEE). Intraoperative cerebral monitoring is performed by a combination of electroencephalogram bispectral index (BIS) monitoring, cerebral oximetry (INVOS 3100, Somanetics Corp, Troy, MI) and transcranial Doppler (TCD).
Arterial cannulation is femoral. In cases of severe aortoiliac atheroma, axillary or direct ascending aortic cannulation may be used.

Figure 1. Arterial cannulation is femoral. In cases of severe aortoiliac atheroma, axillary or direct ascending aortic cannulation may be used.

The chest is opened via a median sternotomy. Cardiopulmonary bypass is instituted via femoral arterial inflow and central right atrial drainage (Fig. 1). Left axillary or direct ascending aortic [3,4] cannulation could be used in cases of severe aortoiliac occlusive or iliofemoral dissection or severe descending aortic atheroma, although this was only necessary in a couple of cases.

In the initial experience, left axillary cannulation was added to the femoral inflow to act as a source for antegrade perfusion to the arch branches reimplemented into the trifurcation graft [2]. In the last 18 patients, we totally replaced the need for axillary cannulation by the use of a modified trifurcation graft with an added perfusion side arm (Vascutek Ltd., Renfrewshire, Scotland, UK).

The arch branches are exposed for a length of 3–4 cm using a “no touch” technique. To facilitate this, the thymus is divided in the midline and the innominate vein is mobilized by dividing all its tributaries. This allows complete mobility of the latter structure without having to divide it and potentially impede left cerebral venous drainage.

The innominate artery is clamped just proximal to its bifurcation and about 1 cm distal to its origin from the arch (Fig. 2A). The innominate artery is then divided between the clamps and proximal stump ligated, allowing removal of the proximal clamp and excellent access to the distal innominate stump, which is anastomosed to the first limb of the three-branched graft (Fig. 2B). After the innominate artery anastomosis is completed and deairing maneuvers performed, the side arm of the trifurcation graft is used for antegrade flow. Median cerebral perfusion flow was 1.0 (0.8–1.4) liters per minute with an aim to achieve a right radial pressure of 50–70 mm Hg.

Completion of the innominate anastomosis removes tension on the convexity of the arch, increases its mobility, and enhances access to and exposure of the left carotid artery and in turn the left subclavian artery. A similar process is followed for the anastomosis and reperfusion of the second and third limbs of the branched Dacron graft to the left carotid and left subclavian arteries respectively (Fig. 2C and 2D).

Note that in roughly half the cases the nature of arch pathology allowed retention of the subclavian on the distal aorta, avoiding the need for this step. Where a large arch aneurysm interferes with access to the left subclavian artery, we utilize a number of maneuvers to facilitate its reconstruction. These include (1) a short (1–2 cm) extension of the neck incision along the anterior border of the left sternocleidomastoid muscle can greatly improve exposure; (2) temporarily decreasing the distal perfusion pressure, which reduces the turgidity of the arch and avails more space; and (3) delaying the left subclavian reconstruction until the descending aorta is clamped and the arch resected, thus leaving ample room for left subclavian anastomosis.

At this stage, the perfused trifurcation graft can be laid easily out of the field over the patient’s neck. It is important to note that during this whole process the circulation was not interrupted to either the heart or the distal organs. Also of note is that all arch branch anastomoses are readily in view and complete hemostasis from these sites can be ensured with ease.

The proximal descending aorta is now readily mobilized. This can be assisted by temporary reduction in distal perfusion to increase its maneuverability. Also, division of the ligamentum arteriosum is key to allowing the recurrent laryngeal nerve to “drop away” from the aortic wall. Complete distal control with a clamp is readily achieved in over half of the cases. In the remainder where this is difficult because of adhesions or fragility, use of intraluminal balloon occlusion together with reduced distal flow (so as to not dislodge the balloon) allows distal perfusion to continue. Once the distal anastomosis is completed (20–30 minutes), a clamp is applied to the graft, allowing resumption of full distal flows. If an elephant trunk procedure is needed, then a brief period of distal arrest is used to allow insertion of the prosthesis into the descending aorta, then the composite descending and (soft graft component of) the elephant trunk is controlled as above to allow resumption of distal flows.

Distal anastomosis is performed between the distal arch/descending aorta and an appropriate size tube Dacron graft with a preattached single side arm graft (Ante-Flo Prosthesis, Vascutek Ltd., Renfrewshire, Scotland, UK) (Fig. 2E), or in elephant trunk cases the preexisting Dacron graft is anastomosed to the descending aorta. After completion of this anastomosis, distal body flow is changed from femoral to the sidearm graft (or directly into the graft in the case of frozen elephant trunk) and a clamp applied to the main arch graft immediately proximal to the perfusion port.

Aortic root reconstruction can now proceed if required, and anastomosis between the arch graft and root is com-
completed. Finally, the trunk of the branched graft is passed deep to the innominate vein and anastomosed to the ascending graft, in end-to-side fashion, again without the need to interrupt cerebral perfusion (Fig. 2F).

Data Collection and Analysis
Clinical, investigative, operative, perfusion, and early postoperative data were prospectively collected in a departmental database, with additional data extracted from operation reports, perfusion reports, and intraoperative computerized records. Follow-up data obtained from patients’ records was collected up to August 1, 2011. Kaplan Meier survival analysis was performed using Predictive Analytics SoftWare Statistics Package 17.0 (SPSS Inc., Chicago). Continuous variables are expressed as median (first to third quartile) to account for their skewed distribution.

Results
Intraoperative
Intraoperative data are summarized in Table 1. Median cardiopulmonary bypass time was 285 (219 to 339) minutes. The median minimum temperature was 27 (22–
31) degrees Celsius. The lower range temperatures represent extra caution exercised early in our experience. Median cerebral perfusion flow was 1.0 (0.8–1.4) liters per minute with an aim to achieve a right radial pressure of 50–70 mm Hg. Cerebral perfusion was maintained on a separate antegrade circuit for a median duration of 165 (133–222) minutes. In 20 patients with adhesions or difficult access where distal clamping proved difficult, distal low flow combined with antegrade perfusion via a balloon occlusion catheter was used with moderate hypothermia (26–28 degrees Celsius).

Early Postoperative Outcomes

Postoperative outcomes are detailed in Table 2. There were two mortalities in the early post operative period. The first was due to right ventricular failure in an 85-year-old female patient. She had undergone emergency arch and root replacement in combination with coronary artery bypass grafting (CABG) for a delayed presentation of an acute Type A dissection with a preoperative right ventricular infarct and dysfunction. The second early mortality was in a 61-year-old male patient with acute Type A dissection associated with preoperative malperfusion of the lower limbs and gut. He underwent emergency ascending, arch, and frozen elephant trunk replacement. The procedure was completed uneventfully, however, he continued to suffer the consequences of preexisting gut malperfusion and died of multiorgan failure.

Three patients (7%) experienced neurological dysfunction. The first patient experienced amaurosis fugax, while the second patient experienced left hemiparesis. Both of these conditions resolved completely. These almost certainly occurred secondary to embolic events rather than hypoperfusion. Both early and delayed computed tomography of the brain in both patients did not show any infarction or hemorrhage. The third patient experienced short-term memory loss and expressive dysphasia that did not completely resolve. This occurred on the background of preexisting cerebrovascular disease and an acute Type A dissection with cerebral malperfusion (Table 2). There were no cases of global dysfunction or watershed infarcts to suggest inadequacy of collateral circulation during arch branch clamping. There was one case of transitory left hand hypoperfusion after ligation of an atheromatous left subclavian artery, which recovered spontaneously and did not require a carotid-subclavian bypass.

Thirty-two patients (74%) did not experience any complications. In eight patients (19%), neither red blood cells nor any other blood product was required. Twenty-one patients were extubated within 24 hours and 20 were discharged from the ICU within 48 hours. Three patients (7%) required a tracheostomy while five patients (12%) returned to theater for bleeding.

Follow-up

Median follow-up duration was 21 ± 19 months and 100% complete. There was one late death, occurring in a patient with nonsmall cell lung cancer 58 months after arch replacement. At three years, survival was 95 ± 3.2%.

No patients required reoperation for residual or recurrent aortic pathology. There were no cases of aortic rupture or acute dissection. At last follow-up 31 (72%) patients were in New York Heart Association (NYHA) class 1. The Kaplan Meier survival curve is displayed in Table 3.

Discussion

The combination of deep hypothermia and antegrade cerebral perfusion remains the mainstay of organ protection during circulatory arrest for arch surgery [5,6], yet the reported outcomes are still less

<table>
<thead>
<tr>
<th>Patients (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Visual loss</td>
</tr>
<tr>
<td>Hemiparesis</td>
</tr>
<tr>
<td>Residual deficit</td>
</tr>
<tr>
<td>Return for bleeding</td>
</tr>
<tr>
<td>Tracheostomy</td>
</tr>
<tr>
<td>Mechanical support</td>
</tr>
<tr>
<td>Renal support</td>
</tr>
<tr>
<td>Ischemic gut</td>
</tr>
<tr>
<td>Ischemic limb</td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>Red cells (units)</td>
</tr>
<tr>
<td>Platelets (units)</td>
</tr>
<tr>
<td>No transfusion (of both)</td>
</tr>
<tr>
<td>No transfusion (either)</td>
</tr>
<tr>
<td>Ventilation time &lt;24 h</td>
</tr>
<tr>
<td>ICU time &lt;48 h</td>
</tr>
<tr>
<td>Hospital stay &lt;7 d</td>
</tr>
</tbody>
</table>

Continuous variables expressed as median (inter-quartile range). Categorical values expressed as absolute values (percentages).
favorable compared to procedures on the more proximal aorta especially in terms of cerebral events. In addition, deep hypothermia carries its own spectrum of complications [1,6], which may include coagulopathy. Periods of global circulatory arrest of as short as 20 minutes have been shown to be deleterious to higher mental function and fine motor skills [1].

The advantages of the branch-first continuous perfusion technique used in our center have been discussed in detail previously [2]. The essential advantage is that there are no periods of global circulatory arrest, thus possibly minimizing cerebral morbidity. Cardiac perfusion is maintained throughout the whole of the arch branch reconstruction phase, significantly reducing the period of time of reliance on cardioplegia and the risk of myocardial dysfunction. Maintenance of distal organ and especially liver and kidney perfusion during arch reconstruction reduces the risk of postoperative vital organ dysfunction and postoperative bleeding and may shorten ICU stays.

The two early postoperative mortalities represent a 4.7% in-hospital mortality rate. Both of these occurred in patients presenting with acute Type A dissection with malperfusion syndromes, which is known to have a high in-hospital mortality rate [7]. Nonetheless our results are in line with contemporary studies reporting 30-day in-hospital mortalities ranging between 3.4% to 13% [8–12]. We also continued to observe a low incidence of renal, gastrointestinal, hepatic, and ventilatory impairment.

Reported rates of permanent stroke in contemporary aortic surgery range from 2.0% to 4.8% [1,5,13–15]. The two transient and one permanent neurological deficit sustained in our series gives an incidence in line with these. Importantly, these deficits most likely occurred secondary to embolic events and not hypoperfusion infarcts, thus supporting the safety of individual arch branch clamping.

Early survival at 3 years in this series was 95%. Although longer follow up is required, these results are comparable to larger studies that have reported 3- to 5-year survival between 71% and 87% [8,10–12]. Importantly, no patient has required a reoperation for aortic pathology. If this persists into the long-term follow-up, it may be a testimony to the benefit that the maintenance of cerebral, cardiac, and distal body perfusion in this technique allows even the most complex reconstructions to be completed meticulously in an unhurried fashion, thus providing complete correction of pathology and eliminating imperfections that may have otherwise been tolerated in view of time pressures. This may also be a reflection of the excellent hemostasis achieved, as all anastomoses’ suture lines remain visible and accessible at each stage of the procedure.

The absence of abnormalities in cerebral monitoring during the reconstruction of the left common carotid artery in cases leading up to 2009 encouraged us to apply the same principle “in reverse” to innominate artery clamping. Again this was supported by no abnormalities being detected on cerebral monitoring during the relatively short periods of innominate clamping required. This eliminated the need for axillary artery cannulation and its low but definite risks of axillary artery injury, dissection, or brachial plexus injury [16,17] as well as increased operative time. The latter is especially undesirable during emergency cases. This is particularly the case in obese patients and those with fragile or small-caliber axillary arteries. This technique has evolved to include an added side-arm to the trifurcation graft to provide direct cerebral perfusion. This modified technique has simplified the procedure, lessened technical demand, and has the potential to bring aortic arch replacement into the armamentarium of the nonaortic subspecialized cardiac surgeon.

There may be a number of potential disadvantages of this technique, which have also been previously discussed [2]. Specifically, a drawback of the modified technique described here is that direct right common carotid inflow is interrupted for the anastomosis of the first limb of the branched graft to the innominate artery. This is, however, analogous to interruption of direct left common carotid inflow during anastomosis of the second limb of the branched graft in the previous technique. We have not encountered any abnormality in intraoperative cerebral monitoring during this phase of the procedure thus far. This is most likely due to the extremely rich collateral network in the head, neck, and body wall connecting the three arch branches’ distribution in addition to the typically short
artery clamp times (typically 10–12 minutes). This collateral system significantly supplements the capacity of the Circle of Willis. Despite this theoretical disadvantage, our early experience has supported the ongoing use of this modification.

We acknowledge that cardiopulmonary bypass times are not significantly reduced by our technique and some might argue that the use of deep hypothermic circulatory arrest (DHCA) (along with the associated periods of cooling and rewarming) would result in similar operative and cardiopulmonary bypass times to those that we report. While we agree that DHCA is a well-established technique for arch reconstruction and that it provides the surgeon with a bloodless and uncluttered operative field we feel that its use is associated with a number of clinically significant disadvantages that are not solely associated with the periods required for cooling and rewarming. It is well established that even short periods of DHCA are associated with subtle higher cerebral dysfunction [1,18,19], cerebral reperfusion injury [20], impairment of normal cerebrovascular regulatory mechanisms [21–23], and the generation of excessive cerebral temperature gradients [24,25]. Although cerebral injury can be reduced by the use of ancillary methods of cerebral protection such as antegrade or retrograde cerebral perfusion [26–28], many of those techniques impose various periods of total circulatory arrest. Furthermore, while much of the emphasis during periods of circulatory arrest is focused on avoidance of cerebral injury, preservation of other organs such as the liver, kidneys, and spinal cord is often not specifically addressed, their protection relying on deep hypothermia alone. It is this global hypoperfusion of other organs that occurs during prolonged periods of DHCA with or without cerebral perfusion that we feel leads to much of the morbidity associated with arch surgery. Although the clinical impact of this organ ischemia may be clinically significant as acute specific organ failure, more often it masquerades as more subtle end organ dysfunction culminating in sepsis, gastrointestinal bleeding, and multi-organ failure. Thus, while our cardiopulmonary bypass times are not shorter than DHCA techniques, it is our opinion that the avoidance of deep hypothermia and, more particularly, global circulatory arrest results in lower morbidity and mortality [29].

We acknowledge the limitations of this series, primarily its small size, institutional bias, and evolution of technique over time. As expected, we have noticed shorter bypass and ischemic times with increasing experience that may translate to improved outcomes toward the latter stages of the learning curve. Care is still required to handle the aorta with a no touch technique so as to avoid the risks of embolic events caused by atheromatous disease.

**Conclusion**

This branch-first continuous perfusion technique brings us closer to the goal of arch surgery without cerebral or visceral circulatory arrest and the morbidity of deep hypothermia. This technique presents another alternative to established techniques in aortic arch surgery. The modification described here technically partially simplifies a demanding procedure while our early experience remains encouraging. Greater numbers and follow-up are anticipated.

**Acknowledgments**

The authors would like to acknowledge the assistance of Dr. John McKay in addition to Ms. Margaret Shaw and Beverley Toone. We also thank Ms. Beth Croce for her excellent illustrations.

**Conflict of interest**

None

**References**

EDITOR’S COMMENTS AND QUESTIONS

Matalanis shows us his technique for an ingenious sequential “branch first” approach to aortic arch replacement. His technique is able to avoid deep hypothermic arrest, albeit at the “expense” of short durations of deprivation of blood flow to individual arch branches. He has accumulated a considerable—and very favorable—experience with this alternative technique.
Urgent Carotid Endarterectomy in Patients with Acute Neurological Symptoms
The Results of a Single Center Prospective Nonrandomized Study

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Abstract

Background: To evaluate the feasibility and the safety of performing urgent (within 24 hours) carotid endarterectomy in patients with carotid stenosis presenting with repetitive transient ischemic attacks or progressing stroke. Methods: Thirty consecutive patients underwent urgent carotid endarterectomy for repetitive transient ischemic attacks (N = 12) or progressing stroke (N = 18) according to the following criteria: two or more transient ischemic attacks or a fluctuating neurological deficit over a period of less than 24 hours (progressing stroke), no impairment of consciousness, no cerebral infarct larger than 1.5 cm in diameter on computed tomography and a carotid artery stenosis of 70% or more on the appropriate side, diagnosed by echodoppler ultrasonography and/or arteriography. Patients with cerebral hemorrhage were excluded. All patients were examined pre- and postoperatively by the same neurologist and surgery was performed by the same vascular surgeon. All the patients underwent a cerebral CT scan within 5 days after surgery. Results: There were 19 men and 11 women. The mean age was 71 ± 7.6 years. The time delay of surgery after the onset of transient ischemic attacks or progressing stroke averaged 19.4 ± 11.5 hours. For patients suffering progressive stroke, one developed a fatal ischemic stroke 24 hours after surgery, five showed no improvement of their neurological status after surgery, but none worsened. Twelve patients experienced significant improvement of their neurological status with an European Stroke Scale of 77.9 ± 25.2 at admission and 95.8 ± 4.6 at discharge, and all but one of those patients had a Barthel’s index value over 85/100 at discharge. The 12 patients with repetitive transient ischemic attacks had an uneventful postoperative outcome. The mean duration of follow-up was 3.4 ± 1.2 years. No patient developed another transient ischemic attack or ischemic stroke during the follow-up period. Conclusions: The results of our series documented the feasibility and the safety of performing urgent (within 24 hours) carotid endarterectomy in patients presenting with repetitive transient ischemic attacks or progressing stroke. This procedure seems to us to be justified by the fact that waiting for surgery may lead to the development of a more profound deficit or another stroke in these neurologically unstable patients whose only chance for neurological recovery is in the early phase.

Key Words
Carotid endarterectomy · Transient ischemic attacks · Stroke in evolution

Introduction

Carotid endarterectomy (CEA), first performed in 1953 by DeBakey [1], is an effective and recognized
vascular elective procedure for symptomatic patients with moderate or severe (≥70%) carotid stenosis and in patients with severe asymptomatic stenosis [2,3]. But the best timing to perform CEA in patients with acute neurological symptoms (repetitive transient ischemic attacks, minor stroke or stroke-in-evolution) has for a long time been subject to controversy and is still a source of debate. In fact, to our knowledge, there are no prospective randomized trials to determine which neurologically unstable patient (presenting repetitive transient ischemic attacks or stroke-in-evolution), might safely undergo urgent or delayed CEA.

In the past, the increased risks of reperfusion injury and conversion to hemorrhagic infarction have led to the historical recommendation of delayed CEA in patients with acute neurological symptoms. But, in recent years, most published data demonstrated that the risk of recurrent stroke in the first few days after a transient ischemic attack (TIA) or minor stroke appears to be much higher than previously estimated. Rothwell et al. [4], assessed the risk of stroke at 7, 30, and 90 days after CEA in NSCET and ECST studies [3,2] and the Charing Cross series results [17], the following inclusion criteria have been used: symptomatic carotid stenosis of 70% or more, with unstable neurological status consisting in repetitive TIA or progressive stroke evolving no longer than 24 h, No impairment of consciousness, No cerebral infarct larger than 1.5 cm in diameter on preoperative CT-scan.

We performed a prospective nonrandomized protocol for urgent (within 24 h) CEA in neurologically unstable patients (presenting with repetitive TIA or progressing stroke) with a symptomatic carotid stenosis of more than 70% in order to assess the safety of this therapeutic approach.

Methods

During a five year period, we performed a single center, prospective, nonrandomized consecutive series of urgent CEA. In accordance with the NASCET and ECST studies [3,2] and the Charing Cross series results [17], the following inclusion criteria were used: symptomatic carotid stenosis of 70% or more, unstable neurological status consisting in repetitive TIA or progressive stroke evolving no longer than 24 h, no impairment of consciousness, and no cerebral infarct larger than 1.5 cm in diameter on preoperative CT-scan (Table 1). There were no exclusion criteria except for age over 80 years. Hemorrhage seen on the initial CT-scan eliminated the patient from the study. The term “progressing stroke” is applied to patients with a neurological deficit that has progressed or fluctuated over a period of at least 24 hours. The diagnosis of carotid stenosis was based on echodoppler ultrasonography and/or selective carotid angiography. The degree of stenosis was determined by means of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. All patients were examined by the same neurologist pre- and postoperatively (PD). Neurological evaluation of the patients was blinded from the surgeon’s clinical examination to avoid under or overestimation in the patient’s clinical status.

All patients were scored by the European Stroke Scale (ESS) [18] at admission and at discharge (maximum ESS score is 100 and indicates a patient without any neurological deficit). Barthel’s index [19] was only evaluated at hospital discharge because it is impossible to determine preoperatively patient’s autonomies. It is considered that a patient is independent at home if his score (Barthel’s index) exceeds 85. The preoperative investigation included in all cases: blood sample analysis, ECG and/or cardiac echography, chest X-ray, carotid echo color Doppler ultrasonography, selective angiography of the carotid arteries, and cerebral CT-scan. No MRI was performed because MRI was not accessible on an emergency basis. From the day of the admission to the discharge from hospital, all patients received heparin at a prophylactic dose, along with statin therapy. As CEA was performed on an emergency basis (within the first 24 hours), no aspirin was administrated preoperatively.

A standard surgical open endarterectomy, with Javid shunt (to maintain cerebral circulation during surgery) and prosthetic patching, was performed under general anesthesia by the same vascular surgeon (NS) in all cases. The postoperative care was performed in a stroke unit, with ECG, noninvasive arterial blood pressure monitoring, and transcutaneous oxygen saturation monitoring for at least 48 hours. All the patients underwent a cerebral CT scan before discharge, within the five days after surgery. In the postoperative period, patients were maintained on a low dose of heparin (4000 IU) and statin therapy together with their scheduled medications. At discharge from the hospital, antiplatelet therapy (acetylsalicylic acid 100 mg daily) was started. During regular follow-up, all patients were...
reviewed by the same neurologist (PD) and the same surgeon (NS) independently from each other at six weeks after surgery and every six months during the first year, and every 12 months thereafter. Assessment of outcome was based on follow-up control examination.

**Statistical Analysis**  
Patient details, including age, gender, and comorbidities were collected in an Excel database (Microsoft Ltd). Categorical data were presented as absolute frequencies and percent values. Quantitative measurements were expressed as mean ± SD. Data on survival, neurological events, and patency was studied directly.

**Results**

**Patients Characteristics**  
The study concerns 30 consecutive patients included out of a series of 638 patients admitted to the emergency department for acute TIA or progressive stroke during a five year period. In these 30 patients, CEA was performed within 24 hours following the neurological event (repetitive TIA or progressive stroke). Of these, there were 12 patients presenting with repetitive TIA and 18 progressive strokes. There were 19 men and 11 women with a mean age of 71 ± 7.6 years. No patient had any neurological deficit before the onset of repetitive TIA or progressing stroke. Baseline patient characteristics and medical history are presented in Table 2.

**Perioperative Characteristics**  
All patients had documented internal carotid artery stenosis of 70% or more. For patients suffering progressive stroke (n = 18), the degree of carotid artery stenosis was 85% or more. The mean delay of surgery after onset of the first TIA or progressive stroke was 19.4 (±11.5) hours (range, 6–48 hours). At operation, the macroscopic examination of the internal carotid artery in all 30 patients showed a complex ulcerated plaque and/or an intraplaque hemorrhage.

**Outcomes**  
One patient (5%) with initial progressive stroke developed a fatal ischemic stroke within 24 hours after the operation, and Doppler ultrasonography performed immediately showed very good patency of the operated carotid artery. Five (28%) of the 18 patients with progressive stroke had an incomplete recovery with limited residual neurological deficit and experienced no clinical improvement but none of them worsened after the operation, whereas the 12 other patients (67%) with residual neurological deficit (as a result of their progressive stroke) showed significant improvement of their clinical status. The 12 patients with repetitive TIA remained free of neurological deficit after the operation. All but one of the 18 patients with progressive stroke had a Barthel’s index over 85 at hospital discharge. The mean ESS of the 18 patients with progressive stroke was 77.9 ± 25 at admission, and was 95.8 ± 4.6 at discharge. All the patients underwent a cerebral CT scan within five days after surgery. No hemorrhagic transformation of cerebral infarcts was detected. No new lesion on postoperative CT scan was found in the 12 cases of TIA. All of the 18 progressive stroke patients had a lacunar size lesion (<15 mm); there had been no enlargement of the lesion postoperatively except in one case in which there was a large infarction (>2 cm). There was no reoperation for cervical hemorrhage or wound infection. No patients developed vocal cord paralysis due to nerve injury. Patients were discharged after a median of four days (range, 4–10 days). The mean duration of follow-up was 3.4 years (±1.2) and was 100% complete in all patients. No residual or recurrent stenosis was documented on echo color Doppler ultrasonography follow-up. No recurrent stroke and/or TIA, no cardiac event, and no death occurred in this series during follow-up.

**Discussion**

Timing of CEA in patients with acute neurological symptoms still remains a challenging but unresolved problem [5–7,20]. The management uncertainty can be explained by the inability to predict who is at higher early risk of a recurrent stroke after a cerebrovascular
event (TIA or stroke). Interestingly, a subanalysis of the NASCET results has revealed that the benefit of CEA
versus medical treatment is greatest if the symptomatic
carotid artery stenosis is operated within two weeks
following the index neurological event [14,15]. Among
the medically treated patients, the risk of ipsilateral
stroke is highest immediately after the initial ischemic
event and subsequently drops dramatically [17].

In recent years, several studies (Table 3) have shown
very good results and outcomes for urgent CEA pro-
cedures. In the Charing Cross series [17], 19 patients
suffering from progressing stroke and 14 patients pre-
senting with repetitive TIA underwent urgent CEA (all
patients were operated within 48 hours after the onset
of symptoms). There was a good evolution in all but
three cases. All the patients had a small infarct size
(<2.0 cm) on preoperative CT scan, were conscious,
and had a mild neurological deficit. The criteria for the
selection of our patients have been chosen in the light
of the results of the Charing Cross series. The choice of
these criteria was based on the assumption that a
severe neurological deficit or impaired consciousness
often implies a large infarction in progress, eventually
but not yet visualized on early cerebral CT scan, lead-
ing to a higher risk of postoperative bleeding because
of hyperperfusion in a large ischemic brain area. In our
study, using these criteria, all but one patient had a
good outcome. One patient suffered a fatal stroke due
to postoperative enlargement of the existing small
cerebral infarction. Intraoperative embolization was
probably the cause because Doppler ultrasonography
performed immediately showed very good patency of
the operated carotid artery.

Gertler et al. [21] reported their experience in neuro-
logically unstable patients with carotid stenosis present-
ing with crescendo TIA and SIE, of whom only one
patient (2.7%) worsened his neurological deficit after
CEA within 24 hours. Based on these good results, they
recommend urgent CEA. Most recently, Leseche et al.
[12,13] reported excellent outcome of urgent CEA in the
acute phase of SIE and crescendo TIA, with no perioper-
ative stroke or death. The mean delay to surgery from
initial examination was five days. For patients operated
for SIE, a complete neurological recovery was observed
in 81% of patients, while 19% maintained a residual
deficit. No patient presented a worsening of his deficit
following urgent CEA. In a meta-analysis of 47 studies on
carotid surgery published between 1980 and 2008, Re-
rkasem et al. [20] found no excess operative risk for early
(urgent) CEA versus delayed CEA.

However, less favorable outcome after urgent CEA
in neurologically unstable patients has been reported
by other investigators. These studies demonstrated a
higher rate of perioperative complications after

### Table 3. Results of Urgent CEA (within 15 d) Reported Recently in the Literature

<table>
<thead>
<tr>
<th>Author and year</th>
<th>No. of patients</th>
<th>Mean interval between symptom and CEA</th>
<th>In-Hospital mortality rate</th>
<th>Complications (stroke rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gertler et al., 1994 [21]*</td>
<td>52</td>
<td>&lt;24 h</td>
<td>0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Schneider et al., 1999 [22]*</td>
<td>43</td>
<td>≤72 h</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Brandl et al., 2001 [23]*</td>
<td>16</td>
<td>&lt;24 h</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Gay et al., 2002 [11]*</td>
<td>21</td>
<td>&lt;24 h</td>
<td>9.5%</td>
<td>–</td>
</tr>
<tr>
<td>Huber et al., 2003 [24]*</td>
<td>67</td>
<td>2 d</td>
<td>3.0%</td>
<td>13%</td>
</tr>
<tr>
<td>Sbariga et al., 2006 [10]*</td>
<td>96</td>
<td>1.5 d</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Karkos et al., 2007 [8]*</td>
<td>42</td>
<td>3 d</td>
<td>4.8%</td>
<td>4.8%/19%</td>
</tr>
<tr>
<td>Bazan et al., 2008 [6]*</td>
<td>764</td>
<td>–</td>
<td>2.0%</td>
<td>2.88%/3.1%</td>
</tr>
<tr>
<td>Ballotta et al., 2008 [25]*</td>
<td>102</td>
<td>8 d</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Gorlitzer et al., 2009 [9]*</td>
<td>28</td>
<td>4 d</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Leseche et al., 2011 [12, 13]*</td>
<td>91</td>
<td>5 d</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Dorigo et al., 2011 [26]*</td>
<td>75</td>
<td>&lt;24 h</td>
<td>2.7%</td>
<td>–</td>
</tr>
<tr>
<td>Capoccia et al., 2012 [27]*</td>
<td>48</td>
<td>&lt;24 h</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Present study*</td>
<td>30</td>
<td>&lt;24 h</td>
<td>3.3%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

*Study concerns patients with acute ischemic stroke.

*aStudy concerns patients with crescendo TIA.
urgent CEA in neurologically unstable patients (presenting crescendo TIA and SIE) compared with delayed CEA. Karkos et al., [7] in a meta-analysis, reported a 16.9% perioperative stroke rate and a 20% combined stroke/death rate for urgent CEA after stroke-in-evolution. Considering crescendo TIA, the analysis revealed a more favorable outcome (6.5% perioperative stroke rate and a 9% combined stroke/death). In a meta-analysis done by Bond et al. [28] and Halm et al. [29], the operative risk of CEA increases when it is performed after stroke-in-evolution (a 14.0% 30-day stroke/death rate), compared to a 2.8% 30-day stroke/death rate after CEA for asymptomatic carotid artery stenosis.

This rather elevated morbidity-mortality should be balanced against the stroke risk in these neurologically unstable patients if surgery had not been performed. Actually, no randomized controlled trial has been done comparing the outcome of crescendo TIA and stroke-in-evolution treated medically versus urgently operated.

Early CEA for symptomatic severe carotid stenosis (≥70%) in neurologically unstable patients may be justified by the instability of the lesion, in order to prevent a subsequent complete or more severe stroke. In all of our patients, an ulcerative or hemorrhagic plaque was discovered intraoperatively. Urgent removal of this unstable embolic source has some logic. An arbitrary 2-week delay for CEA probably exceeds the risk of urgent CEA and may expose the neurologically unstable patient to a risk of recurrent or more disabling stroke, or to an occlusion of the internal carotid artery. Before starting our prospective study, in some cases with a small cerebral lesion, we had chosen medical treatment before performing urgent surgery. Unfortunately in some cases, we observed fatal neurological events a few days later, after the first neurological events (unpublished data).

In contemporary literature, there exists consensus that a patient presenting with an acute, nondisabling neurological deficit with complete or partial recovery should benefit from a carotid endarterectomy without delay. For the high-risk group of neurologically unstable patients (crescendo TIA and SIE), who often present with subocclusive stenosis with friable ulcerated plaque, the current available literature data are less conclusive. Some series reporting a rather high perioperative morbidity-mortality seem to discourage urgent CEA in this setting. However, in our small experience, and in some centers of excellence, the operative outcome of urgent CEA in neurologically unstable patients was favorable. The creation of a “Stroke Unit” could favor the management and development of urgent CEA while allowing better selection and management of these unstable patients.

Limitations of the Study Our results should be interpreted in light of several limitations. First, the number of patients enrolled in this single center prospective study is too small to give definite conclusions. This was the reason why a formal statistical analysis was not performed. However, due to the heterogeneity and paucity of data in the literature, subject to controversy and still a source of debate, our experience may add to the management of these unstable neurological patients. Second, it is important to note that our study is not randomized. Although randomized trials are certainly the gold standard in clinical study, in neurologically unstable patients, such a trial is difficult for ethical reasons.

Conclusion Our consecutive series shows that urgent CEA can be performed safely in selected patients with an evolving or unstable neurological deficit. It also confirms the relevance of some previously noticed criteria for the prognosis of urgent CEA, such as a normal level of consciousness, the absence of large cerebral infarction on preoperative cerebral CT scan, and the limited severity of the neurological deficit before the operation. We may recommend surgery within 24 hours for all symptomatic patients with unstable plaques diagnosed by imaging tools. Urgent CEA seems to us to be justified by the fact that a symptomatic carotid stenosis is an unstable lesion and waiting may lead to the development of another stroke that is more disabling for the patient. The perioperative risk can be reduced with better diagnostic strategies and must be balanced against the natural history if surgery is not performed. Only a large randomized multicenter prospective trial will be able to conclusively assess the effectiveness and outcome of urgent CEA in neurologically unstable patients.
References


EDITOR’S COMMENTS

Dr. Sakalihasan and colleagues show us that prompt open surgical therapy for recurrent TIAs or unstable stroke in evolution can lead to excellent clinical outcomes and apparent salvage of at-risk cerebral tissue. They have taken a courageous posture. While not a large-scale randomized study, this report gives an important “real world” glimpse at what can be accomplished with aggressive, non-timid surgical care. We look forward to watching their experience grow based on these very favorable institutional results. It is important to note that the operated patients were selected from among hundreds of patients presenting during the time interval of this study; clinical judgment in patient selection, in addition to the stated inclusion and exclusion criteria, likely was an important factor in attaining favorable results.
Acute Traumatic Thoracic Aortic Injury
Considerations and Reflections on the Endovascular Aneurysm Repair

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Abstract
Traumatic rupture of the thoracic aorta is a life-threatening lesion and it occurs in 10 to 30% of fatalities from blunt thoracic trauma and is the second most common cause of death after head injury. Immediate surgery is often characterized by a high mortality and morbidity rate. Delayed repair of traumatic aortic injuries has significant survival benefits and a much lower mortality rate compared with early open repair. Despite developments in operative techniques, there still remains considerable operative mortality and morbidity associated with a surgical approach even if delayed. Endovascular stent grafts for the thoracic aorta represents an alternative to the conventional approach for traumatic aortic rupture. Because of the lower invasivity avoiding thoracotomy and use of heparin, endovascular repair can be applied in acute patients without the risk of destabilizing pulmonary, head or abdominal traumatic lesions. However, despite the good deal of convincing evidence for endovascular treatment for thoracic aortic diseases and for traumatic aortic injuries as a valid and efficacious alternative to surgery, several reports show a variety of late complications of thoracic endografts especially for first-generation stent-grafts. In light of this, is the endovascular treatment really safe, efficacious and free from complications in the long term? This manuscript aims to offer a moment of reflection on this important chapter of aortic pathology.

Key Words
Aortic · Traumatic · Endovascular · Acute injury

Introduction
Traumatic rupture of the thoracic aorta is a life-threatening lesion and it occurs in 10 to 30% of deaths due to blunt thoracic trauma and it is the second most common cause of death after head injuries [1,2]. The highest mortality usually occurs within the first few hours after injury; almost 90% of patients die at the scene of the accident and approximately one third of patients who arrive at the hospital die before surgical treatment [3,4].

The first references about aortic rupture date back to Vesalius in 1557, after falling from a horse. Nowadays traumatic aortic rupture is the second most common cause of trauma-related deaths, leading to 8000 deaths per year in USA [5].

The majority of tears or ruptures occur at the aortic isthmus; at this site, the relatively mobile thoracic aorta joins the fixed arch and the insertion of the ligamentum arteriosus. In 1947, Strassman reported in a cohort of 7000 autopsies only 0.7% of patients with traumatic aortic rupture. But several recent investigations have shown that traumatic aortic rupture occurs in 22% of fatal blunt trauma [1,6]. In the era of high-speed motor vehicles, there has been an increased
incidence of traumatic aortic injuries. In fact, injury is often associated with rapid deceleration in road traffic accidents or falls. The use of seat belts has partially modified the characteristics of the trauma impact that leads to aortic injury. However, air bags and seatbelts do not protect against this type of impact. On the other hand, the frequency of lethal injuries in head-on collisions is lowered by the mandatory use of restraints, which protect the victim from thoracic and head lesions, but not from the mechanism producing aortic injury.

The diagnosis and management of traumatic thoracic aortic injuries have undergone some major changes in the last few years. In fact, the replacement of chest X-rays by routine Computed Tomography (CT) scan for screening purposes in high-speed deceleration injuries has resulted in an earlier and more frequent diagnosis of traumatic aortic injuries. Angiography has largely been replaced by CT scan for the definitive diagnosis of traumatic aortic ruptures.

Nowadays, angio CT-scan represents the gold standard for the diagnosis of traumatic aortic ruptures. It is widely available in emergency departments and it allows us to study the total body in a few seconds, also highlighting minimal aortic lesion.

The best time to intervene in the aortic lesion and whether surgery should be preceded or followed by the treatment of associated traumatic lesions have long been a matter of debate. Immediate surgery has been characterized by a high mortality and morbidity rate, ranging between 20 to 40%. In a retrospective report of 144 patients undergoing surgery within an average of six hours after arrival in hospital, there was an intraoperative mortality of 10.2% and postoperative morality of 18.4% with major postoperative morbidity such as paraplegia reaching 10.5% [7]. In a recent multicenter trial involving 274 patients collected over 2.5 years, the overall mortality was 31%, with 14% of operative mortality in stable patients undergoing planned thoracotomy [8]. In light of this very high risk for immediate surgical intervention, in the past the surgical repair of an aortic rupture had been delayed because of coexisting injuries such as central nervous system trauma, severe respiratory insufficiency, extended body-burns sepsis, and contaminated open wounds, rendering the surgical risk too high as reported by Akins in 1981 [9].

Because of the high morbidity and mortality, since 1992 we have delayed aortic repair in all patients who have arrived alive at the hospital unless signs of impending aortic rupture such as hemodynamic instability, massive hemothorax, and/or contrast media extravasation on CT-scan were present [10]. Several studies have shown that delayed repair of traumatic aortic injuries has significant survival benefits and a much lower mortality rate compared with early open repair [11]. In 2005 we reported an improvement of patient outcome with traumatic rupture of the thoracic aorta by delaying surgical repair until after management of major associated injuries and in the absence of signs of impending rupture [12].

In light of this, in our institutions, for the management of traumatic aortic lesions, we routinely adopt the algorithm reported in Figure 1. Surgery or endovascular treatment is delayed in the case of stable patients, while immediate surgical or endovascular repair is reserved for unstable patients with signs of impending rupture.

It is clear that despite developments in operative techniques, considerable operative mortality and morbidity associated with a surgical approach still remain, even if delayed. Endovascular stent grafting of the thoracic aorta provides an exciting new alternative to the conventional approach for treating traumatic aortic rupture and it is emerging as the preferred technique for elective or emergent treatment of descending thoracic aortic lesions. It is a less invasive approach compared with open surgery and it is preferable for stabilization of the aortic lesion in patients with multiple traumatic injuries. Because of the lower invasiveness, avoiding thoracotomy and the use of heparin, endovascular repair can be applied in the acute patients without the risk of destabilizing pulmonary, head, or abdominal traumatic lesions. In early clinical series, endovascular treatment demonstrated lower morbidity and mortality in comparison with open surgical repair even in high-risk patients [13]. At present, several reports in the literature have provided data on comparative results of endovascular therapy with respect to open surgery, supporting the use of stent graft in traumatic aortic injuries, both in acute and chronic cases. In a 2008 meta-analysis, Xenos showed that endovascular treatment of descending thoracic aortic trauma is a valid alternative to open surgical repair. It is associated with lower postoperative mortality and ischemic spinal cord complication rates [14].

In 2008 Demetriades, in a multicenter study of the American Association for the surgery of Trauma re-
ported a considerable reduced mortality rate in the endovascular repair group as compared with open surgical repair [15].

Even if the majority of traumatic injuries are stable lesions, in approximately 5% of them, the risk of rupture may be high in the acute phase. Signs of impending rupture such as uncontrolled blood pressure, contrast medium extravasation on CT-scan, repeated hemothorax, periaortic hematoma, or irregular lesions are considered signs of instability [16].

Even for endovascular treatment in the acute phase we deal with the same question: emergency or delayed treatment? Sometimes the aortic tear, acting with a valve mechanism, may cause a pseudo-coarctation syndrome producing a reduction of flow in the descending aorta with lower extremity ischemia. This complication represents an emergency, accounting for 10% of victims. In these unstable patients, endovascular techniques offer a suitable alternative to emergency open repair, even if some limitations of the endovascular procedures exist such as possible facial bone trauma which contraindicates transesophageal echo or frequent aortic wall intramural hematoma with consequent high risk of stent-graft migration.

Because endovascular treatment requires some peculiar anatomic conditions, not all the patients can be treated. Proper peripheral vascular access (at least 7–8 mm of diameter of femoral or iliac artery) is necessary, but this condition is not always available, especially in young patients. One of the most important anatomic characteristics of any lesion allowing endovascular treatment is the presence of an adequate proximal neck (at least 5 mm of non-diseased aortic wall from the origin of the subclavian artery). The aortic isthmus is usually very close to the left subclavian artery and sometimes the lesion is in contiguity with, or at a limited distance from, the origin of the vessel. Stent grafting of the descending thoracic aorta ideally requires a proximal landing zone distal to the origin of the left subclavian artery and proximal to the visceral arteries.

Several studies have reported the artificial creation of a landing zone by covering the left subclavian artery with the stent graft, with or without previous subclavian to carotid transposition or bypass grafting, increasing the risk of ischemic complications such as stroke, left arm and spinal cord ischemia, or cerebellar infarction [17–19]. Revascularization of the left subclavian artery with transposition or bypass from the carotid artery has been shown to prevent these complications.

Sepehripour in a meta-analysis of 2011 showed that when coverage of the left subclavian artery is anatomically necessary, partial coverage is better than complete coverage in order to avoid these complications. Revascularization may be considered, but these decisions should consider the individual patient scenario [20].

But is the endovascular treatment really safe, efficacious, and free from complications in the long term?
In general, despite the fact that there is a good deal of convincing evidence for endovascular treatment for thoracic aorta diseases and for traumatic aortic injuries as a valid and effective alternative to surgery, several reports show a variety of late complications, especially for first-generation thoracic endografts [21].

Both short- and midterm outcomes after endografting thoracic aortic lesions are encouraging, with significantly lower morbidity and early mortality compared with open surgery. However, despite emerging popularity and growing interest as an alternative to surgery, endograft design and manufacturing have not kept pace with growing clinical ambition. Major challenges associated with endovascular procedures using the current generation of endografts range from the relative rigidity and size of the delivery system to the failure of thoracic endografts to conform snugly with the anatomy of the aortic arch [22].

Various structural and positional changes in older first-generation endografts have been reported. The time-related changes in shape, physical structure and position of the stent-grafts have, as a consequence, secondary endoleaks, graft thrombosis, aneurysm rupture, and reperfusion from collaterals [23]. The aorta of patients with traumatic injuries differs from atherosclerotic diseased vessels for which these grafts were designed. Usually these patients are younger and have normal, smaller proximal aortic diameters, such that grafts are oversized by 10% to 20%. Since smaller endografts are not available, large mismatches between the diameter of the aorta and the endograft may occur, thus increasing the risk for endograft collapse. In case of bigger oversizing, the endograft undergoes significant compression forces and torque at the proximal descending aortic angle. Excessive oversizing, especially if by greater than 25%, may cause wrinkling of the stent graft and make it subject to collapse [24]. The collapse may occur within 24 hours after stent implantation or after some months. Graft collapse may cause total aortic closure and distal malperfusion [25–27].

Usually, it is common to use more than one component to treat a thoracic aortic aneurysm, which causes some risk of device separation as the aortic wall remodels, especially if there is insufficient component overlap or coupling [28]. As a consequence, type I and type III endoleaks are more likely to occur due to challenging seal zones and device migration increasing the likelihood of developing systemic pressures within the aneurysm sac.

Physiological coarctation of the aorta from protrusion of a thoracic stent graft into the arch is a complication of thoracic stent grafting distinct from the more commonly described graft collapse. The protrusion of the stent graft into the arch causes the obstruction of the aorta. Patients may present with symptoms of aortic arch coarctation such as proximal hypertension, left upper extremity ischemia, or left carotid or vertebral insufficiency despite having a patent endograft [29]. Perforation of the aortic wall by a stent graft is an infrequent complication of thoracic stent-graft implantation. This complication is usually due to the metallic component of the stent causing friction against the aortic wall because of continuous pulsatility of the aorta. This complication underlines the importance of completely examining the long-term durability and compatibility of prosthetic materials [30].

Aortoesophageal fistula secondary to thoracic aortic stent-graft placement is an unusual but catastrophic complication of endovascular repair of the thoracic aorta with very limited therapeutic options. The fistulae may arise secondary to the development of pseudoaneurysm, endoleak into the residual aneurysm sac, or erosion of the stent graft through the aorta from graft infection [31–34].

In light of the above and in consideration of the complications which endoprostheses may undergo, continuous and meticulous follow-up of these devices with regular imaging is advised [35].

It is clear that frequent and sustained surveillance is essential for safe management of patients. The primary motivation for close surveillance includes the evaluation of residual aneurysm sac size, presence of endoleak, and device migration allowing an early identification of potential adverse events. In fact a reintervention rate of 10% per year has been reported for treatment of problems identified on follow-up surveillance [36].

The CT-scan is usually the method of choice for periodic assessments during follow-up protocols after endovascular aneurysm repair (EVAR). The routine use of contrast-enhanced CT-scans has become more controversial since repeated scans with their inherent ionizing radiation have been suggested to have carcinogenic potential. This evidence suggests that less-
frequent CT scans may simplify the follow up protocol, reduce radiation exposure and the total cost of EVAR [37,38].

In spite of the fact that endovascular techniques can now be considered an effective alternative to open surgery in the treatment of traumatic thoracic aortic injuries, the long-term durability of a stent graft for traumatic aortic lesions is still unknown. Techniques and technologies continue to improve and the results obtained should be viewed as work in progress.

Early outcomes appear successful, but these results may be deceiving especially for those patients with compromised anatomy and the risk of late stent-graft migration, loss of device integrity and local erosion or rupture of the aortic wall. At present, the lack of long-term data and the evolving technology of stent-graft design should be an incentive for exercising great care in patient selection [39,40].

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References


27. Jonker FHW, Schlosser FJV, Geirsson A, Sumvascsurg.2009.07.007


Dissection of Iliac Artery in a Patient With Autosomal Dominant Polycystic Kidney Disease
A Case Report

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Abstract
Autosomal dominant polycystic kidney disease (ADPKD) is a risk factor for several cardiovascular disorders such as intracranial aneurysm or aortic dissection, preferentially occurring at the thoracic or abdominal level. A 47-year-old man suffering from ADPKD had renal transplantation. Sixteen hours after surgery, he presented with left leg pain. Clinical and ultrasound examination revealed thrombosis of the external left iliac artery. Therefore, we decided to perform intra-arterial angiography to evaluate the possibility of an endovascular treatment. Aorto-femorography showed an obstruction of the external left iliac artery that was found during emergency surgery, consecutive to a dissection, which occurred following the surgery for kidney transplantation. The resected segment of the dissected vessel was analyzed by histology. Collagen fibers organization and density in the adventitia and smooth muscle cells density in the media were similar in the dissected and a normal artery from a healthy donor. By contrast, an almost complete disappearance and fragmentation of elastic lamellae were observed in the media of the dissected artery, most likely responsible for the weakening of the arterial wall and its dissection. Association between ADPKD and single dissection of the iliac artery has been rarely reported. Relationship between inactivation of polycystin/PKD genes and elastic fibers degradation through elevated TGFβ signaling and matrix metalloproteinase 2 (MMP2) elastolytic activity, as recently reported in ADPKD, would be worth investigating.

Key Words
Autosomal dominant polycystic kidney disease · Aortic dissection · Elastic lamellae

Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent genetic renal disorder with an incidence of 1/1000. It is characterized by the progressive formation of fluid-filled cysts in the kidney leading to early onset renal failure. Several cardiovascular disorders have been associated with ADPKD, hypertension being the most common problem [1], while other major complications include intracranial and aortic aneurysms and dissections (for review, see [2]). Here, we report a case of left iliac artery dissection in a patient with ADPKD.

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Case Report

A 47-year-old man presenting with familial polycystic kidney disease (ADPKD) underwent surgery for kidney transplantation. During surgery, any macroscopic anomalies were observed at the level of close iliac artery. However, approximately 16 hours after surgery, the patient presented pain at the level of the left leg. Clinical examination revealed absence of left femoral pulses. Ultrasound examination confirmed thrombosis of the aorto-iliac access. Computed tomography (CT) angiography revealed the absence of perfusion at the level of the transplanted kidney and confirmed the thrombosis of the left iliac artery (Fig. 1A). Therefore, intra-arterial angiography was performed to decide which treatment could be performed. An endovascular treatment was not possible because of the complete thrombosis of the external iliac artery with suspected dissection (Fig. 1B and 1C). The patient underwent emergency surgery, during which a localized hematoma was observed at the level of the arterial anastomosis with extension to the external iliac artery. The diagnosis of dissection was made after reopening of the anastomosis. Because of the fragile aspect of the arterial tissues, we performed a large resection of the dissected segment of the iliac artery that was replaced by an arterial prosthesis. The donor renal artery was reimplanted on the prosthesis. Pieces of the dissected segment were fixed for histological analysis. This study was approved by the hospital-university ethics committee.

The general organization of the iliac artery was analyzed by hematoxylin/eosin (H/E; Fig. 2A and 2B) while a Masson trichrome staining allowed to evaluate the fibrillar collagen framework (Fig. 2C and 2D) and an immunostaining with anti-\(\alpha\)-smooth muscle actin (\(\alpha\)-SMA) showed smooth muscle cells (Fig. 2E and 2F). The H/E staining clearly showed a large blood infiltrate between the adventitia and the media (Fig. 2B). As compared to a healthy iliac artery, no difference was observed in the collagen framework or in the smooth muscle cells organization at the level of the dissected wall. However, an orcein staining showed a striking rarefaction and disruption of the elastic lamellae in the media of the dissected iliac artery (Fig. 3B and at

Figure 1. Imaging of the ADPKD patient. (A) CT-scan showing the polycystic kidney (arrow) and the transplanted kidney (arrowhead). (B) and (C) Aorto-femorography showing the occlusion of the left external iliac artery (arrow).

Figure 2. General organization of the wall of the dissected iliac artery. (A) and (B): hematoxylin/eosin staining. (C) and (D): Masson trichrome staining. (E) and (F): \(\alpha\)-smooth muscle actin immunohistochemistry performed on a healthy iliac artery (A, C, E) and the dissected segment of the iliac artery of the ADPKD patient (B, D, F). Bar = 100 \(\mu\)m.
higher magnification Fig. 3D) as compared to a healthy artery (Fig. 3A and 3C). The dissection occurred at the junction of the external elastic lamella and the media. No inflammatory cells were found in the media or in the adventitia.

Discussion

Spontaneous dissection of the iliac artery is an extremely rare event and may occur as a complication of traumatic injuries or systemic disorders such as Marfan syndrome and α1-antitrypsin deficiency [3,4]. ADPKD has been associated with a large number of cardiovascular disorders. Intracranial aneurysms occur with a 10% incidence in ADPKD patients [5]. Aortic dissection, which usually occurs at the thoracic level, is a rare complication of ADPKD. In this report, we describe the first case of a spontaneous iliac artery dissection associated with ADPKD without any other apparently affected blood vessel. This genetic disease is caused by mutations in the PKD1 or PKD2 genes encoding for, respectively, polycystin 1 and 2. These proteins are expressed by vascular smooth muscle cells (VSMC) and are involved in Ca2+ homeostasis and in cell interactions with their surrounding extracellular matrix that are critical in maintaining the integrity of the media and regulating the VSMC phenotype [2,6]. The density of VSMC and the expression of α-SMA in the media of the dissected wall appeared both normal, which suggests that elastic fibers rarefaction is not related to VSMC apoptosis. Mutations in PKD genes could, however, result in defective interactions between VSMC and the surrounding matrix, which, in turn, would lead to modification of the VSMC pattern of protein expression and to degradation of the elastic tissue. Recently, elevated TGFβ signaling was observed in an advanced stage of ADPKD, coinciding with increased levels of target genes of the TGFβ pathway such as matrix metalloproteinase 2 [7], known for its elastolytic activity and its activation in abdominal aortic aneurysms [8].

In this case report, we observed a potential association between ADPKD and iliac dissection that would need to be validated on a large series of patients.

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References


Figure 3. Visualization of elastic fibers by orcein staining of a healthy iliac artery (A) and (C) and the dissected segment of the iliac artery of the ADPKD patient (B) and (D). Bar = 100 μm in (A) and (B) and 25 μm in (C) and (D).
Simultaneous Surgical Treatment of Type B Dissection Complicated With Visceral Malperfusion and Abdominal Aortic Aneurysm
Role of Aortic Fenestration

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Abstract
Aortic dissection occurs in about 5% of patients with coexistent abdominal aortic aneurysm (AAA); combined type B dissection complicated with visceral malperfusion and AAA is an uncommon aortic emergency and patients presenting with complications of thoracic aortic dissection have a dismal prognosis related to difficulties in treatment strategies. Despite tremendous improvement of endovascular techniques, surgical aortic fenestration represents a quick, safe, and effective procedure able to restore flow in an otherwise malperfused aorta. This procedure has to be kept in mind because subsets of patients cannot be treated conventionally due to either prohibitive risk of aortic replacement, anatomic contraindication, or limitations of percutaneous procedures. Herein we report a case of a patient presenting with type B aortic dissection complicated by visceral malperfusion and concomitant AAA which was successfully treated simultaneously by open AAA repair and surgical fenestration. We focus on the mechanism of malperfusion and on the role of surgical fenestration.

Key Words
Aortic dissection · Visceral malperfusion · Fenestration

Introduction
Aortic dissection occurs in 5% of patients with coexistent abdominal aortic aneurysm (AAA) increasing the risk for aortic rupture [1]; about 30% of acute type B dissections present life-threatening complications with a dismal prognosis due to high mortality caused by this catastrophic aortic emergency [2]. Moreover, association between AAA and type B dissection complicated by visceral malperfusion represents a clinical rarity but presents a challenge in both diagnosis and therapeutic strategies [3].

Herein we report a case of a patient presenting with type B aortic dissection complicated by visceral malperfusion and concomitant AAA which was successfully treated simultaneously by open AAA repair and surgical fenestration. We focus on the mechanism of malperfusion and on the role of surgical fenestration.

A 67-year-old hypertensive man experienced an acute type A dissection and was operated on one year earlier with a Bentall procedure and subtotal arch replacement using two grafts. He was admitted to our hospital complaining of persistent abdominal pain without peripheral pulse deficit; laboratory findings showed abnormal liver function test results and lactate elevation. Aware of the clinical history, a com-
computed tomography (CT) scan was proposed. The scan showed the two grafts used for extended aortic replacement and a type B dissection with an overpressurized false lumen originating below the subclavian artery (Fig. 1A), compressing a very thin true lumen with subocclusion of the celiac trunk and mesenteric artery (Fig. 1B). The spiralized cul de sac of the dissection stopped at the origin of an infrarenal, 5-cm abdominal aortic aneurysm (Fig. 1C).

The CT images were reconstructed with the 3Mensio medical imaging software program for a better visualization of the malperfusion mechanism, and the patient was prepared for an emergent open AAA repair and surgical fenestration.

The abdomen was penetrated through a midline laparotomy and gross inspection showed a dark colored, bruised and pulseless long segment of the small bowel (Fig. 2A). The aorta was cross clamped below the left renal vein, and upon opening the AAA, the cul de sac of dissection with a large false lumen and a virtual true lumen was identified just above the AAA proximal neck (Fig. 2B). Fenestration of the intimal flap was performed, excising as much intima as possible in both a circumferential and longitudinal extent toward

Figure 1. (A) Preoperative CT scan demonstrated extension of the dissection from distal arch to proximal neck of abdominal aortic aneurysm; (B) CT image showing true lumen compression of celiac trunk; (C) 3Mensio CT image demonstrating visceral malperfusion due to the false lumen being overpressurized.
the proximal clamp (Fig. 2C). At the end of the procedure, a 20mm straight woven Dacron graft was sutured to the proximal aortic stump. Distal anastomosis above the aortic bifurcation completed the operation.

Inspection of the small bowel revealed rosy colored loops that, except for a very short segment, was otherwise viable; with recovery of vitality there was no need for resection (Fig. 2D).

The postoperative course was uneventful; a continuous decrease in biomarkers of end-organ ischemia was observed and after completion of a CT scan control (Fig. 3A and 3B) the patient was discharged to home two weeks later. At one year follow up, the patient is doing well and CT control shows a stable diameter at the top of the descending aorta.

As reported by Cambria, occurrence of acute dissection in an aorta previously afflicted with atherosclerotic aneurysm is unusual. In a series of 325 patients with aortic dissection, he identified only 5% of them with coexistent aneurismal disease. He pointed out that this association appears to increase the risk of aortic rupture in both the proximal and distal aorta, also indicating that the presence of a juxtaposed atherosclerotic aneurysm greater than 5 cm constitutes a "complicated" dissection and standard antihypertensive therapy fails to prevent aortic rupture.

The fate of the false lumen following primary repair of an aortic dissection influences the outcome of the patient; remaining patent or partially thrombosed, it may be a source of complications, like for our patient where a life-saving operation converted a type A into a type B dissection.

Type B aortic dissection is generally treated with medical therapy when uncomplicated, but about 30% of cases at clinical presentation are complicated either by hemodynamic instability or by vascular ischemia with high risk of mortality if untreated [4].

The association between AAA and type B aortic dissection complicated with visceral malperfusion represents a clinical rarity but presents a challenge in both diagnosis and operative indications. The majority of patients with complicated type B dissection have a spiral aorta with collapse of the true lumen. In our patient the dissection progressed downward trough the posterolateral wall of the descending thoracic aorta and then spiraled anteriorly, ending at the level of the origin of the abdominal atherosclerotic aneurysm.

The role of atherosclerotic plaque in the natural history of aortic dissection is uncertain. The analysis made by Roberts suggests that atherosclerotic plaque frequently serves to terminate the dissection process but the situation is quite different when atherosclerotic or degenerative aneurysm is present. In such a circumstance, rupture of the aneurysm is the more likely scenario.
The incidence of aortic branch vessel involvement in aortic dissection ranges from 25% to 50% [5]; expansion of the false lumen at the expense of the true channel is the most common mechanism of vascular obstruction. Absence of a distal re-entry site in the dissected aorta or its branches may jeopardize blood flow in the true channel to the point of total occlusion, leading to secondary distal thrombosis inside the aortic branch vessel.

According to evolving CT scan criteria, two types of ischemia mechanisms are depicted: aortic type and branch type. In the first one there is collapse of the true lumen inside the aorta while in the latter the dissection flap narrows the true lumen of a visceral artery [2].

Despite tremendous improvement in surgical and endovascular techniques, some patients cannot be treated either conventionally due to the prohibitive risk of an open procedure, or percutaneously due to anatomic contraindications or limitations of catheter-based interventions. A percutaneous procedure may consume time in a patient that needs quick intervention due to impending bowel infarction [7]. These circumstances associated with the presence of the AAA that is a complication “per se” led us to perform surgical fenestration to restore flow in the true lumen and AAA repair at the same time.

The fenestration technique was first described in 1935, but the largest series have been reported by the Harvard and Yale groups [5,6]. Once control of the aorta is achieved, the vessel is crossclamped, usually below the renal arteries, and transected. The intimal flap is identified and a portion of the dissecting membrane is removed, sliding the scissors up to the level of the proximal clamp. In conclusion, the aim of the procedure is to form a re-entry point to decompress the false lumen and equipoise pressure in both channels of the aorta, permitting a re-expansion of the true lumen.

The interval between the appearance of complications and surgical treatment is related to the poor prognosis of complicated type B dissection. Surgical fenestration as previously described extraperitoneally, or in our case transperitoneally, in association with AAA repair can be performed quickly without specialized endovascular or imaging equipment.
Experience with short- and long-term outcomes following fenestration is scant, however, both the Yale and Harvard series demonstrated a three-year and five-year survival rate of 77% and 55%, respectively, with an almost 100% reperfusion rate. Failure of successful reperfusion was noted only in patients with a delay in the diagnosis of more than 48 hours after onset of dissection. It is of interest to note that no late aneurysmal development was noted in the survivors [5,6,8].

Combined type B aortic dissection complicated by visceral malperfusion and AAA represents an uncommon aortic emergency. Despite tremendous improvement of endovascular techniques, this challenging disease still carries high mortality mainly due to difficulties relieving visceral ischemia. Surgical fenestration represents a safe, quick, and effective procedure; flow is restored above and below the site of operation. The best results are achieved when it is performed immediately on presentation with organ ischemia. In conclusion, this technique should be kept in the surgeon’s repertoire because subsets of patients cannot be treated conventionally due to prohibitive risk of thoracic aortic replacement and/or anatomic contraindications or limitations of percutaneous procedures.

References

An Unusual Complication of Surgery for Type A Dissection Treated by Thoracic Endovascular Aortic Repair

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Abstract
A 58-year-old man was admitted to our hospital for massive swelling in an anterior cervical location. Nine years earlier, he underwent surgical repair of a complex type A aortic dissection. This procedure was complicated by a fistula between the anastomosis of the graft and the descending aorta, resulting in massive presternal swelling. Therefore, we performed thoracic endovascular repair with successful sealing of the prosthetic leak, achieving progressive reduction in the collection of fluid. We propose thoracic endovascular aortic repair as an alternative to open surgical repair for the treatment of complicated cases.

Key Words
Emergency TEVAR · Periprosthetic leak · Presternal swelling

Introduction
Open thoracic or thoracoabdominal aortic repair carries a significant risk of mortality and morbidity, despite recent literature suggesting a significant improvement [1]. Thoracic endovascular aortic repair (TEVAR) offers the possibility of treating patients who are not candidates, or those who are at extremely high risk for conventional surgical procedures because of their existing comorbidities and has gained increased acceptance across the world, with excellent short-term results [2]. Utilizing this therapeutic strategy, we report our successful management of a patient who suffered complications after a cardiovascular operation.

Clinical Case
In 2003, a 58-year-old man was admitted to another institution for a type B aortic dissection treated with medical management. After two days, the patient underwent surgical repair because of retrograde intramural hematoma extending to the ascending aorta as shown by computed tomography (CT). In the theater a 26 mm vascular prosthesis was placed extending from the sinotubular junction (STJ) to the aortic arch immediately distal to the origin of left subclavian artery, with direct reimplantation of the epiaortic vessels. This graft was connected to the descending aorta with another 20 mm vascular prosthesis, anastomosed end-to-side from the neo-ascending aorta to the descending thoracic aorta. This procedure was performed at another surgical institution and is comparable to a technique described by Griepp et al. [3].

Circulatory arrest duration was two hours with anterograde cerebral perfusion from the right axillary artery. This procedure was complicated by right hemiplegia, probably due to cerebral malperfusion. CT of the brain demonstrated extensive bilateral ischemic
cerebral lesions and evoked potentials showed a left decortication pattern.

Last February, the patient was admitted to our hospital due to the appearance of massive presternal swelling. The patient had a medical history that included hypertension and peripheral vascular disease. He was hemiplegic with cognitive impairment. A CT scan showed the presence of a fistula from the end-to-side anastomosis, connecting the graft to the descending aorta (Fig. 1). The lesion resulted in a voluminous collection of fluid extending from the periaortic to the subcutaneous presternal regions (Latero-lateral (LL) × Cranio-caudal (CC) × Postero-anterior (PA) = 8 cm × 10 cm × 7 cm), crossing the diastasis of the manubrium (Fig. 2).

Therefore, the patient was transferred to the operating room where endovascular repair was performed under general anesthesia. A standard cut-down over the left femoral artery was performed and percutaneous right axillary access was achieved. Systemic heparin (100 mg) was then administered. A 28/200/24 mm Relay plus (Bolton Medical, Barcelona, Spain) stent-graft was advanced over a stiff wire and navigated in the true lumen under fluoroscopic guidance. The stent-graft was successfully placed from the previous vascular graft to about halfway down the descending thoracic aorta and the anastomosis originating the leakage was excluded. At the end of the delivery there

Figure 1. CT shows the periprosthetic fistula, as indicated by the red arrow.

Figure 2. Presternal swelling.
was evidence of minimum type 1 endoleak, sealed by postdilatation of the endoprosthesis with a 27 mm balloon. Aortography demonstrated a satisfactory result. The patient’s condition improved and he was discharged 5 days after surgery.

At one month postsurgery a 3D CT scan image showed the successful sealing of the endoleak (Fig. 3) and at three months, reduction of the hematoma (Fig. 4) was evident.

Discussion

Acute aortic dissection of the descending aorta is still a life-threatening condition with high mortality and morbidity. Currently, there is consensus that acute uncomplicated type B dissections are managed medically. Conventional resection and graft replacement of the descending thoracic aorta has been the preferred method of treatment only in cases with complications such as aortic rupture, malperfusion of end organs, and/or persistent pain despite medical treatment. Open repair carries a 2.9% to 7% risk of paraplegia and an operative mortality rate ranging from
15% to 23.5%. Nevertheless, the introduction of endovascular stent grafts is revolutionizing the definitive treatment of these injuries. The potential benefits of TEVAR over open repair include no need for thoracotomy or single lung ventilation, decreased use of systemic anticoagulation, avoidance of aortic cross-clamping, less blood loss, less postoperative pain, and a lower paraplegia rate [3]. Indeed, since its introduction more than a decade ago, TEVAR has shown promising results for patients with various thoracic aortic diseases [4]. These include unstable acute type B aortic dissection, chronic type B aortic dissection, and type B dissection with retrograde extension into the ascending aorta [5]. The concept of this procedure was directed toward sealing the proximal intimal tear, redirecting the flow into the true lumen, and promoting depressurization and thrombosis of the false lumen. In addition, such an approach can effectively treat malperfusion syndrome by re-establishing side branch flow in dynamic obstruction [2].

In accordance with this, we adopted TEVAR to repair a dehiscence of an anastomosis between the transverse prosthesis and the descending aorta. The patient’s condition has improved considerably and, after three months, the severe subcutaneous and intrathoracic collection of fluid has been considerably reduced. A surgical alternative would have resulted in a complex reoperation with circulatory arrest to repair the leak, thus exposing the patient to the risk of new complications, especially neurological.

In conclusion, TEVAR is a reliable and flexible method that can be extended to complicated patients where an open surgical option presents a prohibitive risk of mortality.

References

Editor’s Comments
This case showcases just how dramatic such false aneurysms can become, with a truly massive suprasternal pulsatile mass. This case would have been difficult (although fully possible) to approach by open surgery, making an endovascular approach attractive. As the offending fistula appears to be a defect in a graft-to-graft anastomosis, the chosen endovascular stent grafting may indeed lead to permanent obliteration of the tract and the false aneurysm.
Genes in Thoracic Aortic Aneurysms and Dissections – Do they Matter?
Translation and Integration of Research and Modern Genetic Techniques into Daily Clinical Practice

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Abstract
Since the identification of the fibrillin-1 gene as the causal gene for Marfan syndrome, our knowledge of molecular genetics and the applicability of genetic testing in clinical practice have expanded dramatically. Several new syndromes related to thoracic aortic aneurysms and dissections (TAAD) have been described and the list of underlying genes in syndromal and nonsyndromal TAAD already includes more than 10 different genes and is rapidly expanding. Based on this knowledge, our insights into the underlying pathophysiology of TAAD have improved significantly, and new opportunities for targeted treatment have emerged. Clinicians involved in the care of TAAD patients require a basic knowledge of the disease entities and need to be informed on the applicability of genetic testing in their patients and families. Gene-tailored treatment and management is indeed no science fiction anymore and should now be considered as part of good clinical practice. We provide a systematic overview of genetic TAAD entities and practical recommendations for genetic testing and patient management.

Key Words
Thoracic aortic aneurysms and dissections · Molecular genetic testing · Aneurysm syndrome

Introduction
Over the past decade, expanding knowledge of the genetic basis of Thoracic Aortic Aneurysms and Dissections (TAAD) significantly improved our understanding of the pathogenesis of the disease and improved our ability for risk stratification and medical guidance of patients and their families. Strategies for molecular genetic testing have reached a hinge point with the introduction in routine diagnostics of high-throughput next generation sequencing techniques. It is therefore extremely important that clinicians in the field know the indications and limitations of molecular genetic testing. These will be reviewed in this manuscript.

Etiology and Classification
The etiology of TAAD is complex and heterogeneous. Degenerative aortic disease related to classical cardiovascular risk factors such as smoking, arterial hypertension, and hyperlipidemia are the main cause of TAAD in older patients. In younger patients with no risk factors, other causes, including genetic disease, should be considered. Genetic aneurysmal disease
can be categorized in three main groups: (i) inherited syndromes predisposing to early onset TAAD (<5% of all TAAD) such as Marfan syndrome (MFS), Loey-Dietz syndrome (LDS), and Aneurysm-Osteoarthritis syndrome [1–3]; (ii) familial forms of TAAD (FTAAD - 20% of all TAAD) including patients with confirmed disease in first-degree relatives and evidence for an autosomal dominant inheritance pattern; these patients may sometimes present with associated cardiovascular lesions such as bicuspid aortic valve (BAV), patent ductus arteriosus (PDA), or cerebrovascular disease [4–6]; and (iii) isolated or sporadic forms of TAAD (80%) including patients with no family history or clinical features of a syndromic TAAD disorder. The latter two categories are the so-called nonsyndromic forms of TAAD as opposed to the syndromic forms of the first category.

Table 1 provides an overview of syndromic and nonsyndromic forms of TAAD with their corresponding genes and clinical features. Discriminative features are in bold.

The paradigm disease for genetically determined syndromic TAAD is Marfan syndrome (MFS), caused by mutations in the fibrillin-1 gene (FBN1). The diagnosis of MFS is based on the identification of clinical manifestations and may be supplemented with FBN1 gene sequencing. Cardinal manifestations include dilatation of the aortic sinus, lens luxation, and a combination of additional features defined by the “systemic score.” Dilatation of more distal parts of the aorta occurs in a minority of MFS patients [7–9]; patients who underwent previous surgery of the ascending aorta seem at increased risk. A recent study from Mimoun and colleagues demonstrated that dissection in the descending part of the aorta may occur whatever the diameter of the ascending aorta [10].

In 2004, Mizuguchi et al. identified mutations in the Transforming Growth Factor Beta Receptor 2 gene (TGFBR2) in a large family and four additional probands presenting with aortic dilatation and variable additional clinical features reminiscent of a connective tissue disorder, referred to as Marfan syndrome type2 [11]. In 2005, Loeys et al. published their findings on a large series of patients presenting with widespread aggressive aortic disease with rapid growth and early dissections. They observed an increased prevalence of dysmorphic features including hypertelorism and cleft palate/bifid uvula. Patients harbored mutations in either the TGFBR1 or TGFBR2 gene and the disorder was named after the authors (Loeys-Dietz syndrome, LDS) [12]. Patients with LDS may also present with arterial tortuosity/aneurysms/dissections outside the aorta necessitating extensive vascular imaging at regular time intervals. With the identification of mutations in genes involved in the TGFβ pathway, a new era with regards to our understanding of the pathophysiology and treatment of TAAD emerged. Other gene mutations have been identified including the SMAD3 gene causing Aneurysm-Osteoarthritis syndrome and mutations in the TGFβ ligand. In view of the important clinical overlap between these disorders, the term “TGFβ associated vasculopathies” may be preferred over individual syndrome names.

The genetic background of nonsyndromic TAAD is even more complex and heterogeneous. Genes involved in syndromic forms may also be encountered in patients with isolated aortic disease, emphasizing the fact that the clinical spectrum of these disorders is very broad. Other genes involved in nonsyndromic TAAD include the ACTA2 gene (encoding smooth muscle α-actin), the MYLK gene, encoding myosin light chain kinase and the MYH 11 gene encoding the myosine heavy chain subunit [4,13–15]. The proteins encoded by these genes are involved in the vascular smooth muscle cell apparatus. Patients present with TAAD, sometimes in association with other features such as livedo reticualris, iris flocculi, and cardiovascular disease in the case of ACTA2, patent ductus arteriosus in the case of MYH11, and gastro-intestinal disease in the case of MYLK.

Establishing a correct diagnosis of TAAD in an individual patient primarily requires detailed clinical evaluation of the proband and family members (see below). It should be noted, however, that substantial clinical overlap exists between these subgroups. Therefore, additional molecular genetic testing may be helpful and sometimes even required for confirmation of the specific diagnosis.

Strategy for Clinical Evaluation and Genetic Testing

The absolute prerequisite for further clinical/genetic investigations in TAAD patients is a correct diagnosis of the aneurysm itself, based on careful measurement of the diameter of the aorta according to appropriate guidelines [35]. The measurements obtained need to be correlated to values in normal subjects matched for age, body surface area, and gender [36]. To correlate with normal values, nomograms
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene(s)</th>
<th>Main Cardiovascular Features</th>
<th>Additional Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan (1, 16, 17)</td>
<td>FBN1</td>
<td>Aortic Root Aneurysm, Aortic Dissection, Mitral Valve Prolapse, Main Pulmonary Artery Dilation, Left Ventricular Dysfunction</td>
<td>Lens luxation, skeletal features (arachnodactyly, pectus deformity, scoliosis, flat feet, increased armspan, dolichocephalia)</td>
</tr>
<tr>
<td>Ehlers-Danlos (18–20) (vascular, valvular)</td>
<td>COL3A1, COL1A2</td>
<td>Arterial Rupture and dissection without preceding dilatation/aneurysm, severe valvar insufficiency</td>
<td>Thin, translucent skin, dystrophic scars, facial characteristics (Madonna face, thin lips, deep set eyes)</td>
</tr>
<tr>
<td>TGFβ-related vasculopathies</td>
<td>TGFBR1/2</td>
<td>Aortic Root Aneurysm, Aortic Dissection, Arterial Aneurysms and Dissections, Arterial Tortuosity, Mitral Valve Prolapse, Congenital Cardiac Malformations*</td>
<td>Bifid uvula/cleft palate, hypertelorism, pectus abnormalities, club feet</td>
</tr>
<tr>
<td>Aneurysm-Osteoarthritis (21–23)</td>
<td>SMAD3</td>
<td>Aortic Root Aneurysm, Aortic Dissection, Arterial Aneurysms and Dissections, Arterial Tortuosity, Mitral Valve Prolapse, Congenital Cardiac Malformations*</td>
<td>Osteoarthritis, soft skin, flat feet, scoliosis, pectus abnormalities</td>
</tr>
<tr>
<td>TGFβ2 (24, 25)</td>
<td>TGFβ2</td>
<td>Aortic Root Aneurysm, Aortic Dissection, Arterial Aneurysms and Dissections, Arterial Tortuosity, Mitral Valve Prolapse, Congenital Cardiac Malformations*</td>
<td>Club feet, soft translucent skin</td>
</tr>
<tr>
<td>Shprintzen-Goldberg syndrome (26, 27)</td>
<td>SIK</td>
<td>Mild aortic root dilatation, mitral valve prolapse</td>
<td>Craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mild-to-moderate intellectual disability</td>
</tr>
<tr>
<td>Arterial Tortuosity Syndrome (28)</td>
<td>SLC2A10</td>
<td>Arterial Tortuosity, Arterial Stenoses and Aneurysms</td>
<td>Hyperextensible joints</td>
</tr>
<tr>
<td>Cutis Laxa Syndromes (29)</td>
<td>FBLN4</td>
<td>Aortic Root Aneurysm, Arterial Tortuosity</td>
<td>Hyperextensible joints, mild emphysema</td>
</tr>
<tr>
<td>Familial thoracic aortic aneurysm syndrome (FTA) (30–32)</td>
<td>TGFBR1/2 (3–5%)</td>
<td>Thoracic Aortic Aneurysm/Dissection, cerebrovascular disease, coronary artery disease</td>
<td>Lack of syndromic features</td>
</tr>
<tr>
<td>ACTA2 (10–14%)</td>
<td>Thoracic Aortic Aneurysm/Dissection, cerebrovascular disease, coronary artery disease</td>
<td>Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi, coronary artery/cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>MYLK</td>
<td>Intracranial and other arterial aneurysms</td>
<td>Gastro-intestinal abnormalities</td>
<td></td>
</tr>
<tr>
<td>SMD3 (2%)</td>
<td>TGFβ2</td>
<td>Mitral valve prolapse</td>
<td>Gastro-intestinal abnormalities</td>
</tr>
<tr>
<td>FTAA with bicuspid aortic valve (BAV) (33, 34)</td>
<td>ACTA2</td>
<td>Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi</td>
<td></td>
</tr>
<tr>
<td>FTAA with patent ductus arteriosus (PDA) (6)</td>
<td>NOTCH1</td>
<td>Highly calcified Valve</td>
<td></td>
</tr>
<tr>
<td>MYH11</td>
<td>Patent ductus arteriosus</td>
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</table>

Overview of syndromic and nonsyndromic forms of TAAD with their corresponding genes and clinical features. Discriminative features are in bold.
can be used or z-scores can be calculated, the latter method being more convenient for reporting. Aortic dilatation is confirmed if the z-score exceeds 2, corresponding to an observed value >1.96 standard deviations above the predicted value for age, gender, and body size. In children, growth needs to be taken into account and z-scores >3 have been suggested [37]. Further investigations will depend on the age and cardiovascular risk profile of the patient.

Consideration of a genetic entity is especially of interest in young subjects with no additional risk factors. Detailed family history taking, including pedigree drawing and clinical assessment of first degree relatives, is required to differentiate between familial and isolated forms of TAAD. Next, careful multidisciplinary clinical evaluation of the proband is undertaken, which will help us in the identification of specific syndromes as reported in Table 1.

Since TAAD is a genetically heterogeneous disease with important clinical overlap between the known genetic entities, there is a clear need for simultaneous testing of multiple genes. Until recently, strategies for genetic testing were limited as only one gene at the time could be analyzed, and both the time required as well as the costs for screening of multiple genes were substantial. The need for high-throughput techniques enabling simultaneous testing of several genes was met by the recent development and progress made in the field of Next Generation Sequencing. Previously, our Center reported a mutation detection strategy using massive parallel sequencing of the FBN1 and TGFBR-1 and -2 genes for the molecular diagnosis of MFS and LDS [38]. In a next stage, we implemented a novel screening strategy that allows simultaneous sequencing of 16 TAAD-associated genes. To this purpose, two complementary panels of genes were designed, of which all coding regions and flanking sequences can be amplified in a fully automated fashion followed by sequencing on an Illumina MiSeq sequencer (Illumina, San Diego, California). The first gene panel comprises FBN1, TGFBR1/2, SMAD3, TGFBR2, ACTA2, and COL3A1. The second gene panel comprises MYH11, MYLK, SLC2A10, NOTCH1, FBN2, ADAMTS10, FBLN4, FLNA, and ELN.

Correct interpretation of the results obtained by molecular genetic testing requires basic knowledge of these different genes and clinical entities - all the more since medical and surgical management may differ according to the underlying diagnosis.

Importantly, the simultaneous sequencing of multiple TAAD-associated genes is not always justified. In patients presenting with a thoracic aortic aneurysm in combination with lens luxation for instance, Marfan syndrome is very likely and molecular genetics can be restricted to the FBN1 gene. Or, from a cardiovascular perspective, extensive vascular disease such as aortic aneurysms at different locations and/or involvement of side branches makes a diagnosis of Marfan syndrome much less likely and in these cases, TGFβ-associated disease should be excluded first. A flow chart illustrating the diagnostic process (clinical and genetic evaluation) is provided in Figure 1.

**Genes and Pathogenesis**

In addition to its usefulness in a diagnostic setting, molecular genetics have been very useful in unraveling the complex pathogenesis of TAA formation. One of the most inspiring findings over recent years was the observation of the involvement of the Transforming Growth Factor β (TGFβ) pathway in several connective tissue disorders. The TGFβ superfamily consists of a number of cytokines that regulate diverse cellular functions, including proliferation, differentiation, and synthesis of a wide array of gene products.

The first heritable connective tissue disorder linked to the TGFβ pathway was Marfan syndrome (MFS). The underlying pathogenesis of aneurysm formation in MFS was initially considered to be a consequence of inherent structural weakness of the tissues due to structurally abnormal fibrillin-1 fibers. Prospects for causal treatment were pessimistic in this view since this would require a means to alter the structural composition of inherently weak tissues.

Fortunately, recent developments have changed this insight and it is now recognized that fibrillin-1 containing microfibres also play an important functional role in the complex TGFβ pathway. Although it is clear that the TGFβ pathway plays a role in the pathogenesis of MFS, the mechanism of TGFβ activation remains controversial. On the one hand, it has been suggested that TGFβ is activated as a consequence of improper sequestration of the latent TGFβ complex, which is the result of a reduction of fibrillin-1 below a certain threshold [39]. On the other hand, Charbonneau and colleagues demonstrated that an Fbn1 mouse in which the latent TGFβ binding protein site (LTBPs) was deleted (Fbn1<sup>−/−/−</sup>) did not present...
features of MFS [40]. Hence, instead of reduced TGFβ sequestration, mutant microfibrils probably influence TGFβ activation in a different way. Sakai and coworkers demonstrated that fibrillin-1 was homologous to the family of LTBPs which serve to hold TGFβ in an inactive complex in various tissues, including the extracellular matrix [41]. Fibrillin-1 binds TGFβ and LTBPs [41–44].

Since the large latent complex binds TGFβ, abnormal fibrillin-1 fibers will lead to failed matrix sequestration of the latent TGFβ complex and hence to increased amounts of active TGFβ, which is in turn at the basis of the pleiotropic manifestations in MFS [39]. Increased TGFβ signaling has also been reported in human aortic specimens of patients with familial TAAD and underlying ACTA2 or MYH11 mutations [48]. The exact link is not yet fully understood but links

with MFS. Initially, these disorders were given names, the first one being the Loeys-Dietz syndrome (LDS), caused by mutations in the TGFBR1 and TGFBR2 genes. In 2011, mutations in the SMAD3 gene were identified in patients with a very similar phenotype but also presenting with osteoarthritis, hence the name “Aneurysm-Osteoarthritis syndrome (AOS).” Soon thereafter a family with juvenile polyposis associated with aortopathy and mitral valve disease caused by SMAD4 mutations was reported [45]; and finally, mutations in the TGFβ-2 ligand were very recently identified in several families displaying a very similar phenotype [25,46,47]. It is clear that these disorders are all part of a broad spectrum and it may be more convenient to group them under the term “TGFβ-related vasculopathies.”

Figure 2 provides a schematic and abbreviated overview of the TGFβ signalling pathway with indication of aneurismal diseases linked to it.

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between the contractile cytoskeleton and many aspects of the TGFβ signaling pathway have been established, including trafficking and activity of TGFβ receptors and signaling effectors [49,50].

Gene-Tailored Follow-up and Management in TAAD

A schematic overview of the medical management is provided in Table 2.

Imaging Studies

Confirmation of the exact diagnosis in the proband facilitates the set-up of a personalized strategy for follow-up and treatment in the patient and his/her family. Since the clinical manifestation of the disease is age dependent and may progress subclinically until later in life, lifelong follow-up is required in all mutation-carriers, even if aortic diameters are normal on repeated measurements. The frequency and modality for follow-up and treatment may differ according to the underlying diagnosis as summarized in Table 2. Importantly, clinical monitoring and follow-up with cardiovascular imaging is also warranted in family members of TAAD patients in whom no causal mutation was identified since familial clustering is observed in more than 20% of TAAD cases [51,52].

Echocardiography is the primary imaging tool for evaluation and follow-up of the diameters of the aortic root and ascending aorta. CT or MRI can be used in case of insufficient visualization of the ascending aorta by echocardiography. The imaging study should be repeated in all patients six months after the initial diagnosis to assess evolutionary changes. Further follow-up is guided by the diameter, evolution, underlying diagnosis, and family history. Stable diameters <45 mm in patients with Marfan syndrome or isolated TAA and no family history for dissection require yearly follow-up. Biannual controls are recommended in all other cases.

On initial diagnosis, imaging of the entire aorta and side branches ("head-to-pelvis" study) should be performed in order to detect aneurysms at other sites.
### Table 2. Overview of Suggested Treatment and Follow-up in TAAD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan (1, 16, 17)</td>
<td>β-blocking agents, losartan?</td>
<td>echocardiography q1y when diameter &lt;45 mm q6m in all other cases</td>
</tr>
<tr>
<td></td>
<td>surgery when AoD &gt;50 mm or &gt;46 mm in case of familial history of dissection or rapid growth (&gt;2 mm/y) or severe AR or MR</td>
<td>MRAq5y when aortic diameters outside the sinuses of Valsalva are normal, MRAq1y in all other cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear (dissection/rupture often at normal diameters)</td>
</tr>
<tr>
<td>Ehlers-Danlos (18-20) (vascular, valvular)</td>
<td>Celiprolol</td>
<td>Echocardiography q6mo</td>
</tr>
<tr>
<td>TGFβ-related vasculopathies</td>
<td>Surgery uncertain</td>
<td></td>
</tr>
<tr>
<td>Loeys-Dietz (2, 12)</td>
<td>No trials yet — adopt medical treatment from Marfan syndrome</td>
<td></td>
</tr>
<tr>
<td>Aneurysm-Osteoarthritis (21–23)</td>
<td></td>
<td></td>
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<tr>
<td>TGFβ2 (24, 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial Tortuosity Syndrome (28)</td>
<td>Surgery when AoD &gt;43-45 mm</td>
<td>CT/MRI head to pelvis q6mo-1y</td>
</tr>
<tr>
<td>Cutis Laxa Syndromes (29)</td>
<td>No trials yet — adopt from Marfan syndrome</td>
<td>Same as in Marfan syndrome</td>
</tr>
<tr>
<td>Familial thoracic aortic aneurysm syndrome (FTAA) (30–32)</td>
<td></td>
<td>Consider coronary/cerebrovascular imaging in ACTA2 mutation carriers</td>
</tr>
<tr>
<td>FTAA with bicuspid aortic valve (33, 34)</td>
<td></td>
<td>Echocardiography q6mo-1y (also related to valvular function)</td>
</tr>
<tr>
<td>FTAA with patent ductus arteriosus (6)</td>
<td></td>
<td>Same as in Marfan syndrome</td>
</tr>
</tbody>
</table>

AoD: Aortic Root Diameter; AR: Aortic Regurgitation; MR: Mitral Regurgitation; MRA: Magnetic Resonance Angiography.
and/or arterial tortuosity. Regular extensive vascular imaging from head to pelvis is recommended in patients with a TGFBR1/2, SMAD3, and TGFβ2 mutation and for rare diseases such as cutis laxa and arterial tortuosity syndrome (ATS). In vascular Ehlers-Danlos syndrome (EDS) where dissections often occur at normal diameters, the modality and frequency of vascular imaging is debatable. Evaluation for coronary artery and cerebrovascular disease can be considered in patients with an ACTA2 mutation [53].

**Medical Treatment**

The initial medical approach of TAAD patients should include reduction of cardiovascular risk factors, such as blood pressure control, smoking cessation, and optimization of the lipid profile. Central stimulating drugs, such as cocaine, amphetamine and derivatives are known triggers for aortic dissection and should therefore be avoided [54,55].

Medical treatment with a β-blocking agent in MFS reduces the progression of aortic dilatation in most patients through reduction of wall shear stress in the aorta and is used as a standard therapy in MFS patients [56]. As already mentioned, it has been clearly demonstrated that the TGFβ pathway plays an important role in aneurysmal disease. This knowledge has led the search for strategies to interfere with TGFβ signalization. From studies in nephrology, it was documented that losartan, an angiotensin receptor blocking agent, inhibits TGFβ signaling. An initial experiment with TGFβ neutralizing antibodies in a mouse model for MFS showed a dramatic decrease in aortic root growth as well as restoration of aortic wall architecture [57]. A trial with losartan in MFS mice showed significant rescue of aortic root aneurysm progression as well as aortic wall architecture, compared to treatment with either placebo or propranolol [57]. A subsequent small study in children with severe MFS showed similar very promising results [58]. Large-scale trials in MFS patients are currently underway [59] and need to be awaited prior to large-scale prescription.

In patients with vascular EDS, reduction of fatal vascular events was observed with treatment with celiprolol, a β-blocker with β2 mimetic action [60]. The possible role of medical treatment in other TAAD diseases is not well studied but pragmatically, treatment as for MFS is adopted.

**Surgery**

It is beyond any doubt that elective surgical aortic root replacement leads to better survival in patients with genetic aortic disease. Modalities for surgical intervention are beyond the scope of this contribution. We do want to spend some words on the timing of surgery taking the underlying diagnosis into account.

It has been demonstrated that the risk for dissection or rupture for thoracic aortic aneurysms of non-degenerative origin rises at lower diameters when compared to degenerative aortic disease. Accordingly, the threshold for surgery of the aortic root is lower than the conventional 55 mm. Indeed if conforming to the European Society of Cardiology guidelines on Grown-up Congenital Heart Disease, the conventional surgical indication for MFS is an aortic diameter-measured at the sinuses of Valsalva at 50mm or more. This threshold is reduced to 46 mm in the case of a positive family history of aortic dissection or rapid growth of the aorta (>2 mm/yr). When there is a desire of pregnancy, aortic repair at 45 mm is recommended [61]. In certain other syndromic and nonsyndromic TAAD entities such as LDS or AOS, aortic dissection can occur at smaller diameters, therefore requiring an adjusted treatment policy. Results of surgical intervention in LDS and AOS are good [3,62]. Taking these data into account, the current guidelines of the American College of Cardiology recommend prophylactic surgery in the following cases [63,64]: (i) patients with a mutation in TGFBR1 or TGFBR2 (as well as patients with LDS as familial TAAD), when the diameter of the ascending aorta reaches 42mm measured by echocardiography or 44–46 mm on CT or MR imaging; (ii) patients with familial TAAD and/or mutation in MYH11 or ACTA2, when the diameter of the ascending aorta measures between 45 and 50 mm; (iii) patients with familial TAAD with relatives with an aortic dissection at minimal dilatation of the thoracic aorta (<50 mm); (iv) for all other TAAD patients when the ascending aorta or aortic root reaches a diameter of 50 mm, in case of rapid growth of the aorta (≥5 mm/yr) and/or in the presence of severe aortic stenosis or regurgitation. Patients with a mutation in the MYLK gene can have an aortic dissection at small diameters of the aorta, as indicated by the study of Wang et al. [15]. Guidelines regarding the role of prophylactic surgery in this group of patients are lacking. In contrast to patients with a TGFBR2 mutation, aortic dissection in patients with a TGFBR1 mutation would
rather occur at larger diameters (>50 mm) [65]. In view of these data, early referral for surgery may be questioned.

**Conclusion**

In the current era of improved availability of high-throughput molecular genetic techniques, knowledge of the indications and limitations for these tests in daily clinical practice is increasingly important. In the case of TAAD, additional genetic testing may be helpful for confirmation of the correct diagnosis. Since follow-up and treatment of patients may be adapted according to the underlying condition, clinicians dealing with these patients should acquire this knowledge. Close collaboration between cardiovascular surgeons, cardiologists, and clinical geneticists is strongly recommended in the care of these patients and families.

**Acknowledgments**

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**Comment on this Article or Ask a Question**

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**References**

21. de laar IM, van der Linde D, Oei EH, Bos PK, Bessens JH, Bierma-Zeinstra SM, et al. Phenotypic spectrum of the SMAD3-related...
35. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:440–463. 10.1016/j.echo.2005.10.005
44. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Jr., et al. 2010 ACCF/AHA/ACP/AATS/ACR/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of
EDITOR’S COMMENTS

Dr. De Backer and colleagues, from the distinguished Ghent group, provide a clinically oriented primer on the current state of knowledge regarding the genetics of thoracic aortic aneurysm. They tell us just how to use genetic testing in the present era. As well, they provide useful management and clinical guidelines that take into account the emerging knowledge of aneurysm behavior in specific genetic syndromes. They usher us into the era of personalized aortic management based on molecular genetics.

The Editors only point of difference concerns frequency of imaging. Since the aorta grows very slowly in the vast majority of thoracic aneurysm patients (about 1 mm per year), after the first yearly ECHO, CT, or MRI we done, we decrease frequency of imaging to every two to three years. (ECHOs can be done frequently, if desired, because of low cost and zero toxicity. We use restraint in CT and MRI.)

Imaging Assessment of Periaortic Inflammation in Erdheim-Chester Disease

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¹Department of Medical Imaging, University Hospital–Sart Tilman, Liège, Belgium; ²Department of Pathology, CHC–St Joseph, Liège, Belgium

Abstract
Reaching etiologic diagnoses for retroperitoneal fibrosis may be challenging. We report the case of a 75-year-old male with history of ruptured abdominal aortic aneurysm and subsequent retroperitoneal fibrosis who developed four years later a soft tissue infiltration surrounding the ascending thoracic aorta. Thanks to his medical records and multimodality imaging assessment, the patient escaped an open-chest biopsy through histological reassessment of the abdominal periaortic samples that allowed the definitive diagnosis of Erdheim-Chester disease, a rare non-Langerhans histiocytosis.

Key Words
Aortitis · Histiocytosis · Erdheim-Chester · Magnetic Resonance Imaging · Positron Emission Tomography

Case Report
A 75-year-old male presented with three self-subsidizing episodes of malaise and nausea. Medical history included surgery for ruptured inflammatory abdominal aortic aneurysm, four years earlier; pathology of the surgical specimen showed idiopathic peri-aneurysmal fibrosis. Postoperative follow-up was marked by periaortic graft infiltration involving both ureters, necessitating bilateral ureteral stenting and steroid therapy for eight months. The patient had remained asymptomatic for three years until the onset of malaise. Clinical examination and ECG were unremarkable. The serum C-reactive protein was at 7 mg/L (normal 0–6), and blood cell count showed neutrophilia (85%) without hyperleucytosis and a slight microcytic anemia (hemoglobin: 12.4 g/100 mL). On echocardiography, a 10 mm pericardial effusion (PE) was noticed and subsequent computed tomography (CT) displayed a layer of abnormal soft tissue surrounding the thoracic aorta (Figure 1A, arrows), which was not present on a prior examination (not shown). Whole-body transverse ¹⁸F-fluoro-deoxyglucose positron emission tomography (FDG-PET) (Figure 1B) and high b-value (800 s/mm²) diffusion-weighted MRI (DW-MRI) (Figure 1C) were performed and, respectively, color map-fused with CT (Figure 1D and 1E), showing in a roughly similar distribution, an increased FDG uptake and decreased water diffusion (arrows). No other pathological area was identified. Both molecular imaging techniques helped with differentiating multiorgan malignancy from perivascular inflammatory diseases, allowing hypothesis that the current disease and the previous perianeurysmal fibrosis are actually two expressions of the same disease. We, therefore, discussed either Erdheim–Chester disease, or large vessel vasculitis such as Takayasu and giant cell arteritis. Erdheim–Chester disease is an uncommon non-Langerhans cell histiocytosis characterized by a perivascular, adipose, and connective tissue tropism [1–3] that may be responsible for widespread vascular involvement, including “chronic periaortitis,” a ge-
generic term for perianeurysmal retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, and idiopathic retroperitoneal fibrosis. This tropism noticed in our patient history was a clue to the diagnosis, even though the initial pathological evaluation may have failed for several reasons, including undersampling. We proceeded to a histopathologic reassessment of the perianeurysmal samples obtained 4 years earlier. It revealed inflammatory foci with a predominance of foamy cells (histiocytes) infiltrates with cytoplasmic brown deposition at immunoperoxidase stain with CD68 (Figure 1F, arrows) that eventually allowed the definitive diagnosis of Erdheim–Chester disease. Other immunohistological hallmarks of the disease were a negative staining for both CD1a and S-100 protein (not shown). The patient was treated by further steroid administration of methylprednisolone. Follow-up chest CT showed a marked decrease of the periaortic infiltration (Figure 1G), while the patient remained asymptomatic.

Figure 1. A 75-year-old male with malaise and history of inflammatory abdominal aortic aneurysm rupture four years earlier. (A) Unenhanced transverse computed tomography (CT) of the chest demonstrates a perivascular soft tissue mass, encasing the aortic arch (arrows). (B) 18F-Fluorodeoxyglucose positron emission tomography (FDG PET) and (C) color intensity map fusion with CT showed a remarkable uptake of the tissue. (D) Transverse diffusion-weighted magnetic resonance with a diffusion-factor value of 800 s/mm² and intensity color maps fusion to CT (E) images showed restricted diffusion (arrows) in a roughly identical distribution to FDG uptake. Histological reassessment of the samples obtained during abdominal aortic surgery (F) demonstrates inflammatory foci with predominance of foamy cells (histiocytes) infiltrates with cytoplasmic brown deposition at immunoperoxidase stain with CD68 (arrows), consistent with the diagnosis of Erdheim–Chester disease for which other immunohistological hallmarks were a negative staining for both CD1a and S-100 protein (not shown). (G) Unenhanced transverse CT showing mild decrease of the perivascular soft tissue after treatment.
Acknowledgments

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References


How Would You Correct an Aberrant Right Subclavian Artery?

Bulat A. Ziganshin, MD
(on behalf of the Editorial Office)

Key Words
Aberrant subclavian artery · Treatment approach

A 63-year-old female presented having suffered an embolic event to her right index finger. This resolved successfully with conservative treatment via development of collateral channels. The finger is fully viable, albeit mildly insensitive. She has had some dysphagia, with one specific choking episode when a lozenge became lodged in the esophagus, causing discomfort and cough until it dissolved spontaneously.

Work-up revealed an aberrant right subclavian artery, with associated Kommerell’s dilatation and a 1 cm wide ulcerated area near its origin from the aorta, as well as an arteriosclerotic irregularity of the proximal subclavian artery. Passage of the aberrant subclavian artery behind the trachea and esophagus produced esophageal compression. See computed tomography (CT) scan images in Figure 1.

The question regarding this case was: How would you correct this lesion?

- Open surgery
- Intraluminal endovascular treatment
- Combined surgical-endovascular approach (hybrid operation) with right subclavian artery transposition and thoracic aortic stent graft implantation
- Other approach

The respondents who selected the open surgery option were asked:

Please indicate—open surgery to include which of the following (multiple choice question):

- Left thoracotomy for division of subclavian artery and, thus, interruption of vascular ring
- Neck approach for ligation of subclavian artery (to allow thrombosis of aberrant artery), with carotid to subclavian bypass for distal perfusion
- Ligation of thyrocervical trunk and internal mammary artery (IMA)
- Other

Selection of the “Other approach” option to the main question and the “Other” option to the secondary question prompted a text field where the respondents could describe their approach.

The poll was distributed among all current members of the Editorial Board, who were asked to submit their responses via an online survey tool. The list of Editorial Board members can be found the AORTA journal website (http://aorta.scienceinternational.org). The members of the Editorial Board whose practice does not lie within the scope of this question were asked to disregard this poll. Here we present the results of this poll.

Results of the “Poll the Editorial Board”

Thirty-three members of the Editorial Board submitted responses through our online survey tool. The results are presented in the pie chart of Figure 2 and Table 1.
The results of the poll show the increasing popularity of the hybrid procedures with the majority of the respondents (55%) indicating their preference for the combined surgical and endovascular approach, 30% of the respondents selecting open surgery as their preferred technique, while 12% favored an intraluminal endovascular treatment approach. Interestingly, among the respondents that showed preference for open surgery, seven (70%) indicated the left thoracotomy approach to

Figure 1. Axial CT scan images showing the aberrant right subclavian artery (red arrow).

Table 1. Responses of the Editorial Board members (n = 10) that specified preference for open surgery (multiple choice question)

<table>
<thead>
<tr>
<th>Preferred technique for open surgical treatment of an aberrant right subclavian artery</th>
<th>No. of votes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left thoracotomy for division of subclavian artery and, thus, interruption of vascular ring</td>
<td>7</td>
<td>70%</td>
</tr>
<tr>
<td>Neck approach for ligation of subclavian artery (to allow thrombosis of aberrant artery), with carotid to subclavian bypass for distal perfusion</td>
<td>4</td>
<td>40%</td>
</tr>
<tr>
<td>Ligation of thyrocervical trunk and IMA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2*</td>
<td>20%</td>
</tr>
</tbody>
</table>

*The two respondents that selected the response “Other” indicated the following as their preferred technique for open surgery:

1 – Left thoracotomy, division of right subclavian artery, and connection to ascending aorta.

2 – (1) Medium sternotomy. (2) Suture of the aberrant artery at the level of its origin. (3) Ascending aorta—right subclavian bypass graft OR reimplant of distal right subclavian artery to the right carotid artery.

Figure 2. Pie chart diagram illustrating the responses of the Editorial Board members to the poll.
be their preference. At the same time three (30%) respondents stated that the combined left thoracotomy and neck approach is their preference. Only one respondent (10%) selected the isolated neck approach for ligation of the subclavian artery with a carotid to subclavian bypass for distal perfusion, while no respondents showed preference toward ligation of the thyrocervical trunk and IMA. Two respondents provided other alternative strategies for open surgical treatment (see Table 1).
<table>
<thead>
<tr>
<th>Upcoming Meetings</th>
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<tbody>
<tr>
<td><strong>July 2013</strong></td>
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</tbody>
</table>
| 1. Advanced Aortic and Mitral Valve Reconstructive Surgery  
  July 5–6, 2013  
  Windsor, UK  
  Meeting information available at:  
| 2. International Academy of Cardiology—18th World Congress on Heart Disease  
  July 26–29, 2013  
  Vancouver, Canada  
  Meeting information available at:  
| **October 2013** |
| 3. 27th EACTS Annual Meeting  
  October 5–9, 2013  
  Vienna, Austria  
  Meeting information available at:  
  [http://www.eacts.org/annual-meeting.aspx](http://www.eacts.org/annual-meeting.aspx) |
| 4. The Southern Thoracic Surgical Association (STSA) 60th Annual Meeting  
  October, 30–November 2, 2013  
  Scottsdale, AZ, USA  
  Meeting information available at:  
  [http://stsa.org/60thannualmeeting/](http://stsa.org/60thannualmeeting/) |
| **November 2013** |
| 5. International College of Angiology—55th Annual Congress  
  November 7–9, 2013  
  New Haven, CT, USA  
  Meeting information available at:  
  [http://www.intlcollegeofangiology.org](http://www.intlcollegeofangiology.org) |
| 6. Surgery of the Thoracic Aorta—7th Postgraduate Course  
  November 11–12, 2013  
  Bologna, Italy  
  Meeting information available at:  
  [http://www.aosp.bo.it/content/presentation-course](http://www.aosp.bo.it/content/presentation-course) |
| **December 2013** |
| 7. Innovations in Cardiovascular Interventions  
  December 1–3, 2013  
  Tel-Aviv, Israel  
  Meeting information available at:  
  [http://www.icimeeting.com](http://www.icimeeting.com) |
| **January 2014** |
| 8. STS 50th Annual Meeting & STS/AATS Tech-Con 2014  
  January 25–29, 2014  
  Orlando, FL, USA  
  Meeting information available at:  
  [http://www.sts.org/abstracts](http://www.sts.org/abstracts) |