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A Bentall Is Not a Bentall Is Not a Bentall: The Evolution of Aortic Root Surgery

Scott Maddalo, BA*, Jared Beller, BSE, Abe DeAnda, MD, FACS
New York University Langone Medical Center, New York, New York, USA

Abstract

Background: Aortic root pathology had been a known entity with a progressive and catastrophic course, long before the methods to surgically address them were first developed. Once reliable cardiopulmonary bypass was established, surgeons were able to pioneer new operative techniques, and in the half-century to follow, countless modifications and refinements have provided today’s surgeons with the surgical approaches that are currently at their disposal. History: Denton Cooley and Michael De Bakey reported the first successful surgical intervention for aneurysms involving the ascending aorta in 1956. Nearly a decade later, Hugh Bentall described his modification, and provided a name that would leave a lasting mark on aneurysmal surgery. In the decades to follow, numerous innovative surgeons improved on these original procedures to allow for a more reliable and consistent operation. Further, Tirone David and Sir Magdi Yacoub each described their methods to repair the aortic root while preserving the valve, thus providing their patients with freedom from a prosthetic or mechanical valve and improved quality of life. Conclusions: The development of surgical techniques required to successfully care for patients with pathology of the aortic root has evolved considerably since Cooley and De Bakey’s original report. Although it is common to hear aortic root replacement referred to as a “Bentall,” the methods currently employed have gone through considerable evolution, such that the techniques of today should not be referred to as a Bentall.

Key Words
Aortic root · Bentall procedure · Cabrol procedure · Valve-sparing surgery

Introduction

Aortic root pathology is often discovered incidentally after imaging is performed in patients for unrelated reasons. The most common indications for surgery of the aortic root are dilatation or aneurysm that disrupts the precise hemodynamic environment unique to the root (producing aortic insufficiency) and/or increases the risk of rupture or dissection. In the past, operating on the aortic root was reserved only for catastrophic circumstances. Current surgical repair of aneurysms affecting the aortic root and ascending aorta involves resection of the pathologic section and insertion of a graft. Recent innovations include aortic valve-sparing techniques, which provide patients with increased quality of life due to freedom from anticoagulation therapy, and increased longevity of the valve (compared to tissue valves). In instances where there is also concurrent aortic insufficiency or aortic cusp pathology, a composite valve-graft (either bioprosthetic or mechanical) may be used if the valve cannot be repaired. The purpose of this review is to focus on the historical aspects of aortic root surgery and to illustrate the evolution in operative technique.

Perspective and Evolving Indications

Aneurysms of the ascending aorta had been a well known entity prior to the first reports of their successful surgical management. There was little question as
to the progressive and fatal course, particularly in patients with Marfan syndrome or other connective tissue disorders. Although the majority of patients with isolated aneurysms remained asymptomatic, the risk for catastrophic consequences was known to increase as the size of the aneurysm grew. Despite the known natural history, little could be done to mitigate the risks with medications or to offer a curative surgical option. The surgical techniques currently employed developed out of a stepwise progression that began with the foundational challenges of overcoming cerebral anoxia and organ malperfusion, specifically the development of the cardiopulmonary bypass machine and the safe arrest of the heart. Over decades these techniques evolved, with surgeons seeking to recreate or maintain the intrinsic anatomical structure and function of the aortic root, most recently with the advent of valve-sparing procedures. Creativity, out of necessity, drove the innovations of the 20th century and enabled aortic root surgery to become reproducible, albeit potentially technically challenging, as the procedure remains today.

Prior to the 1970s, aortic root surgery was predominately performed in the setting of acute aortic catastrophe, on largely unstable, critically ill patients. These experiences with poor surgical candidates demonstrated an exceedingly high mortality. The innovative proof of concept that Hugh Bentall described in 1968, and the subsequent long-term track record that would follow, encouraged programs to begin prophylactic surgery, thereby reducing the risk of rupture and dissection, as well as offering a consistent, reproducible surgical outcome that could provide hope to those afflicted with this pathology. Bentall's work would not have been possible without the successes and failures that preceded him, nor would aortic root surgery be what it is today without the modifications by those that followed.

**Functional Anatomy**

The aortic root is the complex anatomical section that lies between the outlet of the left ventricle and the ascending aorta. Two virtual rings form the boundaries of this space. Proximally, the basal ring is defined by the aortic valve annulus. Distally, the sinotubular junction is marked by the superior limit of the valve cusp attachments. In addition to these anatomical landmarks, a critical component of valve physiology arises from the geometric relationships between the sinotubular junction and the basal ring. This region forms the sinuses of Valsalva, which serve to optimize cusp-loading, improve transvalvular hemodynamics, and minimize turbulence throughout the cardiac cycle [1]. In recent years, a more precise understanding of the fluid dynamics that arise from sinus geometry has developed [2]. This knowledge has the potential to guide prosthetic valve design and surgical repair, with the goals of minimizing cusp fatigue and stress, much like the native sinuses. Further, torsion within the aortic root as a result of helical blood flow functions to dissipate shear strains created during left ventricular contraction. A final anatomic consideration is the asymmetry among the three aortic cusps. The noncoronary cusp is the largest of the three and its basal attachment is to fibrous tissue lying in close proximity to the anterior leaflet of the mitral valve. The basal attachments of the left and right cusps are muscular, and because of this, the anterior section of the basal ring is more resistant to dilation.

**Surgical Technique**

**Initial Reports through the 1960s**

Denton Cooley and Michael De Bakey reported the first successful replacement of a fusiform ascending aneurysm in 1956 [3]. Prior to their experience, the means to correct aneurysms in this anatomical location had been limited to narrow-necked saccular aneurysms [4]. These could be corrected with tangential excision and aortorrhaphy. Reliable cardiopulmonary bypass had yet to be consistently performed, and even a brief interruption of aortic flow proximal to the aortic arch meant disastrous neurologic consequences. Cooley and De Bakey’s report of the initial introduction of cardiopulmonary bypass to aortic aneurysm surgery was an incredible leap forward that allowed the surgeon to temporarily halt aortic flow without the compromise in systemic perfusion that would result in the absence of circulatory support. With the aid of cardiopulmonary bypass, surgeons now had the time and surgical exposure necessary to excise the defect and suture in place a homograft before restoring normal cardiac function.

In the years that followed, the surgical group at University of Oregon Medical School was at work cre-
ating and redesigning mechanical ball-valve aortic prostheses [5]. They first performed implantation of their aortic ball-valve prosthesis in the fall of 1961. Following that initial surgery, they worked through several iterations of their prototype, in order to achieve improved results. Their progression began with a three-pronged cage made from a cobalt-based alloy and a sewing margin consisting of a silicone ring coated with a double layer of Teflon cloth. Unfortunately, they observed an unacceptable rate of thromboembolic events in their early series. These sobering results encouraged them to progressively reduce the amount of exposed alloy, while modifying their material selection. By the end of the 1960s, they had altered their model by shortening and completely covering the cage with Dacron®, while using a highly polished, electron-beam welded ball [6].

Throughout the late 1950s and into the 1960s, others replicated procedures similar to the one that Cooley and De Bakey first described [7,8]. With the surgical experience of today, many of the attempted modifications may seem radical, but in the context of their day, creativity was the only option. Initially, ideas like bicuspidization of the valve through excision of the noncoronary cusp seemed promising, as it created a competent valve [9–11]. However, despite creative attempts such as this, no lasting innovation was developed until 1964, when Myron Wheat reported his team’s efforts to replace the entire ascending aorta [12]. Although the procedure performed may not have involved the entire aorta as the title laid claim, its legacy was secured as a description of how to handle pathology extending proximal to the coronary ostia. The patient they describe suffered from a syphilitic aneurysm beginning at the aortic annulus and extending 11 cm to a point “several centimeters before the origin of the innominate artery [12], p.718.” Their approach to the displaced coronary ostia was to resect the aorta 1.5-2 cm proximal to this level, while leaving a tongue of tissue surrounding the two coronary take-offs. In this way, they maintained the integrity of the ostia and ensured the sutures were far enough from the coronary arteries to minimize the risk of thrombosis. Wheat modestly deflected credit and claimed that previously developed techniques “had merely awaited the appropriate patient [12], p.717.” The next step in root revision had occurred. Surgeons now had the means to extend the excision beyond the level of the coronary ostia and avoided the need to reimplant the coronaries.

In 1966, Cooley published what had been his team’s 10-year experience with aortic root and ascending aortic surgery [13]. At this early stage in the development of root surgery, they highlighted the fact that no single method of reconstruction was ideal, and that the patient’s specific anatomy dictated which was the most appropriate method. This prescient view still holds true today, underscoring the importance of an individualized approach with the multiple surgical procedures now at our disposal. Further, at their point in the technical development, they credited the finely woven nonporous Dacron® graft with minimizing the hemorrhagic complications that arose as a result of the routine heparinization needed for cardiopulmonary bypass.

While others continued to work tirelessly, recreating and extending aortic repair, the group at Oregon, including Drs. Herr and Starr, were diligently at work devising mechanical valves that would eventually be used for Bentall’s historic procedure [5,6]. In 1968, they published their ongoing clinical experience and engineering progress [6]. Even at this early point in the evolution of aortic root surgery, bold predictions about future progress were envisioned by Starr. In response to commentary on their article, he closed with his belief that they were already “approaching a time when consideration of earlier surgery will be possible [6], p.218.” Although they were not yet ready to encourage prophylactic surgery, they felt that if their “experience [were to] continue along the lines that it has taken in the last few years, it may well be possible to do so in the near future [6], p.219.”

At the time of Bentall and De Bono’s classic report, a successful approach to proximal aortic pathology using cardiopulmonary bypass had existed for over a decade [14]. There is no doubt that their ingenuity to use a composite valve-graft prosthesis was a major step in the progression of aortic root surgery, and the composite valve-graft, whether using a mechanical (as originally done) or tissue valve, is still considered the gold standard today. In addition to the introduction of a composite valve-graft, the side-to-side anastomosis of the coronaries to the aortic prosthesis added to the legacy of the procedure. Although these two developments were crucial in the trajectory of the field, the authors fail to recognize some of the important steps that led to the possibility of such a technical advance-
ment. Notably, they credit Cooley with the development of a combination valve prosthesis and aortic graft replacement, without mention of the work of Wheat. Despite this, their innovation secured a lasting name within aortic root repair. The early results of subsequent procedures were complicated by the tenuous anastomosis resulting from implantation of the coronaries into the graft with the inclusion technique. Further, pseudoaneurysm formation at the coronary anastomoses grew to be a well known concern following these original methods. The solution to the limitation in proximal excision created a new challenge, one that would fuel the next era of innovation seeking to improve on this technically challenging and often unpredictable procedure.

**Beyond a Classic Bentall: The Modifications Necessary for a Reliable Procedure**

The specific anatomic-pathologic changes seen in the aortic root are not consistent from patient to patient. This is particularly evident when considering the relationship of the coronary ostia to surrounding structures. Commonly, the dilative and degenerative process displaces the ostia to such an extent that direct anastomosis to the graft is facilitated: such was the case in Bentall's original procedure (Fig. 1). However, as the frequency of these operations grew from isolated case reports to larger series, it became evident that there were individuals in whom the restricted mobility of the ostia precluded an uncomplicated anastomosis. In the subset of patients with nondisplacement of the supra-annular segment, an alternative means of anastomosis needed to be devised.

Interposition of a conduit that could serve as an extension from the neoaorta to coronary artery was needed, but the ideal choice of material and specific method had yet to be established. In the mid 1970s, reports began to arise in which such attempts were made, but with inconsistent success. Blanco et al. [15] reported a promising approach, first unsuccessfully, but later with a positive result. In the first patient, both Dacron® and then later a saphenous vein graft were used. Initially, Dacron® was selected, but poorly visualized and inaccessible hemorrhage from the anastomosis site forced them to reinstitute bypass, take down the graft, and make a second attempt to save the patient using vein grafts. The second attempt formed a hemostatic seal and allowed the patient to be weaned off bypass. Unfortunately, the patient died hours after the surgery due to uncontrollable arrhythmias, presumably from prolonged operative time. Despite the outcome of this initial attempt, they were encouraged to recreate this approach and did so successfully in subsequent operations. They praised the interposition of vein segments as it was felt to allow for a more tension-free anastomosis, provide a means for constant perfusion of the arterial tree during operation, and, most importantly, allowed the surgeon to assess the suture lines for potential sites of bleeding prior to removal of the cross clamp. They believed this alteration held the key to consistent reproducibility, essential for any lasting operative technique.

Though some surgeons believed a conduit would be the answer to improving reliability, others felt this added step should only be instituted as needed. In 1976, nearly a decade after Bentall's original description of his method, Zubiate and Kay [16] described their experiences correcting aneurysmal dilation of the ascending aorta. In 6 of the 41 patients they operated on, either the friability of the tissue or undue tension placed when creating the anastomosis forced them to entertain use of a saphenous vein conduit. Rather than direct end-to-end anastomosis from the coronary ostia, as had been attempted before, they elected a more distal section of the main coronary trunks for the distal anastomosis. In this manner, they sutured closed the coronary ostia, and then performed an end-to-side anastomosis onto the corresponding coronary artery.

Two years later, Cabrol described what would serve as the foundation for a series of modifications and alterations [17]. Unique to his approach was a single, 8
Dacron® tube that functioned to supply the entire coronary circulation. In his operative technique, Cabrol first began with an end-to-end anastomosis between the left coronary orifice and the conduit (Fig. 2). He then shifted his attention to the completion of the aortic revision and, following completion of this component, returned to the coronary system. The opposite end of the single Dacron® conduit was anastomosed in an end-to-end fashion to the right coronary ostia. Finally, the single coronary conduit was made continuous with the aortic graft via a single side-to-side anastomosis. Once the anastomoses were completed and adequate hemodynamics confirmed, the aneurysmal wall was closed over the revision, and a 1.5 cm fistula was created to the right atrial appendage. This was believed to be important in preventing tense hematoma formation, while minimizing postoperative blood loss by returning it to the circulation. Despite these creative solutions, Cabrol’s operations were not without their unique complications, which would only become apparent through further experience.

In the years to follow, modifications to Cabrol’s original procedure were described. In addition to Dacron® and saphenous vein conduits, Piehler and Pluth [18] made use of a beveled Gore-Tex® interposition graft. They stressed the importance of restricting the length of this conduit, and recommended against using segments in excess of 15-20 mm. The particular case presented in their report featured asymmetric pathology of the coronary ostia, a presentation not uncommon in their practice. While the left coronary required a conduit due to insufficient displacement for direct anastomosis, the mobility of the right coronary permitted direct connection to the aortic graft via an inclusion technique. As additional operative techniques were added to the surgeon’s armamentarium, the hybrid approach they described further affirmed the importance of decisions that suit a patient’s individual anatomy.

In 1986, Cabrol reported on the outcomes several years following the operative technique he initially described in 1978 [19]. At the time, this was one of the first large cohort studies with promising long-term results, in some cases, up to eight years. Cabrol reported finding no pseudoaneurysms, a complication that was often seen with the classic Bentall procedure [20]. However, only 25% of patients were followed up with angiographic studies. What became apparent from later, larger, longer study periods were the complications owing to the distal aortic anastomosis. In the radiologic literature at the time, false aneurysm formation at this point was evident in up to 20% of patients within a few years [19]. Further, in Cabrol’s cohort of 100 patients, four suffered from late dissections originating from this very site.

There were clearly differences in opinion as to the ideal modifications to Bentall’s procedure that would make it an increasingly reproducible and safe procedure. This is highlighted by D. Craig Miller’s comments that although Cabrol’s approach is ingenious, it may be “a solution in search of a problem [19], p.24”. His concern referred to adding unnecessary complexity to a procedure that is not always required. In his practice, patients who had nondisplaced coronaries with restricted mobility were ideally suited for a procedure akin to the one described classically by Wheat. This algorithm served as a means for Miller to avoid using conduits and encountering the complications inherent to this addition.

A final evolution that became increasingly prevalent during this era was best illustrated by Kouchoukos’ description of his modifications throughout a
series of 168 patients that he reported in 1991 [21]. Prior to 1981, an inclusion-wrap technique, in which the intrinsic aorta enclosed the graft for hemostatic purposes, was used. This was the generally accepted standard, but the risk of tense hematoma formation remained. As Cabrol demonstrated, a solution to this was the introduction of an iatrogenic fistula from the periprosthetic space draining to the right atrium [17]. He was confident that this communication would close spontaneously following the resolution of the coagulopathy after surgery and, if not, it would prove to be hemodynamically insignificant. In the years to follow, a number of reports of late complications owing to this connection were published in the literature [22,23]. Rather than drain the space, a method to decrease the permeability of the graft would achieve the same end. Kouchoukos began preclotting the Dacron® graft with albumin, and this indeed improved hemostasis. Kouchoukos was also instrumental in popularizing an alternative means of dealing with the coronary anastomoses. By excising “coronary buttons,” the aortic-coronary anastomosis was facilitated, and this approach became a standard operative technique. Without the need for aortic wrapping, an additional hurdle was overcome and the potential for additional complications was avoided.

This era of innovation saw a dramatic decrease in early complications and the development of an arsenal of techniques that allowed the surgeon to approach any particular anatomy with the confidence that it could be successfully repaired. Now, without the same impediments faced by the early surgeons, focus began to shift. The aim was to find what would be the ideal way to provide long-term benefits of operation, allowing surgery to be offered not only as a life-saving operation, but also as a prophylactic means to prevent disaster.

**Into the Modern Era: The Trend to Incorporate Valve-Sparing Techniques**

The initial operative techniques developed in the 1960s and modified throughout the following decades are not all that dissimilar from those in practice today. As results became more favorable, and larger study cohorts were established, the surgical approach was able to be refined based on data rather than theory, securing reliable long-term results.

The ability to perform earlier surgery in patients, where the pathologic process had yet to permanently affect the leaflets, was an attractive prospect. This would enable restorative surgery without the inherent drawbacks of valve replacement. A native valve best suits the complex dynamic anatomy of the valve apparatus and enhances the maintenance of left ventricular function and coronary flow under a range of loading conditions. Not only is the possibility of a valve-conserving surgery ideal for hemodynamic factors, but it also eliminates the complications intrinsic to valve replacement surgery (e.g., anticoagulation and degeneration of bioprostheses). Despite the attractiveness of such a procedure, the long-term results remained largely unknown until the late 1990s.

Until large enough cohorts of patients had been compiled and meta-analyses completed, there remained two competing methods of sparing the aortic valve. The first was developed by Sir Magdi Yacoub, and had been used in his practice since 1979 [24,25]. The procedure, which he designed, later became referred to as a remodeling technique. The functional focus was to preserve the native valve, while recreating the aortic sinuses believed to be important in efficient flow of blood from the aortic root into the coronary lumen and relief of stress on the native valve leaflets (Fig. 3). Yacoub achieved this goal by fashioning a scalloped Dacron® graft such that three tongues extended to replace the intrinsic sinuses. Interposed between these three extensions, native tissue was left intact at the attachment of the cusps. Once the graft was attached, the coronary arteries would be mobilized and anastomosed to the neosynthetic aorta. During its development, this procedure seemed promising and, in fact, was adopted by many centers. However, as more evidence accrued, it appeared that this approach left patients susceptible to echocardiographically and clinically significant aortic insufficiency [26–28]. This can be attributed to the lack of stabilization of the aortic annulus. Without fixing the diameter of the aortic annulus, no protection from future dilation and alteration of root geometry is provided. This is especially critical for patients with Marfan syndrome and other connective tissue disorders. Additionally, since aortic tissue was left behind in order to accommodate the suture line, this tissue could continue to become aneurysmal as it was continually exposed to aortic pressures.

In the late 1980s, Tirone David and his colleagues at the University of Toronto developed an alternative
class of valve-sparing procedures [29]. Their procedure went through numerous iterations and variations, but classically the technique became referred to as reimplantation [30,31]. This approach had the benefit of stabilizing the aortic annulus by sewing the native valve directly into a Dacron® graft of a fixed circumference (Fig. 4). This provided greater protection from late complications than did Yacoub's remodeling, but it did not recreate the geometry of the sinuses. The significance of this deficit has yet to prove itself clinically, but theoretically, and experimentally, the lack of sinuses places undue stress on the valvular apparatus. An ideal approach would incorporate the annular stabilizing properties of reimplantation while mimicking the native geometry of the sinuses of Valsalva.

Although Tirone David was instrumental in the development of the reimplantation technique, it is not to say that his group exclusively used this procedure. In their 2006 paper that compared the results of the two techniques, they stated that “no particular criterion was used to select the type of aortic valve sparing” procedure [32], p.348. Throughout the years they

Figure 3. Valve-sparing procedure as done by Yacoub. Figure reprinted with permission from Yacoub et al. [25].
refined their technique, adding numerous modifications. A classification schema beyond simply calling a procedure reimplantation versus remodeling was needed, and despite the objections of David, Miller popularized the David-I through David-V classification (Table 1) [1]. He labeled David’s classic reimplantation procedure using a cylindrical tube graft as David-I, while Yacoub’s classic remodeling procedure was identified as a David-II. In this system, David-III referred to a remodeling variation where a synthetic strip is placed over the fibrous portion of the left ventricular outflow tract, achieving a narrowing and reinforcing annulopasty. The final two methods identified are variations on reimplantation. David-IV refers to the technique of using a graft 4 mm larger than the annulus to allow for plication, and David-V employs an even larger graft (6-8 mm larger than the diameter) in order to facilitate the creation of pseudosinuses. Thus, David-I, -IV, and -V are variations on reimplantation, whereas David-II and -III are variations on the remodeling technique originally devised by Yacoub.

In the late 1990s through the present day, attention shifted to focus on the finest details in technique, such as cusp reinforcement, graft sizing to allow for billowing, and plication as a means to recreate sinuses. Dr. Cameron and the group at Johns Hopkins have published some of the largest series on elective repair of patients with connective tissue disorders in need of aortic root surgery [33]. Although a “classic” Bentall (i.e., composite valve-graft replacement) remains the gold standard in their practice, over the years they have introduced valve-sparing procedures when possible. Their initial valve-sparing approach focused on preservation of sinuses with a remodeling procedure, but it soon became apparent that recurrent aortic insufficiency and annular dilation occurred in a significant number of patients soon after their initial procedure. At their center, as these results began to bear out, they transitioned to the reimplantation technique. This transition coincided with the newly approved De Paulis Valsalva graft, and in May of 2002, this combination became the exclusive procedure for valve-sparing operations at Johns Hopkins [34]. Reimplantation with the Valsalva graft has demonstrated promising results and provides both annulus stabilization and aortic sinuses, supplanting either of the classic valve-sparing techniques.

Table 1. David Classification by Miller for Valve-Sparing Aortic Root Replacement Surgery

<table>
<thead>
<tr>
<th>David Type</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Reimplantation Classic</td>
</tr>
<tr>
<td>II</td>
<td>Remodeling Classic</td>
</tr>
<tr>
<td>III</td>
<td>Remodeling Plus external synthetic strip over fibrous portion of left ventricular outflow</td>
</tr>
<tr>
<td>IV</td>
<td>Reimplantation Plus plication of graft (d +4 mm) at sinotubular junction</td>
</tr>
<tr>
<td>V</td>
<td>Reimplantation Plus plication of graft (d +6–8 mm) at both sinotubular junction and basal ring to create pseudosinuses</td>
</tr>
</tbody>
</table>

d, diameter of aortic annulus.
Conclusion

In the fifty-eight years since De Bakey and Cooley first replaced an ascending aneurysm with the aid of cardiopulmonary bypass, a number of surgeons devised innovative steps to improve patient outcomes. From the creation of the first usable aortic valve replacement to the valve-sparing techniques described by David and subsequent modifications, surgeons can now treat aortic root pathology without removing a patient’s native aortic valve, which greatly improves quality of life. The design of the De Paulis Valsalva graft is another great addition to the surgeon’s arsenal and reinforces the need to continue analyzing and improving surgical techniques based on the dynamic physiologic environment of the aortic root. While it is common to hear surgeons refer to aortic root replacements as a “Bentall”, the procedures currently employed have undergone an evolution, enough so that what is done now does not resemble the aortic inclusion and side-to-side coronary anastomosis technique. Bentall and DeBono rightfully deserve credit for popularizing the root replacement approach, but others have contributed substantially as well.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

References

Differences in Elastin and Elastolytic Enzymes between Men and Women with Abdominal Aortic Aneurysm

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Abstract

Background: Abdominal aortic aneurysms (AAAs) in women differ in some important aspects from those in men. The lower prevalence rate, higher rupture rate and potentially increased growth rate in women with AAA suggest gender to be of importance for aneurysm development and progression. The aim of the study was to analyze wall properties with respect to synthesis and destruction of elastin in men and women with AAA, with and without an intraluminal thrombus. Methods: Patient characteristics and aneurysm wall biopsies were collected from all women (n = 14) treated with open repair for AAA, 2008-2012, and men with similar aneurysm diameter and similar age (n = 23) treated during the same time period. The expressions of elastin, matrix metalloproteinase (MMP)-2 and -9, and cathepsin K were quantified by immunohistochemistry, Western blot, and gene expression analysis on the aneurysm wall. Results: The protein expression of elastin was less in women than in men in the non-thrombus-covered aneurysm wall. In addition, the protein and mRNA expressions of MMP-9 were higher in women (−0.83 versus 0.09, P = 0.041). There was no difference in elastin and elastolytic enzymes between men and women in the thrombus-covered aneurysm wall. Conclusion: Less elastin in the non-thrombus-covered aneurysm wall in women than that in men, and the simultaneous higher level of MMP-9, suggest differences in the elastolytic process in AAA between the sexes.

Key Words

Abdominal aortic aneurysm · Gender · Women · Elastin · MMP-9 · Progression · Rupture

Introduction

Abdominal aortic aneurysms (AAAs) in women differ in some important aspects from those in men. The lower prevalence rate, higher rupture rate and potentially increased growth rate in women with AAA suggest gender to be of importance for aneurysm development and progression. [1–3].

The development of AAA is characterized by the loss of elastin in the medial layer of the aortic wall together with an increased collagen turnover [4,5]. With the depletion of elastin and collagen the aorta loses its elasticity and tensile strength [6]. Elastin, which is synthesized by vascular smooth muscle cells (VSMCs) in the medial layer of the aortic wall, is composed to impart resilience for a lifetime [7,8].

The breakdown of elastin in AAA development is induced by proteolytic enzymes, produced by infil-
trating inflammatory cells and modified VSMCs [9]. The family of matrix metalloproteinases (MMPs) are the proteolytic enzymes most associated with AAA development [10]. Especially MMP-2 and -9, with substantial elastolytic capacity, contribute to both AAA development and growth [11,12]. The family of cathepsins is another group of matrix-degenerating enzymes inducing elastolysis that has been implicated in the formation and growth of AAA [13].

The intraluminal thrombus (ILT), often prevalent in AAA, has been show to influence the deterioration of the underlying aneurysm wall [14]. Beneath the ILT the fragmentation of elastic fibers is more pronounced, the vessel wall is thinner, and there are more inflammatory cells and fewer VSMCs than in the non-thrombus-covered wall [14,15]. The effect mediated by the ILT has been related to its thickness and size; a thin ILT has been shown to be more biomechanically active and to more effectively promote proteolysis in the underlying aneurysm wall, whereas a thicker ILT contributes to the deterioration of the underlying aneurysm wall by inducing hypoxia [16,17].

Women have smaller aortas than men, rendering the relative enlargement in women with AAA greater compared to that of men at any given diameter, but little is known of how it relates to the deterioration of the aneurysm wall [18,19]. Aortic size index (ASI) is a measurement taking the relative dilatation into consideration [20]. Gender differences in vascular aging have been ascribed to the effect of sex hormones [21]. Differences between the sexes in the degradation of the arterial wall, induced by senescence, have been illustrated by the maintenance of elasticity in the aorta of women compared to that of men [22]. Thereto, estrogen has been shown to increase the deposition of elastin by VSMCs [23].

A difference in elastin and elastolytic proteins between men and women with AAA could help explain the gender disparities in AAA progression. The aim of the study was to compare elastin content and some of the elastolytic enzymes mostly associated with AAA development, between men and women with equally large AAA.

**Materials and Methods**

All women treated electively for AAA with open aneurysm repair at Karolinska University Hospital, November 2008 to December 2012, were included (n = 14). Male AAA patients with similar age and aneurysm diameter, treated during the same time period, were also included (n = 23). The patients were treated with open repair (OR) either because they were deemed unfit for endovascular aneurysm repair (EVAR) or because of their comparatively young age. A biopsy of the ventral infrarenal aneurysm wall, preferably in midline, often at the maximum diameter, was obtained during operation. Two biopsies were taken from each patient, if possible: thrombus-covered and non-thrombus-covered aneurysm wall. The thrombus was removed and stored separately.

Patient characteristics were obtained from hospital charts. Body surface area (BSA) was calculated according to DuBois: body surface area ((weight\(^{0.425}\) × height\(^{0.725}\) × 0.007184)) [24]. ASI was calculated: aneurysm diameter (cm)/BSA (m\(^2\)) [20].

All patients had signed an informed consent prior to the surgical procedure. The study was approved by the local Ethics Committee.

**Immunohistochemistry**

Sections (5 μm) of thrombus-covered and non-thrombus-covered aneurysm walls were deparaffinized in Tissue-Clear™ (Sakura, Leiden, The Netherlands) and rehydrated in ethanol. Weigert-van Gieson staining was then performed by immersing the sections in the various solutions: Weigert’s hematoxylin, Weigert’s elastin, and Van Gieson solutions, all from Sigma-Aldrich (St. Louis, Missouri, USA), according to a standardized protocol. Elastic fibers turned dark purple, muscle turned yellow, nuclei turned brown, and connective tissue turned red. The investigator was blinded for sex and AAA diameter when valuing the elastin staining.

**Gene Expression Analysis**

Snap-frozen thrombus- and non-thrombus-covered media were homogenized in Lysing Matrix D tubes with Fastprep® (MP Biomedicals, Solon, Ohio, USA). RNA was isolated with TRIzol (Life Technologies, Grand Island, New York, USA), RLT buffer (from RNeasy Mini kit, Qiagen, Hilden, Germany) and DNase1 (RNase free DNase Set, Qiagen) according to the manufacturer’s protocol. RNA was quantified by a NanoDrop (Nano-Drop Products, Wilmington, Delaware, USA), and RNA quality and integrity were verified using the Agilent 2100 Bioanalyzer System (Agilent Technologies, Santa Clara, California, USA).

For quantification of gene expression, total RNA, was reverse-transcribed to cDNA using Superscript II according to the manufacturer’s protocol (Life Technologies). Real-time polymerase chain reaction (PCR) was performed on the Applied Biosystems (Foster City, California, USA) 7000 Real-Time PCR System with TaqMan Assays-on-Demand Gene Expression Probes for elastin, MMP-9, MMP-2, and cathepsin K. Robust multiarray average normalization was performed and gene expression data were log2-transformed. The housekeeping gene Ribosomal Protein Large PO (RPLP0) was used for normalization.

**Western Blot**

Thrombus- and non-thrombus-covered medial layers were shred and put in tubes with a lysis buffer containing 50 pro-
tease inhibitor and 30 1 mol/L Tris-HCl, pH 8.0. The samples were then granulated with a Qiagen Tissuelyser according to the manufacturer’s protocol, followed by centrifugation for 5 minutes at 220 rpm. The supernatants were sonicated for 5 minutes at high level followed by centrifugation for 10 minutes at 12,000 rpm. The protein content in the supernatants was measured using a Bradford protein assay.

The protein was diluted with lysis buffer and then loaded on a 4-12% sodium dodecyl sulfate (SDS) gel [Novex NuPAGE® 4-12% Bis-Tris gel, 15 well (Life Technologies)] in MOPS-SDS running buffer. The electrophoresis was performed in a cold room for 90 minutes at 100 V. Before transfer by electroblotting in a cold room for 90 minutes at 400 mA, the gel and membrane (Hybond Polyvinylidene Flouride transfer membrane, GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) were equilibrated in transfer buffer. For blocking, the membrane was suspended in blocking buffer (3% bovine serum albumin/Tween Tris-buffered saline) for 60 minutes. The membrane was incubated overnight with elastin (Abcam, Cambridge, United Kingdom), MMP-9 (Cell Signaling Technology, Danvers, Massachusetts, USA), β-tubulin (Santa Cruz Biotechnology, Santa Cruz, California, USA), and Glyceraldehyde 3-phosphate dehydrogenase (Abcam) followed by the second antibody (anti-mouse and anti-rabbit HRP, Bio-Rad Laboratories, Hercules, California, USA) for 45 minutes. For the final step of chemiluminescent detection, the developing solution from ECL Prime Western Blotting Detection Reagent kit (GE Healthcare) and film (Amersham Hyperfilm ECL, GE Healthcare) were used. Densitometry was performed using ImageJ analysis software.

Statistics

The statistical analysis was performed with SPSS 21.0. The independent t test was used for gender comparisons of normally distributed data and the Mann-Whitney U test for continuous, non-normally distributed data. Pearson’s χ² test and Fisher’s exact test were used for parametric and nonparametric categorical variables, respectively. Statistical significance was defined as P < 0.05.

Results

Body Surface Area and Aortic Size Index in Men and Women with AAA

Men and women with AAA were similar in age and had similar aneurysm diameter and body mass index (BMI). Men with AAA had higher BSA than women with AAA, 1.9 versus 1.7, P < 0.001. There was no difference in the absolute diameter relative to BSA (ASI), i.e., AAA diameter (cm)/BSA (m²), between men and women (Table 1). Men and women with AAA were similar regarding smoking habits, occurrence of comorbid conditions, relevant laboratory parameters, and medical treatments, with the exception of beta blockers, which was more frequently prescribed to women (Table 1).

The Non-Thrombus-Covered Aneurysm Wall in Men and Women

Western blot analysis and immunohistochemistry showed that protein expression of elastin in the non-thrombus-covered aneurysm wall was lower in women than in men (Fig. 1) There was no difference in mRNA expression of elastin between men and women (Table 2). Women had a higher mRNA expression of MMP-9 than men (Table 2). Similar results were observed in Western blot analysis (Fig. 1). There were no differences in MMP-2 and cathepsin K between men and women in mRNA expression analysis (Table 2). Prior and current smokers as well as smoking and non-smoking men and women were similar in the mRNA expressions of elastin, MMP-9 and cathepsin K.

The Thrombus-Covered Aneurysm Wall in Men and Women

There was no difference in mRNA expression or protein expression of elastin, MMP-2, MMP-9, and cathepsin K in the thrombus covered aneurysm wall between men and women (Table 3). There were no differences in mRNA expressions of elastin, MMP-2 and -9, and cathepsin K between prior and current smokers or between smoking and nonsmoking men and women.

Discussion

The key findings of this study, less elastin in the non-thrombus-covered aneurysm wall of women compared to that of men with a simultaneous greater expression of MMP-9, imply that the elastolytic process in the aneurysm wall differs between the sexes. Elastin breakdown has been shown to be of importance especially in the initial growth of an AAA, whereas collagen degradation has been associated with the later stages of aneurysm enlargement and rupture [6]. Less protein expression of elastin in the non-thrombus-covered aneurysm wall of women than in men, together with the opposite relation in protein and mRNA expression of MMP-9, suggests a more elastolytic process in that part of the aneurysm wall of women. The lack of difference in elastin content and proteolytic enzymes in the thrombus-covered aneurysm wall between the sexes, found in this study,
suggest that the elastolysis in that part of the aneurysm wall is similar in men and women. The impact of the limited expression of elastin in the non-thrombus-covered aneurysm wall of women remains to be investigated but could contribute to explaining gender differences in AAA pathogenesis. A weaker part of the aneurysm wall, as a result of greater elastolysis, in women could be of importance for the growth and rupture rate of women’s AAAs. The difference in protein expression of elastin between men and women without a simultaneous difference in the mRNA expression could be explained by the limited turnover rate and synthesis of elastin in adults [8]. The similar age and AAA diameter as well as smoking habits of the participating men and women in this study rule them out as possible confounding factors. Tong et al. [19] recently presented results of a higher growth rate in men than in women with AAA and less elastin in men, in the thrombus-covered aneurysm wall. A possible explanation for the contradicting results might be differences in age, AAA diameter, and smoking habits between the participants of the two studies.

MMP-2 has been implicated in the initial AAA development, and higher levels have been observed beneath the ILT [14]. We found no difference in mRNA expression of MMP-2 in men and women either beneath the ILT or in the non-thrombus-covered aneurysm wall. The lack of difference in mRNA expression of MMP-2 and cathepsin K between men and women suggest that the expression of MMP-2 and cathepsin K is of less importance for gender differences in AAA progression.

Women have smaller BSA and suprarenal aortic diameter than men, making the relative aneurysm enlargement in women exceed that of men [18]. ASI is a measure—until recently, more commonly used when categorizing thoracic aneurysms—that takes the relative enlargement into account [25]. Lo et al. [20] recently showed that ASI is an important determinant for AAA progression in women. In this

### Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Men with AAA (N = 23)</th>
<th>Women with AAA (N = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 ± 5</td>
<td>72 ± 7</td>
<td>0.595</td>
</tr>
<tr>
<td>AAA diameter</td>
<td>6.3 ± 0.9</td>
<td>6.0 ± 0.6</td>
<td>0.263</td>
</tr>
<tr>
<td>BMI</td>
<td>26.0 (5.2)</td>
<td>25.0 (3.0)</td>
<td>0.752</td>
</tr>
<tr>
<td>BSA</td>
<td>1.9 (0.2)</td>
<td>1.7 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASI</td>
<td>3.2 ± 0.5</td>
<td>3.5 ± 0.3</td>
<td>0.107</td>
</tr>
</tbody>
</table>

**Risk factors and comorbid conditions**

<table>
<thead>
<tr>
<th>Smoking</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Prior</td>
<td>10 (44)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Diabtes mellitus</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Cardiac diseasea</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Statins</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminb</td>
<td>36 ± 4</td>
</tr>
<tr>
<td>Creatinexb</td>
<td>86 ± 19</td>
</tr>
</tbody>
</table>

**Values are presented as mean ± standard deviation for normally distributed data, median (IR) for not normally distributed data, and frequencies (%) for categorical variables. Significance calculated by independent t test, Mann Whitney U test, Pearson’s chi-square test, and Fisher’s exact test. BMI = body mass index; BSA = body surface area (weight0.425 × height 0.725 × 0.007184); ASI = aortic size index (aneurysm diameter (cm)/BSA (m²)).

*aCardiac disease defined as cardiac insufficiency, coronary artery disease, and atrial fibrillation.

*bLaboratory values obtained 1 or 2 days prior to the elective surgery.
Table 2. Gene Expression Analysis of Elastin, MMP-2, MMP-9, and Cathepsin K in the Non-Thrombus-Covered Aneurysmal Wall of Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Non-Thrombus-Covered Wall</th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men with AAA</td>
<td>Women with AAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastin</td>
<td>4.55 ± 3.21</td>
<td>5.01 ± 3.31</td>
<td>0.722</td>
<td></td>
</tr>
<tr>
<td>MMP-2</td>
<td>1.52 ± 1.22</td>
<td>1.74 ± 1.51</td>
<td>0.744</td>
<td></td>
</tr>
<tr>
<td>MMP-9</td>
<td>−0.83 ± 1.08</td>
<td>0.90 ± 2.59</td>
<td>0.041</td>
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</tr>
<tr>
<td>Cathepsin K</td>
<td>1.68 ± 1.06</td>
<td>2.63 ± 1.01</td>
<td>0.063</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation for normally distributed data. Significance calculated by independent t test. Values are presented log2-transformed and as arbitrary units.

Table 3. Gene Expression Analysis of Elastin, MMP-2, MMP-9, and Cathepsin K in the Thrombus-Covered Aneurysmal Wall of Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Thrombus-Covered Wall</th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men with AAA</td>
<td>Women with AAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastin</td>
<td>−6.03 (1.69)</td>
<td>−6.03 (1.89)</td>
<td>0.830</td>
<td></td>
</tr>
<tr>
<td>MMP-2</td>
<td>−2.13 ± 0.60</td>
<td>−2.41 ± 0.78</td>
<td>0.282</td>
<td></td>
</tr>
<tr>
<td>MMP-9</td>
<td>−2.27 ± 1.08</td>
<td>−2.20 ± 1.35</td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>Cathepsin K</td>
<td>−2.40 (1.58)</td>
<td>−2.82 (1.89)</td>
<td>0.940</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation for normally distributed data and median (interquartile range) for not normally distributed data. Significance calculated by independent t test and Mann Whitney U test. Values are presented log2-transformed and as arbitrary units.

Figure 1. A. Weigert-van Gieson’s staining of elastin in the non-thrombus-covered aneurysm wall of two men. B. Weigert-van Gieson’s staining of elastin in the non-thrombus-covered aneurysm wall of two women. C. Western blot and densitometry of elastin in the non-thrombus-covered aneurysm wall of three women and two men (0.81 versus 2.30, P = 0.200). D. Western blot and densitometry of MMP-9 in the non-thrombus-covered aneurysm wall of three women and two men (0.65 versus 0.22, P = 0.200).
study women were found to have significantly lower BSA than men, but the ASI did not significantly differ between the sexes. We do not rule out that a weaker aneurysm wall, due to a greater enlargement, in women could help explain gender differences in aneurysm development. We cannot, however, conclude that the differences in biomechanical properties found in this study are attributed to such an effect.

There are limitations to this study, of which the small sample size is one. However, the number of patients included in this study is similar to those in other studies within the field of research [12,15]. Another limitation to the study is the potential influence of other enzymes involved in the elastolytic process not addressed in this study; for instance, tissue inhibitor of MMP (TIMP). More potentially influential genes could have been found with the use of microarray analysis, for instance. Finally, the biopsies of the aneurysm wall were all obtained from the anterior wall, and consequently the generalizability of the results to the rest of the aneurysm wall cannot be assured.

In conclusion, less elastin in the non-thrombus-covered aortic wall of women with AAA than in men and the simultaneous higher level of MMP-9 suggest differences in the elastolytic process of AAA in men and women.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

References


Villard, C. et al. Elastin in Aneurysm Walls


Heterogeneity in the Segmental Development of the Aortic Tree
Impact on Management of Genetically Triggered Aortic Aneurysms

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Department of Cardiac Surgery, Christiana Hospital, Christiana Care Health System, Newark, Delaware, USA

Abstract
An extensive search of the medical literature examining the development of the thoracic aortic tree reveals that the thoracic aorta does not develop as one unit or in one stage: the oldest part of the thoracic aorta is the descending aorta with the aortic arch being the second oldest, developing under influence from the neural crest cell. Following in chronological order are the proximal ascending aorta and aortic root, which develop from a conotruncal origin. Different areas of the thoracic aorta develop under the influence of different gene sets. These parts develop from different cell lineages: the aortic root (the conotruncus), developing from the mesoderm; the ascending aorta and aortic arch, developing from the neural crest cells; and the descending aorta from the mesoderm. Findings illustrate that the thoracic aorta is not a single entity, in developmental terms. It develops from three or four distinct areas, at different stages of embryonic life, and under different sets of genes and signaling pathways. Genetically triggered thoracic aortic aneurysms are not a monolithic group but rather share a multi-genetic origin. Identification of therapeutic targets should be based on the predilection of certain genes to cause aneurysmal disease in specific aortic segments.

Key Words
Aortic development · Aneurysms · Aortic dissection · Genetics · Developmental anatomy

"Out of intense complexities, intense simplicities emerge". —Winston Churchill

Introduction and Aim of Research
Thoracic aortic aneurysms continue to present clinicians with considerable clinical challenges, particularly with risk prediction and its implications on management plan. Previous reports [1,2] have identified those conditions arising due to inherited causes (i.e., genetically triggered thoracic or GenTAC diseases) as the second most common cause of aortic disease, most frequently clinically recognizable well before the age of 50. Patients affected by such diseases are at a markedly higher risk of mortality (250-fold in some cases) and morbidity, thus making early detection and definitive management imperative.

Current research indicates, however, that these diseases represent a heterogeneous group of conditions [3,4] sharing only the common feature of “aortic” involvement. Although involvement of the aortic root, aortic annulus, and ascending aorta represents the highest risk to patients, no clear association between any one genetic trigger and a specific area of the thoracic aorta has been definitively established. The fact that GenTAC diseases are usually multigenetic and multifactorial in origin argues against one causative gene or one transcriptional factor being responsible for the disease process in all areas of the thoracic...
aorta. Even in Marfan syndrome, where there is a global genetic defect of fibrillin maturation not only in the thoracic aorta but also systemically, there is still a marked predilection for the aortic root and proximal ascending aorta, as compared to other aortic segments.

Therefore, we seek to examine (a) whether the thoracic aorta develops as one anatomic unit during one continuous stage, and (b) whether this anatomic development is under the control of one set of genes.

For the purpose of this discussion, the thoracic aorta has been divided into four “fields” (Fig. 1)—corresponding to their embryologic development—as follows:

- **First aortic field**: The descending aorta; from the level of the aortic isthmus (just beyond the left subclavian artery) to the level of the diaphragm.
- **Second aortic field**: The aortic arch; from the level of the aortic isthmus to just beyond the origin of the innominate artery.
- **Third aortic field**: The ascending aorta; from the sinotubular junction to just before the origin of the innominate artery.
- **Fourth aortic field**: The aortic root; from the level of the left ventricular outflow tract to the sino-tubular junction, encompassing the aortic annulus and valve and the earliest portion of the aorta—up to the sinotubular junction.

It is important to note that these lines of division do not mark abrupt or sharp transitions but, rather, areas where one area “blends” or “tapers” into the next. This is especially true in the transition between the aortic root and the ascending aorta, around the level of the sinotubular junction.

**Literature Search Methodology**

An extensive search of the medical literature using PubMed, Medline, and Google® Internet search engines, and the National Institutes of Health/National Library of Medicine online databases was performed. Search areas included:

- Developmental anatomy, folding and looping of the primary heart tube.
- Development of the different segments of the thoracic aortic tree.
- Genetics of vascular and aortic development with special focus on segmental effects.

**Results**

*The Early Stages and the First Aortic Field (Oldest Segments)*

Development of the central arterial vasculature (i.e., the aortic tree) begins quite early, before the initiation of circulation. The first signs of cardiovascular development begin as early as embryonic day (E) 17, with vasculogenesis in two areas on the lateral side of the embryo called “blood islands.” By the early part of the 3rd week (around E19), a pair of vascular elements, called endocardial tubes, is seen. In the early part of the 4th week, as the embryo folds, these two lateral endocardial tubes are brought together in the thoracic region where they fuse to form the primitive heart tube [5–12].

Around the same time of the endocardial tube development, vascular chords in the mesenchyme of the dorsal body wall form the paired dorsal aortae, both cranial and caudal to the embryonic primitive
heart tube. These dorsal aortae also attach to the outflow end of this heart tube (Fig. 2).

By E22–E24 (mid-4th week), the primitive heart tube, in turn, undergoes folding along with the generalized axial folding of the embryo. During this process, the endocardial tubes are drawn—along with their attachment to the heart tube—into the ventral aspect of the thorax. At the same time, the part of the paired dorsal aortae attached to the cranial end of the heart tube is pulled ventrally, forming a pair of dorso-ventral "loops," which are the first aortic arches.

The Second Aortic Field (Aortic Arch)

At approximately the same time (beginning E22), mesenchymal cells form five pairs of condensation on either side of the pharyngeal foregut. These five areas correspond to the primitive vertebrate gill bars or branchial arches. Specifically, these five arches in human embryos correspond to branchial arches 1, 2, 3, and 6 in such animals as jawless fish, since the fifth branchial arch either never develops or appears only for a brief period of time before regressing. As mesodermal and endodermal components of these arches are added, their role in human embryos becomes different from that of other animals, thereby giving rise to structures of the lower face, neck, and derivatives of the pharyngeal foregut. Subsequently, these arches in humans are more appropriately termed "pharyngeal arches."

Development of the pharyngeal arches proceeds in a cranio-caudal order. As a new arch is formed, the aortic sac contributes an artery for that arch. In addition to the first aortic arches described above, the remainder of the vessels associated with the pharyngeal arches (i.e., aortic arches) develop in the ventral aspect from an expansion at the cranial end of the truncus arteriosus called the aortic sac (Fig. 3). Aortic arches 2, 3, 4, and 6 develop within their corresponding pharyngeal arches between E26 and E29 (late week 4 to mid-week 5) by a process of vasculogenesis and angiogenesis strongly influenced by migration of neural crest-derived ectomesenchymal cells into these arches.

As the second aortic arch arises by E26, the first aortic arches regress almost completely, without contributing to any mature intrathoracic vasculature. During their regression (around E28), arches 3 and 4 appear. At this stage (Carnegie Stage 13 or approximately E28), the paired dorsal aortae fuse from the level of C7 vertebra to the upper lumbar vertebral level, or at the takeoff of the umbilical artery branch. Finally, the sixth aortic arch forms on E29. Meanwhile, the second aortic arch also regresses without contribution to the intrathoracic vasculature.
By E35 or the end of week 5, segments of the dorsal aorta connecting the third and fourth arches disappear on both sides of the body. This leads to the third arch supplying the head via the cranial extension of the dorsal aorta. Therefore, the third aortic arch gives rise to the right and left common carotid arteries and also the proximal portions of both right and left internal carotid arteries. It is important to keep in mind that the distal internal carotid arteries arise from cranial extensions of the dorsal aorta, while the external carotid arteries develop as outpouching ("sprouts") from the common carotid arteries.

At a relatively late stage, by week 7, the fourth and sixth arches undergo asymmetrical remodeling to provide the blood supply of the structures in the thoracic inlet and the upper half of the thorax (both upper extremities, both lungs, and the dorsal aorta) At this time, the right-sided dorsal aorta loses its connection with the fused dorsal aortae and the right sixth aortic arch. However, it remains connected to the right fourth arch. It also acquires a branch that later becomes the right subclavian artery, as the area where the right fourth arch connects to the aortic sac becomes modified to become the brachiocephalic (innominate) trunk. Meanwhile, the left fourth arch remains connected to the fused dorsal aortae (the early descending thoracic aortic segment), which, incorporating a small segment of the aortic sac, becomes the left subclavian artery. As such, the left fourth arch gives rise to the left common carotid arteries and also the proximal portions of both right and left internal carotid arteries. Therefore, the third aortic arch supplying the head via the cranial extension of the dorsal aorta, while the external carotid arteries develop as outpouching (“sprouts”) from the common carotid arteries.

The Fourth Aortic Field (Aortic Root)

At the time of emergence of the truncal swellings, a second pair of tubercles arises at the anterior and posterior walls of the truncus at the same level. Thus, the anteriorly located tubercle is situated in the pulmonary channel after the septation is completed, while the posteriorly located one will be in the aortic channel. Toward the end of week 9, and after septation has been completed, each outflow tract will contain a triangle of tubercles: two from the older lateral wall tubercles and the third from either the anterior or posterior wall. In each channel, this triangle will give rise to the three cusps of the aortic and pulmonary semilunar valves. As such, the aortic valve and very proximal part of the ascending aorta (i.e., the aortic root) develop as a result of the septation of the distal aspect of the conotruncus, which is an essential component of the primitive heart tube [21–26].

Genetic and Molecular Mechanisms

(a) Development of the dorsal aorta is influenced by multiple genes and signaling pathways. Vascular endothelial growth factor A (VEGF-A) is activated by sonic hedgehog (Shh) molecule and, in turn, activates the Notch signaling pathway through its ligand δ-like α, VEGFR, and phospholipase-C1 enzyme (PLCγ-1). Several other genes are involved, such as Rbm 24; SMAD5, which are downstream signal regulators of the TGF-β receptors; Sox-13 gene (Sry-related HMG box); Sox-18 transcription factor; Hox genes; hypoxia-
inducible factor 1α (HIF-1α); zinc finger protein genes; and cyclo-oxygenase-1 (Cox-1)-derived prostaglandins under the Flil promoter.

In addition, other vertebrate-specific chemokines such as the C-X-C motif cxcr1 and its ligand cxcl12b are involved in development of the lateral dorsal aorta and are required for the ventral migration of the endoderm-derived parts. Thus, the anterior part of the each of the paired lateral dorsal aortae migrates ventrally under the influence of Kdrl, cxcr1, and Flil. Since the posterior part of the dorsal aorta lacks Kdrl, it maintains its anatomic position next to the spine. This process of ventral migration of the first (anterior) parts (forerunners of the first aortic arches and the aortic sac) is also influenced by the increased regulators of the G protein signaling via S1P1, S1P2, S1P3, and Fibulin-1 expression at the ventral aspects of the dorsal aorta.

Other genes that are primarily involved in the formation of the primary heart tube include MesP1, β-galactosidase gene (lac-Z), canonical and noncanonical Wnt signaling of the Frizzled (FZD) gene and β-catenin, Nk2.5, GATA4, and Tbx2 and Tbx3 [33–41].

(b) Genetic and molecular control of the pharyngeal arches is rather complex and involves a number of concurrent processes. First is the migration of ectoderm-derived neural crest cells ventrally to the area of the arch arteries. This is regulated by Tbx1...
which regulates Gbx2 and bone-morphogenic protein Bmp4 expression in the pharyngeal ectoderm. Lbx1 homeobox gene and Pax3 are also implicated in the migration of a specific subpopulation of neural crest cells. The specific sequential patterning of the arches is under the influence of multiple factors: Wnt1 gene is involved in the dorso-ventral patterning and is also expressed at the time of neural crest cell migration. Pitx2c, a left-right differentiation gene, is expressed in the left aortic sac and at the junction of the aortic sac and branchial arches. It plays a role in the asymmetric branchial arch development. This effect seems to be also influenced by the difference in blood flow via platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) patterning of the aortic arches, particularly the fourth arch, involves both Fgf8 and Tbx1 genes; however, the effect of Fgf8 is limited to the aortic arch and not the outflow tract (conotruncus). There also seems to be a synergistic effect between Tbx1 and Chd7 genes. Frizzled (FZD2) gene appears in the pharyngeal mesenchyme around E10, then its expression decreases until E18 when it is only seen in the aorta and pulmonary trunk. Hox gene homologues are responsible for providing each segment of the pharyngeal arches with its positional information, thus acquiring its own identity. Prx1 (MHox) and Prx2 (S8) are both nonclustered homeobox genes involved in the architecture of the great vessels and the ductus arteriosus. Hoxa genes are involved especially in the third arch. There is a synergy between Hoxa1 and Hoxb1 in arch patterning and generation of the cranial neural crest, while Hoxa2 and Hoxa3 are involved in the stability of patterning. The eHAND gene and its dHAND transcription factor are involved in regulating the branchial arch mesenchyme.

Other factors include endothelin (Et-1 or Edn-1) and its endothelin-converting enzyme (Ece-1) signaling, which involves G protein-coupled receptors, independent of SM22 and lac-Z. Tumor growth factor β (TGFβ-1) via Emad2 and fibronectin influences the fourth arch. Smad2 expression is not observed in other arch segments, the ascending or descending aorta. TGFβ1 is required for the growth, alignment and septation of the outflow tract. It regulates Fgf8 which is involved in differentiation of the arterial pole. Septation is also dependent on the expression of Madh6 genes, encoding for Smad6 protein, a signaling protein involved with the TGFβ superfamily, as well as the Frizzled 2 (FZD2) gene and the HIRA gene on chromosome 22. Other factors include Bmp2, Nkx2.5, Pitx2, Fibroblast growth factor (Fgf). Fgf15 is expressed transiently in the aortic arches (D9.5 to D10), but its absence causes failure of the aorta to wedge between the tricuspid and mitral valves. It also affects the proximal outflow tract at level of its connection with the 6th arch. Prominent levels of tropoelastin (TE) are seen in the aorta and pulmonary trunk. Thyroid hormone-receptor associated protein-2 (THARP2) gene mutations have been implicated in the genesis of transposition of the great vessels. Defects in the human homologues of dishevelled gene and β-catenin are associated with conotruncal defects [42–57].

(c) Outflow Tract and the Conotruncus: Cardiac neural crest cells migrate from the area of the 4th arch under the influence of their drivers Wnt1-cre and Pax3cre, along with histone deacetylase 3 (Hdac3). Tbx1 is required for the growth, alignment and septation of the outflow tract. It regulates Fgf8 which is involved in differentiation of the arterial pole. Septation is also dependent on the expression of Madh6 genes, encoding for Smad6 protein, a signaling protein involved with the TGFβ superfamily, as well as the Frizzled 2 (FZD2) gene and the HIRA gene on chromosome 22. Other factors include Bmp2, Nkx2.5, Pitx2, Fibroblast growth factor (Fgf). Fgf15 is expressed transiently in the aortic arches (D9.5 to D10), but its absence causes failure of the aorta to wedge between the tricuspid and mitral valves. It also affects the proximal outflow tract at level of its connection with the 6th arch. Prominent levels of tropoelastin (TE) are seen in the aorta and pulmonary trunk. Thyroid hormone-receptor associated protein-2 (THARP2) gene mutations have been implicated in the genesis of transposition of the great vessels. Defects in the human homologues of dishevelled gene and β-catenin are associated with conotruncal defects [42–57].

(d) The aortic root and proximal ascending aorta. Although this area of the aortic tree carries a high clinical significance, there is a comparative paucity...
with regard to identification of the genetic and molecular factors influencing its development and differentiation. So far, the following genes have been implicated in proximal aortic pathology: Notch1 and SirT1 — a longevity gene limiting Notch1 signaling—have both been associated with bicuspid aortic valve. Abnormalities of chromosomes 45, 13, 18, X, and 21 have all been linked to various conditions including Turner syndrome, hypoplastic left heart syndrome, and bicuspid aortic valve. FLNA (flamin) gene and the Ras-mitogen-associated protein kinase signaling pathway (SHP-2, ki-Ras, RAF-1, and SOS-1) have also been implicated in the same condition. Conversely, defects or deletions of the elastin gene on chromosome 7, also in association with Wnt-Frizzled homologue (FZD9), results in supravalvular aortic stenosis [58–83].

Discussion

From a developmental standpoint, the thoracic aorta is not a uniform, homogenous structure. It does not describe one contiguous anatomic entity, nor do all its segments develop at the same time. In chronologic terms, the thoracic aortic tree can be divided into the above-mentioned four “fields” (see above), each developing at a different stage and from a different cell population ancestry. As elaborated above, the oldest part of the thoracic aorta is the descending aorta distal to the isthmus (T-4 level), with the aortic arch following in chronological order. The distal ascending aorta develops next, followed by the aortic root and proximal ascending aorta. Each of these “aortic fields” develops under the influence of a distinct set of genes and signaling molecules and pathways.

In concurrence with the differences between the thoracic and abdominal aortic regions previously described [84], our review further elaborates on the different embryologic origin, genetic influence, and developmental trajectory of areas with the thoracic aorta itself. Despite the recent emphasis [85,86] on genetic and signaling pathways involved in the vascular smooth muscle development and maturation, which are seen as exerting a global influence over the entire vascular tree, a single gene, receptor, or signaling pathway does not seem to have a generalized effect on the development of specific segments of the aortic tree. As an example, TGF-β effect on the smooth muscle cell gene expression differs depending on the location of the smooth muscle cell in the aorta. TGF-β isoforms have different effects on the smooth muscle transcriptional response in a lineage-dependent manner, with the highest response in lineage of endodermal origin (the outflow tract and proximal ascending aorta) versus the lowest response in mesodermal lineage (dorsal aorta). The same applies to other genes including smooth muscle M-α-actin, SM-myosin heavy chain (MYH-11), SM22α and other SMC proteins (lysyl oxidase, fibulin 4, fibulin 5), and tropoelastin. This further highlights the heterogeneity of the genetic and signaling factors behind the development of each segment (field) of the thoracic aorta. These findings also have an increased significance considering the role of such factors in the regulation of the inflammatory response, atherogenesis, and the extracellular matrix, all of which contribute to the structural integrity of the aortic wall.

Conclusions

In developmental terms, the thoracic aorta is a complex, heterogeneous structure. No single gene, transcription factor, or molecule regulates the entire process of aortic development. Each segment of the aorta develops and differentiates under a distinct set of genetic and transcriptional factors. Therefore, it is inappropriate to speak of “thoracic aortic aneurysm” as a monolithic entity, or of any single cause as responsible for all types and locations of aneurysmal disease. In addition, this heterogeneity may suggest that the areas where these different thoracic aortic segments join are under complex and perhaps conflicting genetic, developmental, and regulatory influence. As such, these areas of juncture (the “weld joints”) may be at a higher risk for anomalies in development, differentiation, connection, or functional regulation, thereby rendering them more susceptible to disease processes.

Registry-based research has emerged recently as a platform for robust investigation utilizing fairly large amounts of real-world population data organized in condition-specific databases. Another advantage is the coordinated efforts between different teams of researchers across several disciplines. The GenTAC National Registry [87] has been established by a collaborative effort between the US Department of Health and Human Services and the National Institutes of
Health to help healthcare providers better understand the links between genes and thoracic aortic and cardiovascular disease. This registry is a repository for data concerning the genetics, anatomy, pathophysiology, and natural history of thoracic aortic conditions. As such, it is uniquely positioned to organize and undertake the methodical classification of each individual condition, in terms of its genetic etiology and the transcriptional and signaling pathways and specific anatomic locale along the thoracic aorta affected. The identification of which areas of the thoracic aortic tree are most commonly affected in which genetic and/or translational or signaling defect would thus provide a sound scientific basis for formulating and implementing disease-specific testing, screening, and therapeutic modalities. This is fundamental to the development of evidence-based, specific practice guidelines, which will translate into improved effectiveness, safety, and efficiency of the management of thoracic aortic disease in this challenging group of patients.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.
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Segmental Aortic Development


Aspergillus Pseudoaneurysm Post Aortic Valve Replacement

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Abstract
Thoracic aortic mycotic aneurysms caused by Aspergillus fumigatus postoperatively are rare and devastating complications. These cases are usually attributed to intraoperative contamination of surgical equipment. We present a patient who had an ascending aortic mycotic aneurysm 20 weeks post aortic valve replacement. A high index of suspicion allowed for diagnosis and prompt treatment, although the patient presented in an unusual manner. Treatment included both medical and surgical therapy to minimize morbidity and mortality. Despite treatment our patient suffered long-lasting consequences due to the aggressive nature of the disease. Cases presented in the literature and this experience show that a high index of suspicion must be maintained in such patients regardless of immune status and postoperative interval, in order to avoid long-lasting sequelae.

Key Words
Thoracic aortic aneurysm · Pseudoaneurysm · Aortic valve replacement · Aortic aneurysm · False lumen

Introduction
Although rare, mycotic aneurysms have high rates of morbidity and mortality. The true incidence is not known, but it has been estimated to be between 0.65% and 1.3% of all aortic aneurysms [1]. Furthermore, the incidence of thoracic aortic aneurysm is estimated to be 5.9 cases per 100,000 people/year [2], making thoracic aortic mycotic aneurysms (TAMAs) even rarer. Mycotic aneurysms were first described by Osler secondary to endocarditis, and the term “mycotic” referred to any type of infection and not just fungal etiology [1,2]. Fungal organisms like Aspergillus species responsible for formation of mycotic aneurysms are rare; more common organisms implicated are Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus, and Salmonella. The incidence of mycotic aneurysms caused by fungi is difficult to ascertain, since there are few reports. The Centers for Disease Control and Prevention estimates the incidence of aspergillosis to be 1 to 2 cases per 100,000 people/year [3].

Mycotic aneurysms may present with a constellation of nonspecific symptoms and signs, most commonly fever, night sweats, leukocytosis, elevated inflammatory markers, sepsis, anterior chest discomfort, dysphagia, cough, wheezing, stridor, and pneumonitis [3–7]. A high index of suspicion is required to ascertain the diagnosis and implement treatment promptly. Mycotic aneurysms have high rates of rupture and are generally associated with poor outcomes despite medical and surgical intervention [1,2,4–7]. However, better antimicrobial therapies and imaging modalities are helping to ascertain the diagnosis earlier. Past studies have shown that 80% of mycotic aneurysms are the result of
Microbial aortitis and 3% are estimated to involve infection of a preexisting aneurysm [4].

**Case Presentation**

A 79-year-old woman underwent aortic valve replacement (AVR) with a bovine bioprosthesis in April 2012. Past medical history included hypertension, paroxysmal atrial fibrillation, and no immunocompromised status. In August 2012 she presented with sudden bilateral loss of vision without fever, chills, or any signs of infection. The most recent echocardiogram showed no issues with the prosthetic aortic valve. However, echocardiogram on admission showed a large vegetation occupying 80% of the ascending aortic lumen together with a large pseudoaneurysm and disruption of the suture line of the aorta (Fig. 1). The Mitroflow® bioprosthetic valve (Sorin Group, Arvada, CO) was working appropriately. Chest computed tomography (CT) scan showed a large pseudoaneurysm, possibly mycotic (Fig. 2). Considering the friable appearance of this mass in the aorta, performing an angiogram was not found to be safe.

In the operating room, the patient was heparinized and cannulated through the left femoral artery and left femoral vein, and placed on cardiopulmonary bypass before opening the chest. Distal control was achieved above the aneurysm (where the aorta was normal) after an uneventful redo sternotomy. The pseudoaneurysm was left intact within its pericardial covering. The patient’s temperature was decreased to 28°C. The large mycotic aneurysm was opened, revealing a large fungal ball sitting in the lumen of the aorta. Amphotericin wash was given several times. The Mitroflow® bioprosthetic valve appeared normal. The entire area of the pseudoaneurysm and fungus ball was excised and sent for bacteriology analysis. At this time, a 24 mm homograft was used to replace the ascending aorta. The patient recovered appropriately. Postoperative chest CT was obtained (Fig. 3). The patient exhibited mental status changes on postoperative day 5, which prompted brain MRI. Two cerebellar ab-
scesses and a hemorrhagic stroke were noted (Fig. 4), for which the patient declined treatment. Currently, the patient is doing well, living with her husband, although she did not recover her vision. The patient completed a yearlong antifungal therapy of intravenous amphotericin and oral fluconazole. The last brain MRI showed much improvement (Fig. 5).

Discussion

We present a rare case of TAMA with an unusual presentation. In the literature, most cases of TAMA caused by fungus have presented with some type of systemic symptom (i.e., fever, tachycardia, hypotension, leukocytosis, etc.) [1,4–7]. Our patient presented with only a complaint of progressive bilateral vision loss. At the time of surgery, the aortic valve prosthesis was intact and free of infection. In our case, the suspected site of infection was the suture line above the valve, possibly a pledgeted suture contaminated in the operating room at the time of aortic valve replacement 20 weeks prior. As alluded to in other case reports, the possible origin of the infective agent in our patient is suspected to be airborne spores arising from the operating room ventilation system. The literature reports an average

Figure 3. Chest computed tomogram. Interval resection of pseudoaneurysm with replacement of the ascending aorta. Thoracic aorta is normal in caliber without evidence of dissection or aneurysm.

Figure 4. Brain MRI. Intraparenchymal areas of hemorrhage noted with the largest along the right parietal lobe measuring approximately 2.9 cm in anteroposterior dimension. Intraparenchymal areas of hemorrhage along right insular cortex, right basal ganglia, and left head of the caudate.

Figure 5. Brain MRI. Resolving brain lesion on right parietal lobe.
of 10 months between surgery and diagnosis [5–7]. A high index of suspicion and prompt surgical and medical therapy must be implemented immediately to avoid long-term morbidity and mortality. Traditionally, treatment has included surgical debridement, including graft excision, and aggressive antifungal therapy; however, mortality remains high, attributed to both the highly aggressive nature of the infection and delay in diagnosis. It is important to note that despite intervention, the patient sustained embolic and hemorrhagic strokes preoperatively, and she did not recover her sight; however, she continues to be well otherwise.

In summary, thoracic aortic mycotic aneurysms caused by *Aspergillus* are a rare but serious entity with high rates of morbidity and mortality, which requires prompt recognition and implementation of medical and surgical therapy.

**Conflict of Interest**

The authors have no conflict of interest relevant to this publication.

References


An Aortic Pseudoaneurysm following Bentall Procedure

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Abstract
We describe a rare case of an ascending aortic pseudoaneurysm detected incidentally at coronary angiography in a 64-year-old man with a history of a Bentall procedure 8 years previously. The patient underwent reoperation, with longitudinal opening and cleaning of the aortic pseudoaneurysm and graft repair of the defect. This report highlights the insidious late onset of pseudoaneurysm and the importance of its detection and treatment.

Key Words
Aortic pseudoaneurysm · Bentall procedure

Case Presentation
A 64-year-old male patient was admitted to our hospital with the diagnosis of acute coronary syndrome. Eight years before this presentation, he had undergone coronary bypass surgery with additional Bentall procedure for a dilated aortic root (5.6 cm) and severe aortic regurgitation, using a St. Jude Medical (St. Paul, Minnesota, USA) composite graft. Physical examination revealed blood pressure of 130/70 mm Hg, a regular pulse of 82 beats/minute and a systolic murmur of 2/6 with normal mechanical valve sounds in the aortic area. Transthoracic echocardiography showed a bileaflet prosthetic valve in the aortic position with a peak gradient of 20 mm Hg and mildly reduced left ventricular function with an estimated ejection fraction of 45%. The ascending aorta was 58 mm across the pseudoaneurysm. At coronary angiography all bypass grafts [aorta-right coronary artery (RCA) and aorta-diagonal artery, saphenous vein grafts] except the left internal mammary artery-left anterior descending artery (LAD) were patent. Aortic root angiography showed an aortic pseudoaneurysm originating from the RCA-saphenous graft proximal anastomosis site in the proximal ascending aorta. A contrast-enhanced multidetector computed tomography revealed a 26 × 14 mm pseudoaneurysm in the front of the ascending aortic graft just above the right coronary anastomosis (Figure 1A–1D).

On the basis of these findings, the patient underwent reoperation, with longitudinal opening and repair of the aortic pseudoaneurysm. At operation an anastomosis dehiscence between the aortic graft and native aorta with a 5 cm defect was observed and the defect was repaired with an interposition Dacron graft. An aorta-LAD saphenous graft anastomosis was also performed. The postoperative clinical course was uneventful.

Conflict of Interest
The authors have no conflict of interest relevant to this publication.
Figure 1. A multidetector computed tomography showing a pseudoaneurysm in the front of the ascending aortic graft just above the right coronary anastomosis. A. Axial section. B and C. Sagittal section. D. Three-dimensional volume rendered image of the pseudoaneurysm.
Aortic Root Replacement for Pseudoaneurysm Arising from Freestyle Aortic Bioprosthesis

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Abstract
A 70-year-old female presented with a new systolic murmur and shortness of breath three years after undergoing aortic root replacement using a 27-mm Medtronic Freestyle® stentless full root bioprosthesis (Medtronic, Inc., Fridley, Minnesota, USA). A large complex aortic root pseudoaneurysm was identified on contrasted computed tomography of the chest and transesophageal echocardiogram. We describe the redo aortic root replacement using a customized Dacron tube/valve composite graft with a proximal “skirt” and a modified Cabrol technique.

Case Presentation
A 70-year-old Caucasian female presented with new-onset systolic murmur and shortness of breath three years after undergoing aortic root replacement using a 27-mm Medtronic Freestyle® stentless bioprosthesis (Medtronic, Fridley, Minnesota) for annular dilation and severe aortic regurgitation. Computed tomography (CT) with intravenous contrast revealed a large complex pseudoaneurysm of the aortic root; transesophageal echocardiogram confirmed the findings and demonstrated severe aortic regurgitation (Fig 1). The pseudoaneurysm had two components: one originating anteriorly near the right sinus of Valsalva measuring 3 × 1.5 × 2.5 cm, and the second originating more posteriorly in the noncoronary sinus of Valsalva and into the left sinus near the origin of the left main coronary artery measuring 2.4 × 0.8 × 1.8 cm (Fig. 2). The overall diameter of the aortic root including the pseudoaneurysm was 6.5 cm. The patient underwent reoperative aortic root replacement with complete excision of the Freestyle® stentless bioprosthesis and implantation of a 28-mm Dacron Hemashield tube graft (Meadox Medicals, Inc., Oakland, New Jersey, USA).

Surgical Technique
Cannulation for cardiopulmonary bypass was performed via a right axillary artery anastomosis to an 8-mm Dacron Hemashield tube graft (Meadox Medi-
cals, Inc, Oakland, New Jersey, USA) to which the arterial cannula was connected and a long femoral venous cannula for drainage positioned using transesophageal echo guidance, with the tip at the junction of the superior vena cava and right atrium. The chest was reentered using an oscillating saw and a segment of right saphenous vein was harvested for possible coronary reconstruction.

**Figure 1.** A. Computed tomography of chest (coronal view) with intravenous contrast showing a pseudoaneurysm of the aortic root. B. Transesophageal ultrasound showing the pseudoaneurysm of the aortic root and the perforations marked by the arrow.

**Figure 2.** A. Artist’s rendering showing the two perforations of the porcine homograft. B. Artist’s rendering showing the coronary buttons, and the 12-mm Dacron graft anastomosis to the left coronary button and saphenous vein graft to the right coronary artery. C. Artist’s drawing showing the creation of a stented valve-Dacron conduit by sewing a bioprosthetic valve into the Dacron graft that has been folded over itself. Once the folded Dacron graft is straightened it creates a skirt to anastomose to the aortic root. D. Anastomosis of the composite Dacron valve graft to the aortic root using mattress-pledgeted sutures. E. Intraoperative picture showing the final appearance of the replaced aortic root. The arrowhead marks the left main coronary artery Cabrol anastomosis to the neoaorta. The arrow marks the saphenous vein graft to the right coronary artery proximal anastomosis to the neoaorta.
Following extensive adhesiolysis, the aorta was cross-clamped immediately proximal to the innominate artery. The heart was arrested with antegrade cardioplegia and the arrest was maintained with intermittent retrograde cardioplegia, accompanied by topical cooling. The aorta was transected in the mid ascending portion, allowing us to confirm that the distal aorta was intact. Inspection of the root showed that the valve had been destroyed by presumed previous endocarditis, although there were no signs of active infection and intraoperative Gram’s stain and cultures were negative. Inspection of the Freestyle® stentless bioprosthesis confirmed our preoperative CT scan findings of a large wall defect in the noncoronary sinus and a second defect in the right coronary sinus. The right and noncoronary leaflets of the bioprosthesis were almost completely unhinged and prolapsing into the ventricle leading to aortic regurgitation. The Freestyle® stentless bioprosthesis was removed completely while preserving both coronary buttons (Fig. 2). Dissection of the left main coronary artery could not be performed beyond the ostium because of its dense adhesions to the pulmonary artery, so a modification of the Cabrol technique with an end-to-end anastomosis of the left button to a 12-mm woven Dacron Hemashield tube graft was used (Fig. 2). The right coronary ostium was densely adhered to its surrounding tissues; thus, a saphenous vein graft was anastomosed end-to-side to the right coronary 2 cm distal to the ostium and the ostium was then oversewn with a 4-0 polypropylene suture (Fig. 2).

The end of a 28-mm Dacron Hemashield tube graft (approximately 1.5 cm) was everted/folded over itself in an elephant trunk fashion to create a proximal “skirt.” A 21-mm Magna valve was sewn to the edge of the everted portion of the graft, initially with three simple tacking sutures at 120-degree intervals, then with a running 4-0 polypropylene suture circumferentially (Fig. 2). The graft “skirt” was then rolled down providing 1 cm of Dacron graft proximal to the valve (Fig. 2). A total of 18 2-0 pledgeted, braided polyester sutures were brought outside to inside of the ventricular outflow tract with no gaps between. The annular sutures were then brought through the Dacron skirt below the bioprosthetic valve from inside to outside to attach the graft, and tied to secure the composite valve-graft to the ven-

... How I Do It

Discussion

We describe the repair of an aortic root pseudoaneurysm arising from a Medtronic Freestyle® porcine graft (Medtronic, Fridley, Minnesota, USA) secondary to primary graft perforation in two areas. Our repair consisted of replacing the aortic root and reimplanting the left main and right coronary arteries. Previous reports have described pseudoaneurysm formation after anastomotic dehiscence [1]; others encountered true graft deterioration and perforation [2,3], and even traumatic disruptions have been described [4]. Isolated pseudoaneurysms of coronary buttons can be repaired using the technique previously described by Schmoker and Miller [5], but in the current case, the valve needed to be replaced as well. Noncoronary sinus of Valsalva perforations and pseudoaneurysms have been described [2,3], with one report identifying two defects in the biograft itself [3], as we did. Repair of the perforation has been successfully done in the absence of infection [5] but usually requires an aortic root replacement. We elected to perform a Cabrol-type reimplantation of the coronary arteries given the dense adhesions impeding their dissection and hindering their length. A valve-Dacron
A graft conduit was created with a proximal skirt to facilitate proximal graft anastomosis and allow the aorto-ventricular junction to retain its flexible nature without myocardium contracting against a rigid structure, thus serving as a shock absorber and improving hemostasis. This skirted Dacron graft technique would also allow a future aortic valve replacement to be performed without the need to perform a root replacement by simply cutting the running and the three tacking sutures holding the bioprosthesis in place.

Acknowledgment

We acknowledge the assistance of Vicky Friedman at MedPIC Medical Illustration for the drawings.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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EDITOR’S COMMENTS AND QUESTIONS

Editor’s Comments

This superb case report from Moon and colleagues illustrates several important points about reoperative surgery on the aortic root, including the following:

● The importance of arterial and venous access outside the chest in cases of root pseudoaneurysm.
● The fact that the coronary buttons are often nonmobilizable in reoperative cases.
● The usefulness of the modified Cabrol (Dacron graft) technique for coronary button reattachment in such cases.
● The handy elephant trunk/skirt technique to facilitate the proximal graft anastomosis.

We highly suspect that in our case the structural deterioration to the graft was caused by infection although we could not prove this with blood cultures or cultures of the graft material. Our patient was, nonetheless, managed with an 8-week course of intravenous antibiotics. Other case reports suggest there might be a weakness to the Freestyle graft at the noncoronary sinus of Valsalva. Pseudoaneurysms of the coronary buttons have also been reported.

2. Are you concerned that your 12-mm graft may be too large for a single coronary button? Are you concerned that the peripheral, nonflowing portion of the lumen of the 12-mm graft may develop thrombus in the future?

The left main coronary was large and we wanted to match the button size with a graft that would provide high flows and so the 12-mm graft was chosen. One can argue that a 10-mm graft would have had a similar result. The peripheral, nonflowing portion of the graft was imbricated on itself and sutured in order to eliminate the nonflowing lumen. This is not very clear from our intraoperative picture, but on closer look at the central dark line of the Dacron graft one can make the curvature as the

Editor’s Questions

1. Why do you think your case and those in your references developed these defects in the wall of the Freestyle graft? Do you have any idea what is the underlying pathology?
blind end is folded downwards and to the right of the patient.

3. Do you always route the Cabrol graft to the left of the main graft? Some surgeons bring it around to the right. We would not. In this particular case the location and orientation of the ostia of the left main button pointed to the left of the patient and this particular layout afforded a smooth pathway without kinks in the graft or the anastomoses.
Second Redo for Composite Graft Pseudoaneurysm with Transcutaneous Rupture

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Abstract

Six months after a composite graft redo operation repairing two pseudoaneurysms at the distal suture line and the right coronary artery, respectively, a patient returned asymptomatic and in good general condition but with new presternal bulges. Computed tomography and angiography diagnosed a new pseudoaneurysm of the left coronary artery, and on frank rupture, acute re-repair was undertaken with the aid of resternotomy hypothermic circulatory arrest. Temporary postoperative neurological dysfunction subsided and recovery was otherwise uneventful.

Key Words
Aorta · Aortic pseudoaneurysm · Suture · Resternotomy

Introduction

Late-occurring pseudoaneurysms are preferably detected and evaluated by routine regular radiological follow-up and dealt with in a timely manner. Acute presentation portends a worse outcome and may mandate alternative surgical strategies.

Case Presentation

The patient, a 58-year-old man, was operated twice for aortic coarctation in childhood; he had no signs of significant re-coarctation. In 1981, he underwent composite graft aortic root replacement (Bjork-Shiley 31 mm) for aortic valve endocarditis, and 31 years later, in 2012, he was reoperated, again due to suspected, culture-negative endocarditis. At reoperation, the aortic valve itself was deemed intact, fully functional, and uninfected, but two separate pseudoaneurysms due to anastomotic insufficiency were corrected at the distal anastomosis and at the reimplantation of the right coronary artery, respectively. After a course of antibiotics, the patient recovered well. Six months later, he returned in good general condition, but with two new presternal bulgings, as documented by a resident with his mobile phone camera (Fig. 1). At palpation, they were fluctuant, nontender, and very subtly discolored. Acute computed tomography (CT) scan (Fig. 2) and angiography (Fig. 3) confirmed leakage at the reimplanted left coronary artery. Surgery was scheduled for the next morning, but during the night, one of the bulges ruptured with ensuing hemorrhage, and the patient was taken immediately to the operating room.

With the patient in stable condition, the groin was cannulated and extracorporeal circulation instituted. The patient was cooled to deep (18°C) hypothermia and then resternotomy was performed, with entrance into a partially thrombosed retrosternal pseudoaneurysm. The ascending graft was identified and clamped. Perfusion was restarted and cold blood cardioplegia was administered antegrade, helping to identify the bleeding at the anticipated location, cranially-dorsally in the left coronary artery anastomosis.
Due to the very severely calcified adhesions surrounding the aortic root and graft (Fig. 2), a decision was made to suture the defect using pledgeted 4/0 monofilament suture rather than attempt a complete reanastomosis of the left coronary artery. Bleeding was controlled, the patient was rewarmed and separated from bypass, and the operation was completed. Apart from temporary neurologic deficit, recovery was, again, uneventful and the patient was discharged 12 days later. Radiological follow-up 18 months later showed no evidence of pseudoaneurysm. Clinically he is well restituted, working full-time.

**Figure 1.** Mobile phone photos of the external appearance, showing two distinct bulgings in an otherwise healed sternotomy incision. Note very thin coverage over the caudal swelling, and the absence of generalized wound discoloration.

**Figure 2.** Computed tomography demonstrating contrast extravasation (thick white arrow; circular collection of dye next to linear calcification) close to the graft and surrounding hematoma. Thin white arrows demonstrate subcutaneous hematoma and incomplete sternal healing.
Discussion

Aortic aneurysms and pseudoaneurysms may, rarely, erode the sternum or chest wall and present as “subcutaneous” bulging or swelling usually accompanied by pain [1]. In this particular patient, the sternum was not completely healed after a redo operation a year earlier (Fig. 2), allowing blood to seep painlessly between the sternal edges. Both CT and angiography were diagnostic of the underlying condition. Surgically, our institution’s previously described strategy of preoperative circulatory arrest before resternotomy, without left ventricular decompression [2], proved efficient in avoiding foreseeable bleeding problems and in myocardial protection.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.
EDITOR’S COMMENTS AND QUESTIONS

Editor’s Comments

The gross photograph of this pseudoaneurysm “necessitating” through the skin is dramatic. The authors’ approach with pre-emptive cardiopulmonary bypass and circulatory arrest yielded an excellent clinical result.

Similar to the authors, we also have found that these coronary button pseudoaneurysms can be repaired through the pseudoaneurysm sac, without need to open the aorta itself.

Editor’s Questions

(1) What is the root cause of these recurrent anastomotic aneurysms in this patient? Do you think it is infection? Was there any evidence of graft or suture degeneration? Do you happen to know if biological glue was used at the first operation?

While difficult to completely rule out, the clinical course and condition over a prolonged observation time has not been consistent with persisting composite graft infection. Apart from the extensive calcifications, there were no specific signs of tissue degeneration. However, as evident from the angiography image, the left coronary artery button was quite large. Whether this reflects the immediate result of the index surgical procedure or represents a gradual degeneration—a coronary button aneurysm—we do not know. Biological glue was not abandoned in our practice at the time of the index operation, but it has been used almost exclusively in acute dissections, to reapproximate and reinforce the dissected aortic tissue; it was not used in this patient.
List of Upcoming Meetings

October 2014

1. Eastern Cardiothoracic Surgical Society 2014 Annual Meeting
   October 8–11, 2014
   Palm Beach, Florida, USA
   Meeting information available at: www.ectss.org/2014meeting

2. 28th European Association for Cardiothoracic Surgery Annual Meeting
   October 11–15, 2014
   Milan, Italy
   Meeting information available at: www.eacts.org/annual-meeting/

3. American Association for Thoracic Surgery Clinical Trials Methods Course
   October 23–25, 2014
   Rosemont, Illinois, USA
   Meeting information available at: www.aats.org/ClinicalTrials/

4. Eurovalve 2014
   October 24–25, 2014
   Rome, Italy
   Meeting information available at: www.eurovalvecongress.com

5. American College of Surgeons Clinical Conference
   October 26–30, 2014
   San Francisco, California, USA
   Meeting information available at: www.facs.org

November 2014

1. Southern Thoracic Surgical Association 61st Annual Meeting
   November 5–8, 2014
   Tucson, Arizona, USA
   Meeting information available at: www.stsa.org/61stannual/

2. Australian and New Zealand Society of Cardiac and Thoracic Surgeons 2014 Annual Scientific Meeting
   November 9–12, 2014
   Gold Coast, Queensland, Australia

3. Veith Symposium
   41st Annual Symposium on Vascular and Endovascular Issues
   November 18–22, 2014
   New York, New York, USA
   Meeting information available at: www.veithsymposium.org

4. European Association for Cardiothoracic Surgery Specialist Course: Valve Sparing Aortic Root Replacement and Aortic Valve Repair
   November 28–29, 2014
   Windsor, United Kingdom
   Meeting information available at: www.eacts.org

December 2014

1. 6th International Congress
   Aortic Surgery and Anesthesia “How to do it”
   December 11–13, 2014
   Milan, Italy
   Meeting information available at: www.aorticsurgery.it
4th International Meeting on Aortic Diseases: New Insights into an Old Problem

Natzi Sakalihasan, MD, PhD (course director)

The main goal of The International Meeting on Aortic Diseases (IMAD) is to gather all cardiovascular clinicians and scientists to share their experiences on basic research, genetic aspects of aortic aneurysms, aortic dissections, aortitis, and their treatment as well as on the new pathophysiological concepts in bicuspid aortic valve, TAVI and surgical treatment of aortic valve diseases and also to provide information about the latest innovations in perfusion. Moreover, it is a great pleasure to share reflections with all worldwide scientists and clinicians interested in aortic diseases thanks to AORTA.

Pathogenesis of AAA

Differences in the aneurysm wall could explain gender differences in prevalence rates and rupture risk

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Background: The impact of gender on AAA is illustrated by both the difference in prevalence and the progression between the sexes. The male dominance in AAA prevalence suggests the aortic wall of men to be more prone to dilatation or the one in women to be resistant to it. The impact of gender on aneurysm formation might be related to an effect of sex hormones on the proteolytic activity, as illustrated in animal models. On the other hand, the increased rupture risk in women with AAA, suggests the aneurysm wall of women to be less resistant. It is possibly related to biomechanical properties acquired during the course of the disease or an effect of "being female" on the continuous degradation.

The biomechanical properties of the aneurysm wall can be ascribed to its structural components: elastin, collagen and vascular smooth muscle cells (VSMCs). They are all susceptible to the degradation responsible for aneurysm disease, yet there is little knowledge of how these structural elements are altered in AAA of women and how it relates to the ones in men. A potential difference in these structural components of the aortic wall of men and women could help explain the difference in rupture risk between the sexes and possibly contribute to clarify if men are more susceptible to AAA formation or women more resistant.

Methods: Three different investigations based on biopsies of aneurysm wall from patients treated electively with open repair (n = 28, 32 and 40, respectively) and aortic wall from age- and gender-matched organ donors (n = 6) will be presented. Expression of elastin, elastolytic enzymes, collagen, collagen cross-linking (hydroxyl pyridinoline (HP) and lysyl pyridinoline (LP)) and markers of VSMCs and apoptosis, immunohistochemical, gene expression and western blot were analysed. HPLC were used for quantification of collagen and its crosslinking.

Results: The protein- and mRNA expressions of MMP-9 were greater in women compared with men (6.48 vs. 4.08, P = .037). Women had more LP than men (1.14 vs. .07 vs. P = .005) and a lower HP/LP ratio (3.28 vs. 8.41, P = .003). Women with AAA had a greater proportion of apoptotic cells (.92 vs. .66, P = .005) and greater protein- and mRNA expressions of the apoptotic markers: tumor protein 53 (p53) and Bcl-2-associated X protein (BAX) (4.83 vs. 4.47, P = .045 and 4.55 vs. 4.10, P = .038).

Conclusion: The difference in rupture risk between men and women with AAA might be related to a less resistant aneurysm wall of women, due to more proteolytic enzymes, pronounced apoptosis and impaired collagen cross-linking in women with AAA. Analytical comparisons of aneurysm and aortic walls cannot solely explain the gender difference in aneurysm prevalence rates. The explanation to the different prevalence rates is dependent on further clarification of the pathogenic pathways of AAA, in both men and women.

Novel mediators involved in oxidative stress and proteolysis in AAA

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In the last years, there are evidences linking the presence of intraluminal thrombus (ILT) with the clinical evolution of AAA. The thrombus may participate in different pathological mechanisms, such as oxidative stress and proteolysis [associated to the presence of red blood cells (RBCs) and neutrophils], which could in turn induce an immune inflammatory, fibrotic and angiogenic response in the adventitia (associated to the presence of immune cells, fibroblasts and neovessels). Oxidative stress is defined as the balance of prooxidant and antioxidant proteins. A key mediator of oxidative stress observed in AAA is iron coming from RBC agglutination and lysis in ILT and/or neovessels in adventitia. We have observed that iron retention by phagocytes in AAA tissue could be associated to systemic increase in hepcidin and decrease in iron transport due to low transferrin levels. The subsequent functional iron deficiency leading to low haemoglobin levels is independently associated with AAA presence and clinical outcome. In the other hand, we have observed decreased antioxidant protein expression in RBC membrane of AAA patients (e.g. catalase and peroxiredoxin-2), further
supporting a redox dysbalance in AAA. In addition, activated neutrophils releases different mediators of proteolysis, among them neutrophil elastase, associated lipocalin (NGAL) which could favour aortic remodelling through neutrophil chemokinesis and/or by modulating matrix metalloproteinases (MMPs) stability and expression. In AAA patients, we observed increased NGAL levels in neutrophils and plasma, suggesting that NGAL could participate in AAA pathogenesis. On the whole, our data strongly suggest the involvement of RBC/iron dependent oxidative stress and PMN induced proteolysis as main mechanisms of AAA evolution.

Telomere shortening and oxidative stress in abdominal aortic aneurysm and varicose vein: comparing two dilative vascular pathologies

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Oxidative stress has been suggested as a key contributing factor for vascular diseases, but the exact mechanism underlying the alterations observed is not fully elucidated. The telomere is a simple repeating sequence of TTAGGG bases, located at the ends of chromosomes. Natural telomere shortening can be accelerated by iatrogenic or environmental factors including oxidative stress. Shorter telomere length (TL) is considered a good marker of cell aging and senescence, suggesting a key role in endothelial damage. We compared two vascular dilative pathologies such as Abdominal Aortic Aneurysm (AAA) and Varicose Vein (VV) in order to further evaluate the role of oxidative stress and telomere shorting in endothelial cell damage and vascular disease progression. AAA patients displayed shorter TL associated with increased oxidative stress not only in endothelial cells and vascular smooth muscle cells but also in circulating lymphocytes and keratinocytes suggesting the systemic nature of the disease. At vascular tissue level, VV patients had shortened telomere and high oxidative stress, similarly to AAA patients. Conversely, blood lymphocytes from VV patients had TL similar to healthy controls and significantly longer than the same cells from AAA patients. Moreover, oxidative stress in plasma from VV patients was significantly lower than from AAA group. Linear regression analysis showed a statistically significant inverse correlation between blood lymphocytes TL and plasma level of oxidative stress. Our results suggest that, unlike AAA, telomere attrition in VV tissue is not a systemic phenomenon but it may be attributable to tissue microenvironment conditions and possibly to high local oxidative stress.

Short communications from selected papers

**Role of natural killer cell cytotoxicity pathway in human abdominal aortic aneurysms**

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Objective: The goal of this study was to investigate the role of Natural Killer Cell Mediated Cytotoxicity Pathway in the pathobiology of human abdominal aortic aneurysms (AAAs).

Methods and Results: A genome-wide microarray expression profiling identified 3,274 differentially expressed genes between aneurysmal and control aortic tissue with False Discovery Rate (FDR) of < 0.05. Analysis of biological pathways, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG), indicated extreme overrepresentation of immune related categories. The enriched categories included the GO category Immune Response (GO:0006955; FDR = 2.1 × 10-10), and the KEGG pathways Natural Killer (NK) Cell Mediated Cytotoxicity (hsa04660; FDR = 5.9 × 10-9). In this pathway, 47/86 (55%) of the expressed genes were significantly different between AAA and the controls. We studied the protein expression of 9 different members of the NK Cytotoxicity Pathway in human AAA and compared the results to aortic tissue samples taken from the infrarenal aorta of age and sex-matched controls. Eight (VAV1, VAV3, PLCG2, HSC7, TYROBP, PTK2, TNFA, and GZMB) of the corresponding mRNAs of these proteins had been shown to be significantly elevated and one (PLCG1) significantly decreased in AAA compared to non-aneurysmal aortae. Immunohistochemical analyses agreed with the mRNA results. Double staining was carried out with antibodies against CD68 or CD8 together with DAP10 (HSC7), DAP12 (TYROBP), PTK2B or PLCG2. Many inflammatory cells, mainly in the adventitia and media in the AAA wall stained positive for PLCG2, but only a few of those cells expressed CD8. Double staining was also seen with anti-CD68 and anti-TYROBP as well as with anti-CD68 and anti-PLCG2 indicating that macrophages express TYROBP and PLCG2. PTK2B expression was seen in many cell types, including CD8-positive leukocytes.

Conclusions: These results provide strong evidence that the NK Cytotoxicity Pathway plays a role in human AAA. Based on our microarray and immunohistochemical studies, the pathway is activated in AAA. The data provide valuable insight for future studies to dissect the pathogenesis of human AAA.

**Transglutaminase 2—a potential role in aneurysm progression**

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Abdominal aortic aneurysms (AAAs) are dilatations of the abdominal aorta that are prone to rupture with fatal consequences. Although the pathogenesis of AAA is multifactorial, AAAs are characterised histologically by a reduced elastin/collagen ratio, thinning of the aortic media and elastin breaks. Elastin is cross-linked to accessory proteins, by the action of transglutaminase 2 (TG2) and this may provide a means of protecting elastin fibres from proteolysis. TG2 has been shown to be induced in experimental aneurysm development, has been implicated in arterial repair and may also play a distinct role after injury, and in line with this, we have seen intense immunohistochemical staining for TG2 in samples obtained from elective AAA surgery.

Mice floxed in the TG2 gene were crossed with transgenic mice expressing cre-recombinase in the germline to generate TG2-/- mice on a stable C57Bl/6 background. At 8-weeks of age these mice underwent laparotomy under anaesthesia and either normal saline, 0.25M CaCl2 or 0.5M CaCl2 was applied to the vascular surface of the exposed aorta. Vessel measurements pre-injury were obtained from calibrated captured images using Image Pro Software v7.0 (MediaCybernetics, USA) and were repeated at the time of euthanasia at either 6-weeks or 6-months post-surgery.

There was no difference between male control (C57Bl/6) and TG2--/- mice in pre-injury aortic diameter although the female control aortas were slightly larger (0.55 vs. 0.52 mm, p = 0.003). Neither group showed a significant increase in aortic diameter following saline application. Application of 0.5M CaCl2 resulted in a larger % increase in aortic diameter than 0.25M CaCl2 in both the control (74.4% vs. 36.5%) and the TG2--/- (91.8% vs. 25.0%) mice at 6-weeks. There was, however, no significant difference between the two genotypes at this time-point. At 6 months the mean aortic diameter in the C57Bl/6 group was 67.4% greater than at baseline, i.e. the dilatation was similar (or improved) compared to that at 6-weeks. In contrast, vessel diameter increased by 183.1% in the TG2--/- group indicating further progression. These initial data suggest that aneurysm initiation and progression may be distinct processes and that TG2 may have a role in the latter, possibly through its arterial repair function. Further work is planned to confirm these findings and to investigate the role of the homologous enzyme FXIII-A in aneurysm development.
Modulation of abdominal aortic aneurysm vascular smooth muscle cell function by pharmacological inhibition of the native Orai1 Ca\(^{2+}\) channel

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Introduction: Loss of medial vascular smooth muscle cells (VSMCs) is a key histopathological feature of end stage abdominal aortic aneurysm (AAA) disease. Maintenance of the VSMC population in early stage disease (e.g. at screen detection) is a potential therapeutic avenue to attenuate AAA progression. We have previously demonstrated that store operated calcium entry (SOCE) through the Orai1 Ca\(^{2+}\) channel can manipulate human VSMC function \([1]\). Here we investigate if beneficial functional modulation can be achieved in VSMC from human AAA by blocking the Orai1 channel with our novel, potent and specific small molecule inhibitor, JPIII.

Methods: VSMC were explanted and cultured from patients undergoing open AAA repair with ethical approval as previously described \([2]\). Gene expression was studied by rPCR, calcium imaging using the ratiometric Ca\(^{2+}\) indicator dye, Fura-2AM with SOCE stimulated by thapsigargin (TG) or platelet derived growth factor (PDGF) and functional assays (proliferation, migration, apoptosis) by time lapse fluorescent microscopy with an IncuCyte FLR. The novel SOCE inhibitor JPIII was assessed for specificity (HEK Cells) and potency was assessed in the A7r5 VSMC cell line. JPIII responses were compared to vehicle control (dimethylsulfoxide) in all (HEK Cells) and potency was assessed in the A7r5 VSMC cell line. JPIII was potent and specific small molecule inhibitor, JPIII.

Results: The transcripts for the Orai1 channel and its Ca\(^{2+}\) store sensor, STIM1, were detectable in the human AAA VSMC. JPIII was potent and specific for SOCE in A7r5 cells. SOCE was observed in response to TG and PDGF in the AAA VSMC and could be blocked by JPIII. In the functional experiments JPIII inhibited PDGF driven migration into a linear wound (p < 0.05) and proliferation over 7 days (p < 0.01) compared to the vehicle control. In addition, JPIII protected the AAA VSMC from staurosporine induced apoptosis compared to vehicle control treatment (p < 0.01). Similar results were observed in the murine aortic VSMC expressing the dominant negative Orai1 mutant.

Conclusion: SOCE is present in human AAA VSMC and can be inhibited by the novel drug JPIII with beneficial functional effects on proliferation, migration and apoptosis. Inhibition of the Orai1 channel warrants further study as a potential therapeutic avenue for human AAA disease.

References


Genetics of AAA

Results from the AAA Meta-GWAS consortium

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Genome wide association studies (GWAS) have become a widely used tool for the identification of disease loci. To date, individual GWAS, combined with multi-centre followup validation, have identified six loci (CDKN2BAS1, DAB2IP, LRPs1, IL6R, LDLR, SORT1) associated with abdominal aortic aneurysm (AAA). Combining individual GWAS using metaanalysis dramatically improves the statistical power to detect associations at genome wide significance.

A meta-genome wide association study was performed using six GWAS case-control cohorts from the United Kingdom (n=1846 AAA cases / 5435 controls), Netherlands (n = 813/2790), United States (n = 725/1231), New Zealand (n = 608/612 & n = 397/387) and Iceland (n = 430/22000). Independent validation using additional cases and controls (~5000 of each) is currently being undertaken. The meta-GWAS identified all the previously reported loci as being amongst the most significant associations. The top hit was CDKN2BAS1 (lambda inflation adjusted p-value 5.8 x 10^{-7}). Other previously reported regions had values of: LDLR p = 2.8 x 10^{-12}, IL6R p = 7.4 x 10^{-10}, LRPs1 p = 1.1 x 10^{-9}, SORT1 p = 4.5 x 10^{-9}. DAB2IP p = 4.6 x 10^{-7}. An additional 16 previously unreported AAA loci are currently undergoing independent validation. Of the 22 putatively identified AAA loci 7 are associated with coronary artery disease (CAD) in the CARDIoGRAM meta-analysis.

In conclusion, AAA meta-GWAS analysis appears likely to significantly increase the number of genetic loci associated with AAA. Importantly, several biologically plausible regions have not been previously associated with atherosclerotic arterial disease and may, therefore, represent AAA specific pathobiological mechanisms.

This work is presented on behalf of the AAA Meta-GWAS consortium.

Decision Making from Gene to Intervention for the Marfan Syndrome

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Background: Marfan syndrome (MFS) is an autosomal dominantly inherited connective tissue disease with a phenotype that involves many organ systems and that is caused by mutations in the gene coding for fibrillin-1, FBN1. Aneurysms of the aortic root give rise to the high mortality of MFS. Until today, prophylactic surgery with replacement of the aortic tissue is the single prophylactic measure that prevents patients from suffering acute dissection or rupture of the aorta. In Marfan patients timing of elective surgery hinges upon the aortic diameter, where operations are usually recommended at measurements between 4.5 and 5.0 cm. The problem is that the clinical presentation of Marfan is often indistinguishable from other genetic aortic syndromes (GAS). These GAS comprise syndromes such as the Loeys-Dietz syndrome (LDS) types 1-4, the vascular Ehlers-Danlos syndrome (vEDS), osteogenesis imperfect (OI) or familial thoracic aneurysm/dissections (TAAD).

Methods: We present international guidelines with specific recommendations for elective aortic root replacement according to different GAS and we review the diagnostic criteria of these GAS.

Results: Recommendations for timing of elective surgery depend on the diagnosis of a specific GAS. The firm diagnosis of these GAS requires demonstration of a specific mutation in the FBN1 gene for Marfan syndrome, in the TGFB1R, TGFB2, TGFB2, or SMAD3 gene for LDS, of COL3A1 gene for vEDS, or COL1A1, or COL1A2 genes for OI, and ACTA2, MYH11 or MYLK genes for TAAD.

Conclusion: Decision making for elective surgery in GAS should be based on clinical and molecular diagnosis of GAS.

What’s new in the genetics of thoracic aortic aneurysm?

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Thoracic aortic aneurysm/dissection (TAAD) is an important cause of death in industrialized countries. TAAD often occurs in the young and many patients have a positive family history, which indicates that genetic factors significantly contribute to the etiology of TAAD. Up to now, several genes have been identified for both syndromic and non-syndromic forms of TAAD: FBN1 for Marfan syndrome, TGFBR1, TGFBR2, TGFBR2 and SMAD3 for Loey’s-Dietz syndrome, COL3A1 for vascular Ehlers-Danlos syndrome, EFEMP2 for autosomal recessive cutis laxa type 1, SLC2A10 for arterial tortuosity syndrome, SKI for Shprintzen-Goldberg syndrome, MYH11 for TAA associated with patent ductus arteriosus, ACTA2 for TAAD associated with stroke, premature coronary disease and patent ductus arteriosus, NOTCH1 for calcified bicuspid aortic valve associated with TAAD, FLNA for the combination of periventricular nodular heterotopia and TAAD, and MYLK and PRKG1 for non-syndromic TAAD. So far, the products of the non-syndromic genes (including ACTA2 and MYH11) all function in the contractile apparatus of the vascular smooth muscle cell, while several of the syndromic gene products are part of the TGFβ signalling pathway. The study of the pathophysiological mechanisms involved in the Marfan and Loey’s-Dietz syndromes has further emphasized the central role of TGFβ signalling in TAAD. Given the technological revolution that next generation sequencing has caused, many additional gene identifications are expected. It remains to be seen whether these new genes will also be part of the vascular smooth muscle cell contractile apparatus or the TGFβ signalling pathway, or that additional pathways will be revealed.

### Short communications from selected papers

#### Genetic variants in SEPP1, SELS, TXNRD2, GPX4 and SOD2 are associated with peripheral atherosclerosis and poor left-ventricular function in a comprehensive analysis of polymorphisms in selenoprotein genes in AAA and AOID

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**Objectives and Aim:** Enhanced oxidative stress contribute to cardiovascular diseases. Selenium, as a component of selenoproteins, protects tissues from oxidative damage and thus have beneficial effects to cardiovascular system. In this study the role of common genetic variants in selenoprotein genes: SEPP1, SELS, TXNRD1, TXNRD2, GPX4 and SOD2 gene in the development of abdominal aortic aneurysm (AAA) and aortoiliac occlusive disease (AOID) were evaluated.

**Materials and Methods:** In this case-control study patients with AAA, AOID, and controls were analyzed. Patients were characterized in terms of coronary and non-coronary atherosclerosis and its complications. Genotyping was performed using the TaqMan-based assays.

**Results:** The significantly decreased frequency of the homozygotes of the GPX4 variant allele in AAA, as compared to AOID was found (P < .05). This difference was enhanced by a two-loci interactions between GPX4 and SELS, TXNRD2 or SOD2. The associations of SEPP1 coding sequence variant with decreased left-ventricular ejection fraction in patients (P < .01) and coexistence of peripheral atherosclerosis in AAA (P < .05) were also found.

**Conclusions:** This study identifies variant alleles of the selenoprotein genes and SOD2 gene as potential genetic markers that indicate stronger predisposition to occlusive types of vascular diseases and its complications, than to AAA. The work has been supported by the NSC in Poland under grant No. NN403250440.

#### Familial vascular Ehlers-Danlos syndrome caused by a mutation in COL5A1


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Different forms of Ehlers-Danlos Syndrome (EDS) exist, with specific phenotypes and associated genes. Vascular EDS, caused by heterozygous mutations in the COL5A1 gene, is characterized by a fragile vasculature with a high risk of catastrophic vascular events at young age. Classic EDS, characterized by fragile, hyperextensible skin and joint laxity, is caused by heterozygous mutations in the COL5A1 and COL5A2 genes. To date, vessel rupture in four unrelated classic EDS patients with a confirmed COL5A1 mutation was reported. We describe a familial case of clinically vascular EDS, diagnosed in a mother and her two sons, who all died at an early age from arterial ruptures. Diagnostic Sanger sequencing in the proband failed to detect aberrations in COL5A1, COL1A1, COL1A2, TGFBR1, TGFBR2, SMAD3 and ACTA2. Next, the proband’s DNA was analyzed using a next-generation sequencing approach targeting 554 genes linked to vascular disease (VASCULOME project). This revealed a novel heterozygous mutation in COL5A1, resulting in an essential glycine substitution in the triple helix domain, nearly the C-terminus of the protein (c.4610G>T; p.Gly1537Val). This mutation was also present in DNA isolated from autopsy material of the index’s brother. No material was available from the mother, but the mutation was excluded in her parents, siblings and in the father of her sons, suggesting that the COL5A1 mutation occurred in the mother’s genome de novo. This is the first report of familial clinical diagnosed vascular EDS with a mutation in COL5A1 displaying a similar phenotype to that caused by a COL3A1 mutation.

#### Diagnostic and prognostic biomarker potential of miR-24 in abdominal aortic aneurysm disease and rupture

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MicroRNAs (miRNAs) have been identified as crucial posttranscriptional inhibitors of gene expression in response to stress and injury in cardiovascular disease (CVD) by regulating the expression levels of their target mRNAs. Lately, they have received much attention regarding their suitability as biomarkers for CVD. Aim of this current study was to explore the diagnostic and prognostic value of detecting circulating levels of miRNAs in AAAAs. Using a PCR-based array platform, we profiled the 168 most abundant blood miRNAs in 20 patient plasma samples with AAA disease, undergoing surgical repair of their enlarged aorta vs. 20 samples from an age, risk factor, and medication matched screening cohort without aneurysm. We were able to identify a total number of 12 miRNAs that were significantly altered in diseased patient samples as compared to controls. Next we investigated these 12 miRNAs in plasma (as well as in aortic tissue) from ApoE−/− mice with angiogenesis (AngII)-infusion induced AAAs, in order to determine the potential prognostic value of miRNAs being released into circulation. Indeed we were able to detect that the expression of 4 out of the 12 miRNAs (miR-126 and -668 both increased; miRs-24 and -210 both decreased), was substantially altered in
Circulating microRNA expression signature in PET positive abdominal aortic aneurysms: new potential biomarkers
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Rupture of abdominal aortic aneurysm (AAA) is a cause of significant mortality and morbidity in aging population. Its prediction is a challenging issue in the field of vascular diseases. Recently, we showed that a positive uptake of fluorodeoxyglucose (FDG) in the aneurysmal wall observed by positron emission tomography (PET) was correlated with higher instability of the wall which could lead to its rupture [1]. Identifying circulating biomarkers correlated with a positive PET could help discriminating patients at higher risk of rupture. During last decade, small non-coding RNA, microRNA (miRNA), that are potent post-transcriptional regulators of gene expression, were found to be present in blood and to represent valuable biomarkers for a variety of diseases, notably in cancers.

We evaluated the expression level of 372 miRNAs by using the miScript PCR system (Qiagen) in the plasma of 45 AAA patients among which 24 displayed no FDG uptake (A0) and 21 had a positive PET (A+). In a first approach, 4 pools of plasma samples from the A0 and the A+ groups were analyzed. 45 miRNA were found significantly modulated (p < 0.05) in A+ (26 downregulated and 19 upregulated) as compared to A0. Among them, miR-155 and miR-204 were found to be, respectively, downregulated and upregulated in A+ patients. A similar modulation of these two miRNAs was previously observed in the aortic tissue and blood of AAA patients compared to healthy donors [2,3].

This preliminary study identified a series of miRNAs as potential new biomarkers of PET+ AAA, at high risk of rupture. These results need to be validated on an individual basis and extended to a larger group of patients. However, by crossing data from transcriptomic analyses of aortic tissues from A0 and A+ patients (manuscript in revision) and known target genes of the modulated miRNAs, relevant signaling pathways involved in risky AAA progression will be soon identified.

References
plantation and treatment with protease inhibitor doxycycline leads to accelerated aneurysm growth. These findings suggest a role for additional pathophysiologic mechanisms most importantly impaired tissue repair.

**Methods:** Aortic aneurysm vessel wall tissue was collected from 10 patients undergoing elective, open aneurysm repair. Control tissue from 10 multi-organ donors was obtained from the infrarenal aorta. Tissue samples were handled and processed for immunohistochemical and RNA analysis in accordance with local ethical guidelines.

**Results:** Evaluation of vascular tissue repair pathways show the uniform activation of the Hedgehog, Wnt, Notch, TGFβ, BMP and FGF pathways (p < 0.05) in mesenchymal AAA cells through increases in their downstream transcription factors. Immunohistochemical evaluation of mesenchymal cells responsible for vascular repair revealed a phenotypical shift of VSMC towards a synthetic cell type (p < 0.01), validated by the decreased expression of miR-143 (p < 0.001) and 145 (p < 0.05) as crucial regulators of the contractile VSMC phenotype. Gene expression of collagens I and III are increased 2-fold (p = 0.09) and 44-fold (p < 0.01) respectively combined with increased collagen presence in spectral imaging (p < 0.001) in AAA. Further evaluation shows the increased presence of PPARγ (p < 0.05), consistent with findings in dystrophic disorders.

**Conclusion:** Results from this study characterize AAA as a dystrophic disorder and implicate dystrophy as novel pathophysiological mechanism. These new findings could be responsible for the failure of pharmacologic interventions and simultaneously present new targets for pharmacological treatment of this chronic disorder.

Fibrin clot structure in the angiotensin ii murine model of abdominal aortic aneurysm

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**Background and Aims:** Patients with AAA form denser clots which are resistant to fibrinolysis [1]. In-vivo modelling is commonly used for the assessment of disease states and the identification of potential therapies. The aim of this study was to assess the fibrin clot structure in a murine model of AAA, and in doing so develop assays which can be used to quantify changes in clot structure when novel therapeutics are tested in-vivo.

**Methods:** Male, ApoE−/− mice were infused with either Angiotensin II (AngII) or 0.9% NaCl (control) using subcutaneous mini-osmotic pumps [2]. After 28 days, blood was collected from the IVC onto sodium citrate, and aortas photographed in situ. Fibrin clot structure was studied turbidity, turbidity/lysis, and confocal microscopy. Plasma levels of D-dimer were measured using ELISA. Aortic size and clot density were measured using Image-J. Results are presented as mean ± standard error of the mean.

**Results:** Fifteen mice (7 AngII and 8 controls) were included. The abdominal aorta, thoracic aorta and aortic ratio (abdo/thoracic) were all significantly larger in AngII mice AngII than controls (Abdominal aorta 1.9 ± 0.3 mm vs 0.6 ± 0.1 mm, p < 0.001, thoracic aorta 1.1 ± 0.1 mm vs 0.6 ± 0.1 mm, p = 0.003, ratio 1.7 ± 0.2 vs 1.0 ± 0.1, p = 0.001). Fibrin clots produced using plasma from AngII mice tended to form quicker (11.1 ± 1.0 min vs 13.5 ± 0.8 min), have higher maximum absorbance (0.10 ± 0.03 vs 0.09 ± 0.01), and slower lysis (50.6 ± 8.8 min vs 41.2 ± 5.3 min) compared with controls, although these results failed to reach statistical significance. Fibre density was not significantly different between AngII mice and controls (286.3 ± 130.2 vs 361.3 ± 88.7 fibres per 100 μm2), and D-dimer levels did not vary between the two groups (88.5 ± 133.8ng/ml vs 842.1 ± 62.2ng/ml).

**Conclusion:** Fibrin clot structure is not significantly altered by infusion of AngII and AAA formation in an in-vivo model, suggesting that the abnormal fibrin structure in patients with AAA may be due to more complex, chronic inflammatory-coagulation interactions.

**References**

Epidemiology of AAA

**Five-year outcomes in men screened for AAA population-based cohort study**

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Acquiring contemporary data on prevalence and natural history of abdominal aortic aneurysms (AAA) is essential in the effort to optimize modern screening programs. Since the start of a AAA screening programme, targeting 65-year-old men, in Uppsala, Sweden, in 2006, a pending longitudinal population-based cohort-study was initiated offering all men in the County of Uppsala AAA-screening every 5-years, at the age of 65, 70, 75 and 80 years. This is a first analysis of that initiative.

Out of 2736 men screened at age 65 (2006–2007); 24 had completed AAA repair (6 died within 0–4 years), 239 had died, and 194 had moved, after 5 years (2011–2012). Thus, 2811 70-year-old men were re-invited, and 2247 (79.9%) attended.
The AAA prevalence increased from 1.5% at age 65 to 2.4% at age 70. Of 2041 men with <25 mm at age 65, 0.7% had developed an AAA at age 70. Of 40 men with a sub-aneurysmal aorta (25–29 mm) at age 65, 52.5% progressed to AAA at age 70. In a Cox regression analysis; sub-aneurysmal aorta at age 65 (Hazard Ratio 0.878), and smoking (Hazard Ratio 2.78) were independent risk factors for AAA formation.

Among 44 men with a screening detected AAA at age 65, 22 (50%) completed AAA repair with no 30-day mortality. During the 5-year follow-up period no ruptures occurred among those attending screening at age 65. Among 532 non-attenders at age 65, one had elective repair for an opportunistically detected AAA at age 66 and one had emergency repair for a ruptured 70 mm AAA at age 69 and died during surgery. In conclusion, AAA screening in a contemporary setting is safe at 5 years, with a single AAA-rupture among non-attenders. AAA-formation was common among men with subaneurysmal dilatation, indicating a possible need for surveillance of this group.

10-Year follow-up of the Western Australia randomized trial of AAA screening
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Background: The Western Australian randomised controlled trial of screening for abdominal aortic aneurysm (AAA) began in 1996 and the mid-term results were reported in 2004. The long-term (12 year) results are now available. Although the original trial included men aged 65–83, the latest update focuses on men age 65–74 years.

Methods: Men aged 65–74 years were identified through the electoral roll and randomised to Invitation for screening (n = 13,266) and Control (n = 13,239) groups. Screening using ultrasound was undertaken in 1996–9 and subsequent AAA procedures and mortality were monitored using record linkage of Health Department records from 1996–2010.

Results: The attendance rate was 68% and the prevalence of AAAs ≥ 3 cm was 6.6% and ≥ 5.5 cm was 0.4%. At a median follow-up of 12 years, 48 men in the Invitation for screening group and 52 in the Control group died from AAA — a rate ratio of 0.92 (95%CI 0.61 – 1.38).

Conclusions: Using the Australian electoral roll to identify and invite men vs non-screened men failed to show a difference in mortality rates; apart from a lower 90 day mortality in screened men treated with EVAR (0 vs 3%, p = 0.04).

Summary: Men with AAA, diagnosed within the population based screening program, have a stronger socioeconomic situation and better risk profile than the non-participants. This does probably affect the prevalence rates, since one could suspect that the non-participants have poorer smoking habits and comorbidity profile. Further improvement should be performed of the present invitation to screening programs, in order to minimize low participation rates in the particularly deprived areas. The differences in co-morbidity and socioeconomic situation between screened and non-screened AAAs that are treated with elective repair does however not influence the excellent outcome after treatment for AAA. The low event rate overall after AAA surgery in Sweden can of course contribute to this lack of shown differences in outcome.

Characteristics and outcomes of men screened vs not screened for AAA in Sweden
Rebecka Hultgren
Dep Vasc Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Background: The rationale and cost effectiveness of screening for AAA in elderly men has been thoroughly investigated. Based on these results; screening for AAA in elderly men started in some selected counties in Sweden in 2005, and by 2013 screening was offered to most elderly men nationally. Sweden has a population of 9.7 million inhabitants, and only the smallest county (57000 inhabitants) has chosen not to screen. The benefits of a population based screening program will of course also be related to the participation rate, and the distribution of comorbidity and risk factors in the screened vs non-screened cohort. In the MASS trial; invited non-participants in the screening had a higher mortality rate than the control population. Based on the experience from other screening programs one could suspect that the persons identified by screening with AAA would have a better outcome than non-screened men when treated with vascular surgery for AAA. Some recent results from ongoing and published investigations from screened men in Sweden will be presented.

Results: The participation rates vary in selected groups from 60 %– 85% in Sweden, and have been studied in detail in two counties; on a group- and patient specific level. (Zarrouk, Svensjö, Linne). The participation rate in the population based screening program in Stockholm County for the first 24300 screened men, was highly dependent on the socioeconomic situation of the male population. A low income was strongly correlated to a lower participation rate (OR 2.76, 2.46 – 3.10), and immigrants, with < 5 years in Sweden (OR 3.25, 1.94 – 5.47) and marital status, ie; single; (OR 2.23, 2.08 to 2.39). Similar findings are reported from the Malmö region. The comorbidity profile for participants and non-participants in the screening program was different; the non-participants have a higher occurrence of most investigated diagnoses except tumours: COPD (2.9 vs 1.3%, p < 0.001), diabetes (9.7% vs 8.0, p < 0.001), stroke (4.5% vs 2.8%, p < 0.001). All persons treated in Sweden for AAA, and registered in SWEDVASC 2008–2013 were analyzed regarding morbidity and mortality in a Swedish multicenter study. Since screened men are younger than the average AAA patientgroup, the group was matched for age (350 screened vs 350 non-screened patients). The results from AAA treatment overall in this agegroup is excellent; 1 % mortality at 30 days (2% OR, 0% EVAR), and 4% at 1 year. Comparison between screened and non-screened men failed to show a difference in mortality rates; apart from a lower 90 day mortality in screened men treated with EVAR (0 vs 3%, p = 0.04).

Summary: Men with AAA, diagnosed within the population based screening program, have a stronger socioeconomic situation and better risk profile than the non-participants. This does probably affect the prevalence rates, since one could suspect that the non-participants have poorer smoking habits and comorbidity profile. Further improvement should be performed of the present invitation to screening programs, in order to minimize low participation rates in the particularly deprived areas. The differences in co-morbidity and socioeconomic situation between screened and non-screened AAAs that are treated with elective repair does however not influence the excellent outcome after treatment for AAA. The low event rate overall after AAA surgery in Sweden can of course contribute to this lack of shown differences in outcome.

Some last lessons from MASS
Simon Thompson
University of Cambridge, Cambridge, United Kingdom

The MASS trial has contributed the majority of the worldwide randomised evidence on the value of screening for AAA. 67,770 men aged 65–74 were randomised to invitation to ultrasound screening or to a control group not offered screening. Follow-up continued for an average of 13 years [1].

The trial showed that invitation to screening reduced AAA-related mortality by 42%, and all-cause mortality by 3%. There was an increase in the number of ruptures in the later years of follow-up amongst those with an aorta originally screened as normal; this slightly diminished the AAA mortality benefit seen in earlier years. The majority of these ruptures had an aortic diameter at screening in the range 2.5–2.9 cm. A policy of aneurysm screening for men aged 65 was estimated, based on the MASS trial parameters, to be extremely cost-effective [2,3].

So what extra conclusions can be drawn from these long-term follow-up results? First they show that one-off screening of men yields a substantial and long-lasting reduction in deaths related to AAA. Second, they emphasise that the benefit of a screening programme will be enhanced by achieving a high initial attendance rate and good adherence to clinical followup, preventing delays in undertaking surgery, and maintaining a low operative mortality after elective surgery. Third, they suggest that, while rescreening of all those originally screened as normal is not justified, rescreening (for example after 5 years) of those in the 2.5–2.9 cm range may be. Fourth, even though the prevalence of AAA in men is decreasing, a reevaluation of cost-effectiveness based on up-to-date parameters shows that AAA screening of men aged 65 is still very cost-effective [4]. This raises the obvious question of whether AAA screening in women, perhaps at around age 70, may be similarly cost-effective.
Surveillance of small AAA
Simon Thompson

University of Cambridge, Cambridge, United Kingdom

The international RESCAN project collated individual data for patients under surveillance for small AAA (diameter 3.0–5.4 cm). The aims were to assess the determinants of growth and rupture rates, and to provide evidence on the cost-effectiveness of different surveillance intervals. A total of 18 studies provided data with repeated ultrasound measurements of AAA diameter over time in 15,471 patients [1].

For each 0.5 cm increase in AAA diameter, growth rates increased by about 0.6 mm per year and rupture rates approximately doubled. To limit the risk of rupture between surveillance scans to less than 1%, surveillance intervals of 2 years for aneurysms measuring 3.0–3.9 cm, 1 year for 4.0–4.9 cm, and 6 months for 5.0–5.4 cm, would suffice [2]. These intervals would also limit the risk of reaching the 5.5 cm surgical threshold before the next scan to below 10%, but are longer than those currently used in most countries. If adopted, they would reduce the number of surveillance scans undertaken and their associated costs, but could slightly increase rupture rates. In an evaluation of the surveillance intervals used by the UK national screening programme, we have shown that increasing the surveillance interval for 3.0–4.4 cm aneurysms from 1 to 2 years is likely to be cost-effective, while increasing the interval for 4.4–5.4 cm aneurysms from 3 months is not similarly cost-effective [1].

Growth rates of small AAA are increased in smokers, but decreased in patients with diabetes. Rupture rates in the small AAA range are almost fourfold higher in women than men, are doubled in smokers, and increase with higher blood pressure [3]. While such factors could theoretically be taken into account to tailor surveillance intervals for each individual, the effects are generally not substantial enough to justify the consequent organisational difficulties. An exception is the sex difference in rupture rates of small AAA are increased in smokers, but decreased in patients with diabetes. Rupture rates in the small AAA range are almost fourfold higher in women than men, are doubled in smokers, and increase with higher blood pressure [3].

References

Aortic Aneurysms in the young (below 40 years age)
Tripathi Ramesh K, Verma Himanshu, Vora Simit, Robbie K George
Narayana Institute of Vascular Sciences, Narayana Hospitals Healthcare, Bangalore, India

Purpose: To describe the pattern of Aortic Aneurysms treated in a tertiary care hospital in India and the special significance of aortic aneurysms in patients below 40 yrs.

Methods: A retrospective review of hospital records revealed 154 patients treated for Aortic Aneurysms from January 2011 to June 2014. The mean age was 53 ± 3 with a male: female ratio of 7:3. Forty eight (31.2%) patients below the age of 40 were identified and further studied for presenting symptoms and signs, type of aneurysms, treatments offered and their outcomes.

Results: Of the 48 patients in the age group ≤ 40 yrs, risk factors identified were hypertension, tuberculosis and past history of typhoid. All patients presented with abdominal pain and 13 (27%) patients had rupture. Aetiology included idiopathic non-specific aortitis 29 (60.4%), Tuberculosis 7 (14.5%), Takayasu Disease 6 (12.5%), Salmonellosis 3 (6.2%), Connective tissue disorders 2 (6.25%) and Kawasaki disease 1 (2%). Treatment strategies included 11 EVARs, 7 TEVARs, 26 Hybrid repairs, 1 Covered stent and 14 open repairs. There were 7 peri-operative deaths (14.5%), 2 in Hybrid repair group and 5 in open repair group. Overall actuarial 1-year survival was 77%.

Conclusion: Aortic Aneurysms in the young in India form a clustered group of inflammatory aneurysms and represent challenging anatomy and pathology. Open surgery is hazardous due absence of tissue planes and encasement of vessels by severe inflammatory tissues. Endovascular or hybrid treatments are suitable and have good outcome over a short-term follow-up.

Short communications from selected papers

Do hernias contribute to increased severity of aneurysmal disease among abdominal aortic aneurysm patients?
Mariana Estrelinha1, Florian Corvinus2, Carolin Zimmermann3, Diane T. Smelser4, Helena Kuivaniemi5,6, Irene Hinterseher6
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Introduction: Some published studies have suggested that patients with abdominal aortic aneurysm (AAA) have a high prevalence of abdominal wall hernias. Based on the current knowledge that generalized connective tissue disorders play a role in the pathogenesis of both of these entities, this study tested the hypothesis that hernias in AAA patients contribute to increased d severity of AAA.

Material and Methods: The information about inguinal and incisional hernias from 195 AAA patients was collected through a questionnaire. The patients were divided into 4 groups based on the severity of the aneurysmal disease: 1) survivors of ruptured AAA (n = 22); 2) patients after elective open repair (n = 90); 3) patients after elective endovascular repair

References
The overall prevalence of inguinal hernias was 25% in the entire group and 9%, 24%, 35%, and 23% in the sub-groups 1 through 4, respectively, with no differences between the groups (p = 0.15) based on univariate analysis. The prevalence of inguinal hernias did not differ (p = 0.15) between the two open surgery groups (groups 1 and 2), or when comparing all 3 operative procedures as a combined group to group 4 (p = 0.73). The prevalences of incisional hernias were 18% and 24% for groups 1 and 2, respectively, with no significant difference (p = 0.39).

Conclusion: Despite a reported declining prevalence of AAA in some geographical regions, whether these findings are generalizable for the rest of Europe is unknown. Thus we decided to set up a screening program in order to detect AAA in Liege, Belgium.

Material and Methods: During our ongoing study, over a first 3-month period, abdominal aortic ultrasound was performed on 541 participants, (198 women 343 men) to measure the maximal suprarenal and infrarenal aortic outer-outer diameter as well as the maximal diameter of the common iliac arteries. Moreover, we have measured arm and ankle blood pressure in each subject and the clinical characteristics of the patients, were collected.

Results: The overall AAA prevalence was 4.62% (n = 25). In female participants aged ≥ 74 years the AAA prevalence amounted 1.01 %. While in male patients aged ≥ 65 years, it rose to 6.71%. Statistical analysis showed that male gender, aging, history of ischemic heart diseases, hyperlipidaemia and varicose veins were significantly associated with AAA.

Conclusion: Despite a reported declining prevalence of AAA in some recent population-based studies, we found that the prevalence of AAA in Liege population remains high in men aged 65 years or more. The prevalence of AAA seems to vary in different geographical regions. However, we need a larger sample to confirm our preliminary findings.

Recent advances and future directions of AAA

Medical treatment for AAA: past and future
Jonathan Golledge
James Cook University & The Townsville Hospital, Townsville, Australia

Medical management of patients with small abdominal aortic aneurysms is needed to reduce cardiovascular events, limit aneurysm rupture, reduce requirement for surgical intervention and improve outcome after interventions if needed. Current guidelines suggest that patients with small abdominal aortic aneurysms in which surgery is being considered should receive aspirin, a statin, adequate blood pressure control and a smoking cessation programme where appropriate to minimise the risk of cardiovascular events and improve perioperative outcome. Currently there is no indicated therapy to limit the requirement for surgical intervention in patients with small abdominal aortic aneurysms. Over the last decade there has been a large number of studies examining the pathogenesis of abdominal aortic aneurysms mainly employing animal models. There are also a growing number of randomised trials in patients aimed at identifying therapies able to limit AAA expansion. In this presentation current work being undertaken to identify a therapy to limit AAA expansion will be discussed.

The IMPROVE trial: results of a randomized trial of open vs endovascular repair for ruptured AAA
Janet T. Powell

Charing Cross Hospital, London, United Kingdom

Background: Ruptured abdominal aortic aneurysm is a common vascular emergency and an important cause of sudden death, with about 6000 deaths per annum in the United Kingdom. Repair of the rupture by open surgery has a mortality of 40–50% but mortality from endovascular repair may be much lower.

Objectives: To assess whether a strategy of endovascular repair (if aortic morphology suitable, open repair (if not) versus open repair reduces 30-day and mid-term mortality (and costs) for unselected patients with suspected ruptured abdominal aortic aneurysm.

Design: Randomised controlled trial with telephone randomisation, with computer-generated assignment of patients in a 1:1 ratio, using variable block size and stratified by centre.


Participants: 613 eligible patients (480 men) with a clinical diagnosis of ruptured aneurysm made at the trial centre.

Interventions: 316 patients were randomised to the endovascular strategy (immediate computerised tomography followed by endovascular repair if anatomically suitable and open repair if not) and 297 to open repair (with computerised tomography being optional).

Main outcome measures: The primary outcome was 30-day mortality, with 30-day costs and time and place of discharge as early secondary outcomes as well as the influence of clinical parameters and aortic morphology on 30-day mortality. The outcomes of 1 year and 3 year mortality, costs, quality of life and cost-effectiveness as well as individual patient metaanalysis of 3 European trials will follow.

Results: 30-day mortality was 35.4% in the endovascular strategy group and 37.4% in the open repair group, Odds Ratio 0.92 [95%CI 0.66 to 1.28], p = 0.62 and after adjustment for age, sex and Hardman index Odds Ratio 0.94 [95%CI 0.67 to 1.33]. Women may benefit more than men (interaction test p = 0.02) from the endovascular strategy Odds Ratio 0.44 [95%CI 0.22 to 0.91] versus 1.18 [0.80 to 1.75]. More patients in the endovascular strategy (94%) versus open repair group (77%) were discharged directly home, p < 0.001. Average 30-day costs were similar between the randomised groups, with an incremental cost saving for the endovascular strategy versus open repair of £1,186 [95% CI, -625 to +2997]. The 30-day mortality was inversely proportional to lowest systolic blood pressure and aneurysm neck length and mortality after endovascular repair was 4-fold lower when local (versus general) anaesthesia was used.

Conclusions: The 30-day operative mortality, including those who died before repair, was similar in the two randomised groups. For those who received endovascular repair, it took longer to reach the operating theatre but their mortality was 25% versus 37% for those who received open repair. Since patients receiving endovascular repair are more often dis-
charged directly to home (and sooner), the 12 month outcomes may still show the superiority of an endovascular strategy.

The RAVI-study and the TicAAA-trial
Anders Wanhainen
Dep. of Vascular Surgery, Uppsala University, Uppsala, Sweden

The RAVI-study (Improved Reproducibility of Abdominal Aortic Aneurysm (AAA) measurements using Volumetric Imaging). Current assessment of AAA size and growth is based on ultrasound (US), a measurement technique limited by high variability. This has consequences on clinical decision-making as well as on science, for example sample size calculations for an intervention study to prevent AAA growth. The RAVI-study investigates the reproducibility of AAA measurement by means of volumetric technique by MRI and 2-dimensional ultrasound technique. 30 patients with an AAA of 30–45 mm are examined by means of ultrasound and MRI at baseline, 6 months, 1-year and annually thereafter up till 5 years. An interim analysis (1-year) indicates that the reproducibility of AAA measurements can be improved by MRI compared with ultrasound and volumetric assessment of the AAA rather than just anterior-posterior aortic diameter measurements.

The TicAAA-trial (Does Ticagrelor inhibit growth of small AAA? A randomised controlled trial). A key limitation of contemporary treatment strategies of AAA is the lack of therapy directed at reducing expansion. Platelet activation and intraluminal thrombus renewal are key events in AAA progression, and clinical and experimental data suggests that antiplatelet treatment with aspirin may be associated with reduced growth rates for AAAs. The TicAAA-trial is an ongoing investigator sponsored multi-centre randomized controlled trial investigating whether treatment with Ticagrelor (Brilinta, Brilique) inhibits growth of small AAA. A total of 140 ASA-naïve patients with an AAA of 35–49 mm are randomized to Ticagrelor or placebo (1:1). Ticagrelor is a potent antiplatelet drug that acts by a selectively and reversibly binding to the platelet P2Y12 receptor, blocking the actions of the platelet agonist adenosine diphosphate (ADP). The primary efficacy variable is difference in log-transformed AAA-volume determined by MRI at 12 months vs. log-transformed volume at baseline. The study is powered to detect a 20% reduction in growth rate.

HIV associated aneurysms
Martin Veller
University of the Witwatersrand, Johannesburg, South Africa

The HIV epidemic in Southern Africa has unearthed a number of conditions that are caused by this pathogen. In the vascular field an association with occlusive and aneurysmal arterial disease on the basis of an arteritic process has been described.

Arterial aneurysms associated with HIV have clinical and histological characteristics that differ from the other known cause of aneurysms. The majority of patients presenting with this condition have low CD4 counts with other manifestations of the infection. For this reason we believe this to be an AIDS defining condition.

HIV associated aneurysms have been found in most major arteries and are usually saccular in nature as a result of a localized region of cytoclastic activity in all layers of the arterial wall. Patients tend to present with multiple aneurysms. Treatment of the aneurysm is based on the usual principles of care for aneurysms but because of the poor health of many of these patients, endovascular modalities are favored.

Should patients with CAD be screened for aortic aneurysms?
Rodolphe Durieux1, Hendrik Van Damme1, Nicos Labropoulos2, Alasev Yazici1, Victor Legrand1, Adelin Albert1, Jean-Olivier Defraigne1, Natzi Sakalihasan1

1University Hospital of Liège, Liège, Belgium; 2Stony Brook University Medical Center, Stony Brook, NY, United States

We studied the association between abdominal aortic aneurysm (AAA) and coronary artery disease (CAD) in a large contemporary series of patients undergoing coronary angiography. Over an 18-month period, abdominal aortic ultrasound was performed on 1,000 patients undergoing coronary angiography for suspected or known CAD, or prior to valve surgery.

The overall number of previously repaired, already diagnosed, and new cases of AAA in the study population was 42, yielding a prevalence of 4.2%. Among the patients with newly detected AAs, only two had an...
AAA diameter of $\geq 54$ mm and were therefore treated surgically. In men aged $\geq 65$ years, the prevalence reached 8.6%, while in men with three-vessel CAD it was 14.4%. Multivariate analysis showed that age $\geq 65$ years ($p = 0.003$), male gender ($p = 0.003$), family history of AAA ($p = 0.01$), current smoking ($p = 0.002$), and three-vessel CAD ($p < 0.001$) were significantly associated with a higher prevalence of AAA.

Although the association between AAA and CAD has been described previously, this is the first study that clearly correlates the frequency of AAA with the severity of CAD. Despite the fact that some recent epidemiologic studies suggest a decrease in the prevalence of AAA in the general population, we demonstrate that the disease remains widespread in the population of patients with three-vessel CAD.

The majority of patients with a diagnosis of CAD will continue to have routine follow-up visits with the cardiologist and previous studies have shown the feasibility and accuracy of a rapid evaluation of the abdominal aorta during routine transthoracic echocardiography. While our findings do not prove the cost-effectiveness of screening for AAA in these high risk patients, they do support the usefulness of a quick ultrasound examination of the abdominal aorta during routine transthoracic echocardiography in such patients.

### Optimal preparation using simulation both in elective and ruptured case

**Isabelle Van Herzeele, Liesbeth Desender, Heidi Maertens, Frank Vermassen**

Ghent University Hospital, Ghent, Belgium

Recent advancements in simulation science permit patient-specific rehearsal of endovascular repair of an infrarenal abdominal aortic aneurysm (EVAR).

By incorporating patient-specific imagery into endovascular simulations, real patient cases can be practiced before treatment of the actual patient.

Evidence is emerging that this rehearsal may be valuable to improve case planning by selecting the appropriate patients and correct devices.

Furthermore, rehearsals may influence the treatment plan by identifying the optimal introduction side, by adjusting the position of the contralateral limb to facilitate cannulation or by spotting pitfalls. The contrast use and the radiation dose for the patient, physician and the endovascular team may be decreased by the identification of the optimal C-arm angulation (proximal and distally) in advance to eliminate the parallax.

Patient-specific rehearsals may optimize the preoperative preparation of the endovascular team by providing unlimited practice, using a variety of endovascular devices and techniques leading to a more efficient use of the hybrid angiosuite.

Furthermore, research has suggested that patient-specific rehearsal may also enhance human factor skills such as decision-making, coordination, leadership, communication and confidence during the real procedure. These cognitive and interactive skills complement technical competency are vital in the efficient and safe execution of complex tasks, especially in crisis situations. In ruptured cases, this patient-specific rehearsal may be used preoperatively (in stable cases) and postoperatively for debriefing or to increase the experience of the various endovascular teams with the overall management of ruptured aortic aneurysms.

### Minimizing radiation exposure during endovascular aortic procedures

**Nicos Labropoulos, Matthew Comito**

Stony Brook University Medical Center, Stony Brook, United States

Utilization of endovascular procedures has become exceedingly popular amongst vascular specialists. Endovascular aortic repair (EVAR) represents one of the most complex endovascular procedures today. EVAR exposes patients and staff to significant doses of ionizing radiation. Medical imaging studies now represent the greatest man-made source of radiation to the general population and patients undergoing EVAR are a prime example. Virtually all patients undergoing EVAR have a pre-op CT scan, intraoperative fluoroscopic imaging and lifelong surveillance imaging. Furthermore, knowledge basics about radiation has not been developed and incorporated into training, while appropriate behavior in the interventional suite is very often ignored, leading to unnecessary radiation exposure. Exposure to ionizing radiation has both stochastic and deterministic effects on the human body. Stochastic effects occur without a threshold dose of ionizing radiation. After ionizing radiation causes damage to DNA, the error-prone process of DNA repair is just the catalyst necessary for neoplastic processes to occur. On the contrary, deterministic effects of ionizing radiation are dose-dependent. Before the threshold dose is reached, no damage to the exposed tissue will occur. An example of a deterministic effect of radiation exposure is skin erythema. Variation in technique, screening and surveillance protocol along with the equipment used for patients undergoing EVAR used may affect the dose of radiation exposure to the

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**Table 1. Characteristics of screened patients, globally and according to absence or presence of AAA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 1000)</th>
<th>No AAA (N = 958)</th>
<th>AAA (N = 42)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>64 ± 11.6</td>
<td>63.8 ± 11.6</td>
<td>70.3 ± 8.94</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>490 (49%)</td>
<td>462 (48.2%)</td>
<td>28 (66.7%)</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>Male gender</td>
<td>699 (69.9%)</td>
<td>658 (68.7%)</td>
<td>41 (97.6%)</td>
<td>0.004</td>
<td>0.005</td>
</tr>
<tr>
<td>Family history</td>
<td>79 (7.9%)</td>
<td>73 (7.6%)</td>
<td>6 (14.3%)</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoker ever</td>
<td>703 (70.3%)</td>
<td>666 (69.5%)</td>
<td>37 (88.1%)</td>
<td>0.03</td>
<td>0.005</td>
</tr>
<tr>
<td>Past smoker</td>
<td>434 (43.4%)</td>
<td>414 (43.2%)</td>
<td>20 (47.6%)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>269 (26.9%)</td>
<td>252 (26.3%)</td>
<td>17 (40.5%)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Coronary profile</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>No significant lesion</td>
<td>267 (26.7%)</td>
<td>263 (27.5%)</td>
<td>4 (9.5%)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>1 vessel disease</td>
<td>361 (36.1%)</td>
<td>350 (36.5%)</td>
<td>11 (26.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vessel disease</td>
<td>238 (23.8%)</td>
<td>228 (23.8%)</td>
<td>10 (23.8%)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>134 (13.4%)</td>
<td>117 (12.2%)</td>
<td>17 (40.5%)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Mean number of affected coronary arteries ± SD</td>
<td>1.2 ± 1</td>
<td>1.2 ± 1</td>
<td>2 ± 1</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Aortic diameter (mm), mean ± SD</td>
<td>18.1 ± 6.02</td>
<td>17.3 ± 3.50</td>
<td>41.9 ± 13.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* after exclusion of the 10 patients with previous AAA repair.

Data are presented as mean ± standard deviation (SD), number of patients (N), or percentages.
patient and staff involved. There is a large variation in the dose of
radiation to the patient. This is indicative of variation in technique of
the user. The effective dose in the studies included ranged from 5.8mSv
to 11.968mSv. While sometimes dose was not specified, not all studies specified
which type of EVAR was being evaluated. Thoracic EVAR (TEVAR) resulted in lesser effective dose (mSv) than abdominal aortic repair. Not
all studies commented on the specific type of equipment used. The use of a hybrid angiography suite (mounted interventional imaging system) resulted in less radiation exposure to users and patients than
rooms with portable C-arms. The largest percentage of radiation exposure in patients undergoing EVAR is represented by the pre-op and
post-op surveillance imaging. Follow up CT imaging represents 80%
of total radiation exposure after 1 year which is over 90% at 5 years and
gets higher in a lifetime. To reduce the effective dose of radiation to
the user, the C-arm should have the least amount of obliquity as possible. The AP shot had the least exposure (4.53–4.98mSv/hr) to the
user while the 90 degree lateral had the maximum exposure (69mSv/hr).
The ends of the head to toe axis had the least exposure while the lateral
edges of the angio table had the greatest amount of radiation recorded.
The distance from the tube and the importance of magnification
cannot be overstated. It has been recommended to reduce or
avoid the use of CT for following-up the patients. The use of special
drapes and the development of newer equipment have led in a signif-
cicant reduction in the radiation exposure without reducing the
image quality. Despite of what has been traditionally taught there is no
safe dose of radiation. The level of the radiation repair genes is variant
and currently, there is no test for the repair genes. There is a lack of
awareness and education on radiation safety. With the increasing use
of such procedures the risk is likely to increase and therefore prevent-
ive measures both for the patients and the staff are essential.

Can the FEM be used as a predictor for rupture risk in
clinical practice? Method and validation so far
T. Christian Gasser
Royal Institute of Technology (KTH), Stockholm, Sweden

Based on a large number of interventions, a maximum transverse diameter of, on average, 55 mm appears to be the best indicator for elective
abdominal aortic aneurysm (AAA) repair. In addition to aneurysm size, other rupture risk factors such as asymmetric geometry, gender, family
history, fast aneurysm expansion, a thick intra-luminal thrombus layer etc.,
should also be considered for the decision to perform elective AAA repair.
Specifically, diameter-based (static) and growth-based (dynamic) effects
comprise the wall’s structural integrity and increases risk for rupture.
Modern imaging modalities provide an accurate three-dimensional view of
the aneurysm; information that is not being fully exploited in current
clinical practice [1]. Data recorded from image modalities synergistically
combines with the biomechanical rupture risk assessment, where param-
eters like the Peak Wall Rupture Risk Index (PWRI) are computed. The PWRI reflects the cumulative risk from many known risk factors, and hence, fully
supports a multidimensional individual rupture risk assessment [2].
This presentation outlines the derivation of static and dynamic rupture risk-
relevant parameters from standard Computer Tomography-Angiography
(CTA) images together with general patient data. To this end parameters
that represent the biomechanical risk for rupture are computed with the
A4clinics software (VASCOPS GmbH, Austria). This information is then
compared to the average aneurysm patient, which allows a relative risk
assessment that links the individual data with the clinically-established,
diameter-based intervention criteria. The diagnostic value has been retro-
spectively validated by comparing non-ruptured to ruptured AAAs [2] and
histology [3]. In conclusion, CT-A scanning provides much more informa-
tion than is currently being considered for the decision to perform elective
AAA repair. A biomechanical post processing of CT-A scans at moderate
costs could significantly improve the management of AAA patients.

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Short communications from selected papers

Pro-inflammatory role of stem cells in abdominal aortic
aneurysms
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Bernard-Eckroth1, Gerard Tromp2, David P. Franklin1, James R.
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Objective: The pathogenesis of abdominal aortic aneurysm (AAA) forma-
tion includes inflammation, vascular smooth muscle cell apoptosis, extra-
cellular matrix degradation, and oxidative stress. It is well established that
multi-potent stem cells (SC) have an important role in cardiovascular
health and disease but the role of SCs in AAA formation remains contro-
versial. We sought to describe the presence of SCs in human AAA tissue.
Additionally, we investigated the differentiation of SCs within the aneu-
rysmal aorta.

Methods: Infra-renal aortic wall specimens were collected from patients
(N = 7) undergoing open AAA surgical repair. Non-aneurysmal infra-renal
aortic control samples (N = 5) were collected at autopsies. Using immu-
nohistochemistry, we compared the abundance of STRO1+, cKit+, and
CD34+ cells in aortic tissue. Using double immunofluorescence staining,
we evaluated SC differentiation into smooth muscle cells (SMC; SM22),
fibroblasts (FSP1), and macrophages (CD68). We then investigated the co-
localization of CD68+ cells with the cellular marker of proliferation
Ki67.

Figure 1. Biomechanical rupture risk assessment by relating
the individual patient to the average AAA patient. The Rupture
Risk Equivalent Diameter (RRED) expresses the size of an aneu-
rysm in the average patient population, which is at the same
risk of rupture than the individual case.
The ectopic adventitial adipocytes of abdominal aortic aneurysm
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Background: Abdominal aortic aneurysm (AAA) is a common manifestation of cardiovascular disease among the elderly [1]. The molecular mechanisms that underlie the pathogenesis of AAA remain unknown [2,3]. We utilized comprehensive matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS) of intraoperative dissected human AAA samples to visualize compositional changes in cellular metabolites related to AAA.

Material and Methods: We studied 30 patients who underwent elective open surgery to repair infrarenal AAAs at the Division of Vascular Surgery, Hamamatsu University School of Medicine. The localization of each lipid molecule in the aortic wall was assessed by MALDI-IMS[4-6]. Conventional and immunofluorescence staining were performed for histopathologic examination. The total lipid content in the homogenized aortic tissue was determined.

Results: MALDI-IMS revealed a characteristic distribution of triglyceride (TG) specifically in the aneurismal adventitia of distended aorta (fig.1A,B)[7]. Pathological analysis revealed that characteristic TG distribution was derived from ectopic appearance of adipocytes in adventitia (fig.1C). Accumulated adipocytes were found to locally produce proinflammatory cytokines and matrix metalloproteinases, with subsequent disruption of the local collagen network (fig.2A). Peroxisome proliferator-activated receptor gamma 2 was expressed not only in these adipocytes, but also in fibroblast-like cell marker positive cells (fig.2B)[8,9].

Conclusions: We propose that ectopic adventitial PPARy2 expression in fibroblast-like cells contributes to mechanical weakening of the AAA wall via two pathways. One is transformation from fibroblast-like cells into adipocytes. The other is the decrease of collagen production.

Screening of microRNAs expressed in isolated cells of human abdominal aortic aneurysm for the identification of potential biomarkers
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MicroRNAs are stable biomarkers which have only been studied in experimental abdominal aortic aneurysms (AAA). Macrophages M1 and M2 and vascular cells, essentially smooth muscle cells (SMC) are found in the complex AAA tissue.

In our study, these cells were isolated by laser microdissection from 20 human AAA biopsies obtained during surgical repair and control SMC from 14 healthy aortic biopsies harvested during organ retrieval. RNA from 2 samples of each isolated cells was screened on human miRNAs microarray. Differential expression of selected miRNAs was evaluated by quantitative RT-PCR between healthy SMC and aneurysmal SMC, between M1 and M2 macrophages and common aeurysmal cells and healthy SMC. In order to select miRNAs, a detection value threshold was chosen to be the detection value of miR-29b, described in experimental AAA to be a potential biomarker. Moreover, miRNAs were selected when the detection value on microarray was at least of 2-fold change. Differential expression of miR-21 and miR-29b, two potential biomarkers identified in experimental models of AAA, was also evaluated between aneurysmal and healthy SMC.

Out of the 850 human miRNAs tested for each samples, 92 were found to be present in AAA after normalization of the detection values. Forty-seven miRNAs were common to each tested cells; 54 miRNAs were found in SMC, of which 35 were common to AAA and control aortas and 12 specific to AAA; 85 miRNAs were found in macrophages of AAA, of which 37 were common to M1 and M2 macrophages and 5 specific to M1 macrophages, 28 to M2 macrophages. Ten miRNAs were selected by these means to be evaluated by quantitative RT-PCR. We found miR-199a-3p to be overexpressed in M1 macrophages compared to M2 macrophages. We also found an overexpression of miR-21 and miR-1207-5p in M2 macrophages. miR-29b was found less expressed and let-7f overexpressed in aneurysmal SMC.

In conclusion, we confirm the results of experimental models of AAA in human. The analysis of isolated cells allows to find additional differential expression of miRNAs as potential biomarkers of AAA.
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Introduction: The presence of an AAA has a substantial negative effect on a patient’s life expectancy. Although the focus in AAA treatment is on rupture, cardiac death is the principal cause of excess mortality in these patients. This controversy largely reflects a sharply increased vascular risk in AAA patients. It has been argued that AAA patients are at high risk for cardiovascular disease and should be treated accordingly. We developed a model to test whether and to what extent cardiovascular disease (CVD) risk management can improve survival of AAA patients. In addition we used data from the PHAST trial to explore the current level of risk management in AAA patients.

Methods: A Monte Carlo-Markov decision model is constructed with data derived from an extensive literature review and the patient cohort of the PHAST trial, a randomized, multicentre trial evaluating the effect of doxycycline on AAA progression (NTR 1345). The impact of AAA management, measured in quality adjusted life years (QALYs), on the occurrence of CVD will be investigated for three strategies; optimal cardiovascular risk management, aneurysm repair, and a combination of the first two. Additionally, data of the PHAST trial is used to assess current practice of AAA management in the 286 participating patients.

Results: The Monte Carlo analysis showed that in AAA patients, aneurysm repair alone (open and EVAR for AAA > 5.5 cm) resulted in an improved life expectancy of 0.63 QALYs. Optimal cardiovascular risk management alone for AAA resulted in a gain of 1.00 QALYs. Data from the PHAST trial showed that 70% of patients received statins, 66% was on antihypertensives and 40% used anti-platelets. Yet, the majority of patients was undertreated as 39% had apolipoprotein B levels over 0.9 g/L, and 60% of the patients exhibited blood pressure values over the target value of 140/90 mmHg. Furthermore, 65% of patients was overweight (BMI > 25), 17% was obese (BMI > 30), and 33% of patients was still smoking.

Conclusion: This study shows a high potential gain for strict cardiovascular risk management in patients with AAA disease. An inventory in the PHAST population shows that 30% of the AAA patients is not receiving risk management, and that those receiving risk management are generally undertreated.

Promising first experience of endovascular treatment of ruptured abdominal aortic aneurysms

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Objectives: To describe the implementation and evaluate short-term outcome of the first Danish experience of endovascular repair of ruptured abdominal aortic aneurysm (rAAA).

Design: Historical prospective cohort study including all patients at OUH (DK) treated for rAAA and/or iliac artery aneurysms rupture from 1st of October 2012 until December 2013.

Results: 53 patients were treated due to rAAA or iliac aneurysms at our institution in this period. Of these, 27 (51% 95% confidence interval (CI): 0.38–0.64) patients were treated with EVAR and 26 (49%) by open repair.
Two patients (7%, 95% CI: 0.01–0.22) died within the first 30 days post-operatively in endovascular group. One patient died peri-operatively due to myocardial infarction verified by autopsy. The other one died due to massive coagulopathy and multiorgan failure shortly after the procedure. In the group with open repair, 7 patients (30.7%) died within the 30 days. Consequently, the mortality of all patients treated for rupture at our institution was 19% compared to 32% in Denmark.

**Conclusion:** Endovascular treatment of rAAA is feasible and overall post-operative mortality and morbidity of rAAA can probably be reduced by its implementation.

**References**


**Figure 2.** Occlusive aorta balloon due to hemodynamic unstable condition and angiography.

**Figure 3.** Control angiography after placement of aortouniliakal stent graft and additionally aortic cuff because of endoleak typ 1A with intentional covered right renal artery. No endoleak. Underwent crossover bypass after EVAR.

Two patients (7%, 95% CI: 0.01–0.22) died within the first 30 days post-operatively in endovascular group. One patient died peri-operatively due to myocardial infarction verified by autopsy. The other one died due to...
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The incidence of incisional hernias (IH) after open abdominal aortic aneurysm (AAA) repair is high. Prophylactic mesh augmentation (PMA) during laparotomy closure has been proposed in high-risk patients.

**Methods:** A multicenter prospective randomized controlled study was conducted on patients undergoing elective repair of AAA through midline laparotomy (Clinical.Trials.gov: NCT00757133). In the study group a retro-muscular PMA was performed with a large-pore polypropylene mesh (Ultrapro™, width 7.5 cm). The primary endpoint was the incidence of IH at 24 months.

**Results:** Between February 2009 and January 2013, 120 patients were recruited at 8 Belgian centers. Patients’ characteristics at baseline were similar between the groups. Operative and postoperative characteristics showed no difference in morbidity or mortality. A highly significant difference of IH incidence was found after PMA compared to conventional closure, respectively 0% (CI: 0% – 5.5%) versus 27.6% (CI: 16.7% – 40.9%) (p < 0.0001; Fisher’s exact test). The estimated “freedom of IH” curves (Kaplan-Meier estimate) were significantly different across study arms (X2 = 18.93, p < 0.0001). No adverse effects were observed, apart from an increased mean (SD) time to close the abdominal wall for PMA: 46.2 min (18.6) versus 29.6 min (18.6).

**Conclusion:** Prophylactic retro-muscular mesh augmentation of a midline laparotomy in AAA patients is safe and effectively prevents the development of IH, with an extra time investment of 17 minutes.

**SCIENTIFIC PROGRAM**

**Friday September 12**

**Clinical management and treatment of thoraco-abdominal and abdominal aortic diseases**

**Short and intermediate outcome of EVAR with the use of new generation endografts**

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Effective proximal sealing in EVAR remains the cornerstone of this kind of intervention and failure to achieve it has serious consequences. The refinements in the design of the new generation endografts were mostly aiming to provide active fixation and deployment in difficult anatomic situations eliminating the defects of the past generations in the proximal fixation. We conducted this multicenter study to assess the short (1-month) and intermediate (1-year) outcome with the use of the new generation endografts implemented in endovascular repair (EVAR) over the last years.

Retrospective analysis of prospectively collected data of 400 EVARs from four centers from January 2009 to February 2012 was undertaken. Endografts utilized in the period of the study were the Endurant (Medtronic), Zenith LP (Cook), Excluder and Excluder C3 (Gore), Anaconda (Vascutek) and Ovation (Trivascular). Patients’ demographic data, risk factors, type of operation (elective vs. urgent), type of endograft used (supra- vs. infra-renal fixation, bifurcated vs. uni-iliac) and aneurysm morphological characteristics (proximal neck diameter, length, angle, calcification and thrombus and sac diameter) were analysed in respect to endoleak presence and sac expansion during the first post-operative year. All cases as per protocol were investigated with CT scanning on the 1st month and 1st year. Multivariate and logistic regression analysis was used for associations.

The mean age was 71.3 years (SD 7.9), 381 were males, in 349 cases (87.25%) the intervention was elective, the mean AAA sac diameter was 57.1 mm (SD 12.54), the mean proximal neck length and diameter were 29 mm (SD 12.93) and (24.6 mm, SD 3.1), respectively. Only in 32 cases (8%) the proximal neck angle was <60°. Type 1a endoleak was present in 13 cases (3.25%) in 1-month, but in 1-year only 4 of them were present and 2 more developed. In logistic regression, initial sac diameter >55 mm (p = 0.031) and proximal neck diameter >30 mm (p = 0.032) had significant association with type 1a endoleak. Neck angle >60° and length <15 mm had no significant association. Type 2 endoleak was present in 75 cases (18.75%) in 1-month which all persisted in 1-year with the addition of 6 new accounting for a total of 81 cases (20.25%). No significant association was found for the development of type 2 endoleak. Sac expansion in 1-year was detected in 18 cases and in logistic regression it was associated only with the presence of any type of endoleak (p = 0.019). No rupture occurred during the first year after EVAR.

New generation endografts appear to perform satisfactorily even in difficult anatomic conditions. Risk of type 1a endoleak is low, and it is associated only with the initial sac and proximal neck diameter, while the 1-year sac expansion is associated only with the presence of endoleak.

**Ruptured aortic aneurysm: experience in Thong Nhat hospital**

Que Do Kim

Thongnhat hospital, Ho Chi Minh Ville, Vietnam

Ruptured abdominal aortic aneurysm (AAA) and Thoracoabdominal aortic aneurysm (TAAA) is one of the most fatal surgical emergencies, with an overall mortality rate of 90%. Most AAs rupture into the retroperitoneal cavity, which results in the classical triad of pain, hypotension, and a pulsatile mass. However, this triad is seen in only 25–50% of patients, and many patients with ruptured AAA are misdiagnosed. It is likely that different sites of rupture of AAA determine a variety of common and uncommon clinical presentations, the recognition of which can save many lives. The reduced physiological impact of endovascular aneurysm repair (EVAR) compared with conventional open repair has been demonstrated. The overall anatomic suitability rates for EVAR is about 50% to 80%. The average post-operative mortality rate was 24%, ranging from 9 to 45%.

**Keywords:** abdominal aortic aneurysm; ruptured aneurysm; aortic rupture; rupture; emergency; surgery; endovascular aneurysm repair.

**Short communications from selected papers**

**Outcomes of persistent intraoperative Type 1a endoleak following standard endovascular aneurysm repair (EVAR)**

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**Objective:** The aim of this study was to analyse outcomes for patients with persistent intraoperative type 1a endoleaks following standard EVAR.

**Method:** The study group was identified from a consecutive cohort of 209 patients undergoing EVAR (2011–13). Post-operative imaging and case notes were reviewed. Primary outcome measures: freedom from type 1a endoleak and survival. Secondary outcomes: freedom from sac expansion and secondary interventions.
Results: 33 patients (16%) (Median [Range]; Aneurysm Diameter: 63mm [53 – 98], Neck Length: 21mm [12 – 55], Neck Diameter: 25 [20 – 36]) had persistent type 1a endoleak, despite intraoperative adjunctive manoeuvres in 30 cases. One patient was lost to any follow-up. At first post-operative CT angiogram (Median; 33 days [3 – 61]), 31 patients (94%) demonstrated resolution of the endoleak without secondary intervention. Overall survival = 85% (median follow-up 27 months [9 – 41]). At median follow-up 23 months [2 – 38] 30 patients (91%) had a stable/shrinking aneurysm. One patient had successful secondary intervention 8 days post-EVAR with Onyx embolization. No recurrence of the endoleak was noted in any patient.

Conclusion: Despite adjunctive intra-operative manoeuvres, persistent type 1a endoleaks can be relatively common. This short-term study indicates that they may be observed and will usually seal spontaneously without significant sac expansion or adverse event.

Functionality and biological response of the Multilayer Flow Modulator implanted in the abdominal aorta of adult miniature swine

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Objective: In vivo pre-clinical testing offers the opportunity to evaluate the Multilayer Flow Modulator (Cardiatis, Isnes, Belgium) by means not readily available with in vitro methods. The purpose of this preclinical animal study was to evaluate the performance of the device in an in vivo environment prior to its clinical application. The study was intended to evaluate device functionality (accurate deployment of the device) and vessel biological response to the implanted device.

Methods: Thirteen animals were implanted with the study device in the abdominal aorta, seven animals for thirty days and six animals for six months. Device functionality and immediate thrombosis were assessed during implantation. Upon completion of the study period, each animal underwent a necropsy to examine how the implanted device had affected the artery and surrounding tissue. Neointima and stenosis formation were recorded via morphometry, and endothelialization via histopathological analysis.

Results: At thirty days and at six months, all of the explants were widely patent. Histopathological finding showed the MFM caused little mural damage at thirty days and mild mural damage at six months. In most areas, flattened, endothelium like cells lined the luminal surface of the neointima (Figure 1). Scanning electron microscopy also showed the device was well tolerated, inciting only a minimal neointimal covering and little fibrin or platelet deposition. The histologic appearance of those cells did not change significantly from thirty days to six months. The device was well tolerated with minimal inflammation response, and healing response was good. Neointimal thickness of 239.7 ± 55.6 μm and 318.3 ± 130.4 μm, and percentage area stenosis of 9.6 ± 2.6% and 12.6 ± 5% were recorded at thirty days and six months respectively. No statistical differences were found between these results at thirty days and six months.

Conclusion: This study aimed to evaluate the MFM device for functionality in terms of deployment and biocompatibility of the implanted device. The MFM devices were delivered to their respective implantation sites without difficulty. The MFM also incited little neointimal and stenosis formation in the aorta. The values of stenosis, which were less than 50% are judged to be not significant when compared to circumstances for vascular reintervention of a stented artery.

Management of aortitis and mycotic aneurysms

Mycotic Aneurysms. Is endovascular treatment the way to go? Experience from India
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Purpose: Mycotic aneurysm of the aorta and paravisceral aorta is a life threatening condition. Endovascular options have been explored as repair by either in situ replacement or extrabdominal reconstruction can be quite challenging. We review our experience of surgical and endovascular management of mycotic aortic aneurysms.

Method: From January 2011 to June 2014, a total of 154 patients with aneurysms of the thoracic and abdominal aorta underwent surgery for aortic at our institution. Nineteen (12.3%) of these patients (mean age, 61.4 years; M:F 9:1) were treated for mycotic aneurysms of the descending and thoracoabdominal (n = 9), suprarenal (n = 6), and infrarenal (n = 4) aorta. Eleven (57.9%) patients had sepsis history. There was an increased white cell count, C-reactive protein and procalcitonin levels in 68.4% patients. Clinical presentation included fever in 57.9%, abdominal pain in 84% of the patients. There were 5 (26.3%) contained and 3 (15.7%) free ruptures. Common pathogens from blood cultures were Staphylococcus aureus, Salmonella and acinetobacter species. Careful debridement of all infected tissue was essential. Endovascular stent grafting was used in 3 patients, hybrid repair in 7 patients and open repair with in situ graft in 9 cases. No extra-anatomic procedures (axillofemoral or femorofemoral crossover bypass graft) were carried out. All patients had peri-operative antibiotics that were extended to a minimum of 6 months post-perioperatively.

Results: Total mortality was 7/19 (36.8%). Peri-operative mortality was 5(26.3%). Patients presenting with rupture had high mortality at 50%. There was no demonstrable difference in the outcomes for hybrid versus open repair, perhaps due to small and heterogeneous nature of the two groups. Medium-term follow-up (mean, 12 months; range, 1–40 months), showed a infection free survival of 63.1%.

Conclusions: Mycotic aortic aneurysms remain a life-threatening condition more so if the patient presents with rupture. Endovascular/hybrid surgeries are as effective as open surgery in non-ruptured cases. Lower virulence of offending organisms and long-term antibiotics may be the key to long-term survival.

Takayasus’s aneurysms

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Takayasu’s arteritis is a T-cell driven, non-specific granulomatous inflammation of all layers of the vessel wall. In response to the inflammation, cellular proliferation in the intima and media may lead to occlusion and stenosis of the artery, or weakening of the media and adventitia which can result in dilatation and aneurysm formation. The most frequently affected vessels are the subclavian arteries, carotid arteries and the aorta, including
the origin of its visceral branches. Dilation or aneurysm formation is usually only found in the aorta.

The diagnosis is most frequently made on the basis of the clinical manifestations and an elevated ESR and CRP are during the acute phases of the disease. Imaging is essential to delineate the full extent of the vascular involvement. PET may play a role. Treatment consists of immunosuppression usually using high doses of prednisone in the acute phase. This regime is usually effective in addressing the inflammation in the vascular wall and abating the constitutional symptoms but two thirds of patients with Takayasu’s arteritis experience relapses of symptoms or progression of vascular disease. Methotrexate and some other agents are used without prednisone during phases of remission in order to minimise the corticosteroid side effects. Agents such as infliximab have shown promise but are usually unaffordable in the countries in which this disease predominates.

Surgical and endovascular interventions play an important role in treating occlusive and aneurismal manifestations. The indications for intervention are the same as they are for other pathologies, usually only when life or limb sparing. Fortunately, few interventions are required in the acute phase, as failure rates for procedures performed when acute inflammation is present, are high. Revascularisation in our practice is deferred, if at all possible, until pharmacological therapy has completely suppressed the inflammation, which we believe to be indicated by a normal CRP and ESR.

Endovascular aortic repair in aortobronchial and aortoesophageal fistulas
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Aortobronchial fistula (ABF) and aortoesophageal fistula (AEF) are rare but potentially lifethreatening complications of both treated and untreated aortic disease due to exanguinating hemorrhage. By classification, primary fistulas occur as communications between the untreated aorta and the bronchial tree/esophagus due to aneurysm rupture, penetrating aortic ulcer, advanced esophageal or lung cancer, or ingestion of foreign body. Secondary fistulas originate from reconstructed aorta (prosthetic graft) or develop secondary to complications of a visceral surgical procedure (anastomotic insufficiency). Compared with results of open surgery for thoracic aortic aneurysm (TAA) with a mortality of 14%, open aortic surgery in ABF and AEF is endowed with a significantly increased mortality of 24 and 50%, respectively, clearly reflecting the complexity of those lesions. Therefore, less invasive concepts to reduce perioperative mortality have been evaluated with special attention on thoracic endovascular aortic repair (TEVAR).

 Placement of esophageal stents has emerged as a valuable tool, however, they were not able to seal the lesion completely and therefore cannot exclude risk of mediastinitis. Definitive surgical correction seems vital to obtain a reasonable long-term perspective and possible techniques include esophageal resection with gastric pull-up, esophagoplasty, or the “Thal” fundoplication.

Aortoduodenal Fistulas: An aortenteric fistula is an abnormal communication between the aorta and the bowel lumen. It is usually caused by previous aortic surgery and involves the duodenum (ADF) in most cases. The treatment of this high-mortality condition is based on the correction of enteric and vascular defects. The enteric procedure was described as: duodenorrhaphy, duodenal resection/reconstruction, antibiotic or abdominal. Vascular treatment was described as: extranatomic bypass, in situ graft, direct closure of the aortic defect, endovascular procedures and arterial reconstructions. The most common cause of death was ADF recurrence (41.8%), which was significantly high in the patients who underwent simple duodenorrhaphy. Delayed or avoided enteric repair after endovascular treatment emerged as an option, but needs additional supporting research.

Challenging cases in aortic pathology
Failure of stent-graft at long-term follow-up
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An 83 years old woman, previously operated for colon cancer, was treated for a pararenal aneurysms on march 2013. The procedure consisted in a double chimney for the SMA (advanta 9-58+protectég 9–80) and LRA (viabahn 6-100+protectég 6 –80) and a home made fenestration (Cook TFFB 32–125) for the RRA (advanta 6–22) with good immediate result. The 3 months CT scan confirmed the good result of the procedure and the 6 months duplex scanner too. The 12 months duplex demonstrated a type one endoleak and an increase in sac diameter of more than one centimeter. The subsequent CT scan showed a dilatation of the distal portion of the proximal neck, a distal migration of the stent graft with consequent partial disconnection of the fenestration. The two chimney remain in stable position. The patient was treated by proximal extension of the stent graft (gore C-TAG 34–100) extension of the two chimneys (SMA; advanta 9-59+protectég 9 –80 - LRA: viabahn 6-50+protectég 6 –80) and relining of the fenestration for the RRA (advanta 6-22+zilver 7–30). The one months CT scan control shows the good results of the procedure. The case underline the need for a close follow-up especially in complex procedure like this one because the risk of type one endoleak due to gutters or evolution of the proximal neck is relatively high and exposes the patient to the risk of rupture.

Endovascular techniques first to treat an increasing aneurysm post-EVAR
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Introduction: An increasing aneurysm post-EVAR (endovascular repair of infrarenal abdominal aortic aneurysm) is most often due to a proximal attachment and sealing problem, and represents the most common reason for secondary intervention. Although the incidence of EVAR failure seems to decline, owing to advancements in graft-technology and better understanding of the technique, recent reviews still report crude annual secondary intervention rates ranging from 1.7–4.3% [1]. We present endovascular options to address primary EVAR failure.

Management of Type I endoleak: Type I endoleaks result from an inadequate initial proximal/distal sealing zone, but can also develop due to progression of disease. In the presence of an adequate proximal landing zone, a proximal cuff placement is the obvious solution. In case of a distal type I endoleak a limb extension can easily be applied. A highly angulated proximal neck poses an additional problem for many stent-grafts. The use of endostaples can secure the position of the primary stent-graft to the aortic wall or the proximal cuff [2]. When shorter proximal neck length prohibits the use of a standard cuff, fenestrated stent grafts (F-EVAR) can provide a safe and effective solution. In our experience, F-EVAR represents a less morbid alternative than open repair, with a high technical success rate, and a high target vessel patency and durability in midterm follow-up [3].

Management of Type II endoleak: Type II endoleaks are common if one looks hard enough, with an incidence of 10–25% in published series [4,5]. Their course is benign in the majority of cases, with 75% resolving spontaneously, at least on standard imaging techniques. A conservative approach to type II endoleaks is generally accepted when the aneurismal sac does not increase. Transarterial coil or onyx embolization is the first line treatment modality in case of aneurysm expansion. Recent series confirm the efficacy of the technique, but stress the need for continued surveillance in this patient cohort [6]. Translumbar fluoroscopy-guided
embolization can offer another minimal invasive technique, before moving towards conventional open techniques such as laparotomy with ligature of lumbar/inferior mesenteric arteries, or conversion.

Management of Type III endoleak: Type III endoleaks originate either from fabric tears or an inadequate seal between endograft components. Reported incidence ranges from 0.1% to 6.4%. An endovascular approach with the deployment of an additional stent-graft to bridge the defect or so-called “endlining” is generally well accepted. The procedure is usually straightforward, but can be more cumbersome in case of complete limb separation or severe vessel tortuosity.

Endotension: An increase in aneurysm size after EVAR without evident endoleak poses a diagnostic and therapeutic problem. The incidence of endotension is 1.5–5% [2]. In this setting, a thorough diagnostic algorithm including contrast enhanced ultrasound, CT angiography with delayed contrast phase and possibly a digital subtraction angiography is required, to exclude endoleaks. Treatment is individualised according to the general condition of the patient and the underlying cause for aneurysm expansion. An initial “relining” with strict follow-up is justified in some cases, but open conversion may be the only way to identify the cause and prevent eventual aortic rupture.

Conclusion: Endoleaks and aneurysm increase are considered the Achilles heel of EVAR. Despite decrease of such complications in contemporary practice, secondary interventions remain needed in a considerable percentage of patients. Whenever safely possible, endovascular techniques should be attempted.

References

Aortic root and thoracic aortic aneurysms

Managing the aortic root during pregnancy

Julie De Backer

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In patients with known aortic disease, pregnancy entails a risk for aortic dissection/rupture, which is related to both hemodynamic and hormonal changes. The risk for pregnancy-related complications is determined by several factors, including:
1. the underlying disease,
2. the aortic diameter,
3. previous surgical interventions.

The risk stratification depends on these factors and may vary from low-risk to very high-risk where pregnancy may even be contra-indicated. Management of women with known aortic disease should be initiated prior to pregnancy with adequate counseling regarding the risk of the pregnancy for the mother and fetus as well as the inheritance risk. Prophylactic surgery may be indicated in certain instances and medical treatment to decrease the rate of aortic growth is mandatory in all cases. Careful monitoring of aortic diameter and blood pressure throughout pregnancy is necessary and the mode of delivery is also dictated by the history and actual size of the aorta. In this presentation, underlying diseases, counseling and management throughout pregnancy will be systematically addressed.

Practical ascending aneurysm genetics for the surgeon

John A. Elefteriades

Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA

Genetic studies over the past several decades have helped to better elucidate the inheritance patterns and specific genomics of thoracic aortic diseases. Seminal work from various researchers has identified several genetic factors and mutations that predispose to aortic aneurysms. Syndromic aneurysms have been associated with Marfan disease, Loeys-Dietz syndrome, aneurysm osteoarthrosis syndrome, arterial tortuosity syndrome, cutis laxa syndrome, Ehlers-Danlos syndrome, and TGFβ2 mutations. Mutations in MYH11, TGFβ1, TGFβ2, MYLK, SMAD3, TGFβ2 and ACTA2 genes have been linked to familial non-syndromic cases. This presentation will focus on key genetic and genomic factors that are associated with thoracic aortic diseases. The presentation takes a common sense approach suitable for surgeons and other non-genetics practitioners.

References

Combined coronary artery bypass grafting (CABG) and hybrid repair of arch of aorta aneurysms

Ramesh K Tripathi1, Himanshu Verma1, Praveen Kumar2

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Purpose: To report our initial experience of CABG combined with concomitant endovascular Hybrid repair of Aortic Arch Aneurysms.

Methods: A retrospective review of 23 consecutive patients with Aortic Arch Aneurysm treated by a cardiac and vascular team at a tertiary hospital was carried out. Of these 9 patients (8 Males; 1 Female; median age 59 years, range 48–80 years) had an arch aneurysm > 5.5 cm and > 2 vessel coronary artery disease. In the Hybrid OR, this subgroup underwent CABG (All off-pump) followed by Ascending Aorta to Innominate and Left Common Carotid and Subclavian Bypass and Thoracic Endovascular Aneurysm Repair (TEVAR).

Results: Success rate of all combined procedures under a single general anaesthesia and midline sternotomy was 100% with a mean Fluoroscopy time of 6 minutes (range 2–14 minutes) and a surgical duration time of 399 minutes (range 268–589). Median Intensive Therapy Unit stay was 5 days (range 1–9 days), while hospital stays were 11 days (range 8–19 days).
There were no deaths from the procedure and this benefit was seen till a minimal follow-up of 12 months with no need for TEVAR-related secondary interventions. Complications were trivial and self-limiting.

Conclusion: Combined CABG with Arch Aneurysm Hybrid TEVAR procedures performed by Cardiac and Vascular Surgery teams appears feasible, safe and saves patients a second sternotomy. Combined surgery in hybrid OR avoids staged procedures and improves resource utilization.

Redo surgery after Type A aortic dissection repair

John A. Elefteriades
Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA

In late follow-up after Type A aortic dissection repair, dilatation of the residual dissected aorta can occur, distal to the end of the original repair. This usually involves the aortic arch and the proximal third of the descending aorta. Reoperation under such circumstance is challenging. We present results for this scenario from our center, as well as reviewing important technical principles for surgeons, including the following:

- **Safe Re-entry**
  - Femoral artery exposure before sternotomy
  - “Towel Clip” Bail Out
  - CPB rarely req’d before sternotomy
  - Retrosternal sponge technique

- **Limited Tissue Dissection**
  - Ao (surround)
  - RA

- **“No Touch” for SVGs**

- **Myocardial protection/Systemic Hypothermia/Retrograde**

- **Methods of Brain Protection**

- **Elephant Trunk Options**
  - Four methods to gain control of elephant trunk
  - ”Finger-thumb” technique
  - Arch clamp
  - Adenosine asystole

- **Deep hypothermic arrest.**

Reference


Yale data on appropriate criteria for intervention for the ascending aorta

John A. Elefteriades
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This presentation reviews the current general concepts and understandings of the natural history of thoracic aortic aneurysms and their clinical implications. Our database has now expanded from hundreds to thousands of patients followed, permitting more powerful statistical conclusions. Our studies show that the normal aorta in the general population is very small (3.2 cm for the ascending aorta). Aortas greater than 5 cm are rare in the real world. The aneurysmal aorta grows at a mean of 0.2 cm/year, and larger aneurysms grow faster than smaller ones. Size continues to be a strong predictor of natural complications and a suitable parameter for intervention. The dissection size paradox (which shows some aortic dissections occurring at small aneurysm sizes) is explained by the huge number of patients with small aortas in the general population. As we enter the era of personalized aneurysm care it is likely that specific genetic mutations will facilitate determination the appropriate size criterion for surgical intervention in individual patients.

References


Short communications from selected papers

Lessons learned from using the multilayer fluid modulator outside of indications for use in 38 cases

Niamh Hynes, Mohammed Sultan, Sherif Sultan
Western Vascular institute, Galway, Ireland

The purpose of this study is to scrutinize 38 cases of Thoraco-abdominal aortic aneurysm (TAAA) treated with a Multi-layer Flow Modulator (MFM) outside of the indication for use (IFU) which were identified during collecting data for the independent MFM global registry “MFM GR”. All of the cases were performed on a compassionate basis in continental Europe, for patients in whom co-morbid disease severity precluded more invasive treatment alternatives.

**Patients and Methods:** There were 30 males with mean age 70.8 years and 8 females with mean age 67.8 years. The mean TAAA diameter was 7.1 cm. 10 patients presented with rupture TAAA. 23 patients had previous intervention, 20 of whom had Thoracic Endovascular Aortic Repair (TEVAR) with commercially available thoracic endografts and three had open repair. One patient had a combined procedure in which both commercially available endografts and an MFM were deployed at the same primary setting. 13 patients had chronic Stanford Type B Aortic Dissection with aneurysmal dilatation of more than 6 cm. Six patients had Mycotic aneurysms. Four patients had saccular aneurysms, while the number with TAAA Crawford type I, II, III, IV were 1,7,5,2, respectively.

**Results:** No incidence of death, paraplegia, cerebrovascular accident, renal or visceral compromise was documented during the perioperative hospital stay. During a mean follow-up of 10.03+/−6.96 months, total mortality was 89.5% (34 patients), of which 27 (71.1%) were aneurysm-related. All cause survival, freedom from aneurysm related death and rupture-free survival were 17.5%, 25%, 31.5% respectively at 18 months. There were 8 visceral branch complications, (6 Superior Mesenteric Artery (SMA) and 2 renal arteries). 14 endovascular secondary interventions (37.8%) in 11 patients were required during follow-up. None of the dissecting aneurysms treated achieved complete thrombosis and remodeling of the false lumen during follow-up. All treated aneurysms showed a mean aortic diameter growth of 0.71 cm/+/−0.65 cm (range 0–2.61 cm) with a mean growth rate of 0.12+/−0.16 cm. Factors having a significance influence on risk of aneurysm-related death included maximum aneurysm diameter (p = 0.035, HR = 0.73, 95%CI[0.55–0.96]), Previous TEVAR (p = 0.03, HR = 0.41, 95%CI[0.18–0.91]), the number of MFM devices deployed (p = 0.05,
Background: The present prospective registry is aimed at clarifying the results of elective frozen elephant trunk (FET) surgery using the Evita Open Plus device and were included. Pre- and intraoperative data, as well as early clinical results were prospectively stored in an electronic database. Follow-up was conducted by scheduled outpatient visits and control contrast-enhanced CT scans before hospital discharge, at 3 and 12 postoperative months, and every year thereafter. Although minor changes may exist among the participating centers, surgical strategy included circulatory arrest under moderate hypothermia (24–26°C) and antegrade selective cerebral perfusion.

Results: Average age was 63.6 ± 11.3 years. Indications to surgery were true aneurysm (44%), post-dissection aneurysm (20%), chronic dissection (26%) and pseudoaneurysm (10%). Selective cerebral perfusion time was 75.7 ± 39.7 min. Operative mortality was 8.2% (one due to aortic causes). Most frequent morbidities were renal failure (18%), pulmonary complications (15%) and revision for bleeding (8%). Cerebral stroke occurred in 4.1% of cases and spinal cord injury in 6.8%; nonetheless, the latter were permanent in only 2 cases (2.7%). Actuarial survival at 20 months was 85.9% ± 5.2 (3 late deaths). During follow-up, we observed 2 aortic reoperations, 2 endoleaks, 1 pseudoaneurysm, no cases of endotension, and a 51.9% rate of false lumen thrombosis (dissection cases only). The registry included 4 patients who received concomitant FET and distal endovascular completion for extensive descending aortic aneurysm (Figure 1).

Conclusion: The FET procedure for chronic aortic disease using the Evita Open Plus device is reproducible and characterized by acceptable operative mortality/morbidity and contained rates of neurological complications. Continued follow-up will be required in order to detect the occurrence of late aortic complications.

References

Dilation of the ascending aorta: collagen analysis in tissue obtained from patients with bicuspid aortic valve disease compared with tricuspid aortic valve
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1Martin Luther University, Halle-Wittenberg, Halle, Germany; 2UKSH-Campus Luebeck, Luebeck, Germany

Background: Dilation of the ascending aorta is a common occurrence in the elderly and patients with bicuspid aortic valve (BAV) disease. The aim of the current study was to characterize collagen content in advanced...
Bicuspid aortic valve: molecular tissue factors identified prognostic for future aortopathy
Nimrat Grewal1, Adriana C. Gittenberger-de Groot1, Marco C. DeRuiter1, Robert J.M. Klautz1, Robert E. Poelmann1, Sjoerd Duim1, Johannes H.N. Lindeman1, Salah A. Mohamed2, Hans-Hinrich Sievers4, Ad J.J.C. Bogers3, Marie-José Goumans1

1Leiden University Medical Center, Leiden, The Netherlands; 2University of Lübeck, Lübeck, Germany; 3Erasmus University Medical Center, Rotterdam, The Netherlands

Objective: The clinical course of many patients with a bicuspid aortic valve (BAV) is complicated by ascending aorta dilation. Unfortunately, aortic diameter, which is currently the only selection criterion for surgery, is insufficient for identifying patients that are prone for aortic dilation. Some patients with a non-dilated aorta during concomitant cardiac surgery may still develop aortic dilation in future, while others will never. We investigated structural differences between the aortic wall of BAV and tricuspid aortic valve (TAV) with and without dilation. Furthermore for a possible patient-tailored risk stratification we studied molecular biological markers which might be predictive for aortopathy in BAV.

Methods: Ascending aorta biopsies of BAV (n = 36) and TAV (n = 23) both without and with (> 44 mm) dilation were investigated immunohistochemically for the expression of markers for: differentiating and mature smooth muscle cells (SMCs), myoblast differentiation (lamin A/C), cardiovascular aging (progerin), vascular remodeling (TGF-β, phosphorylated Smad2, MMP9) and cellular dedifferentiation (c-Kit, phosphorylated-c-Kit, HIF1α and eNOS).

Results: All BAVs showed significantly less inflammation (p < 0.001), less expression of mature SMC markers (p < 0.01), lamin A/C (p,0.05) and progerin (p < 0.05) as compared to all TAVs. Based on the signaling pathway characteristic for cellular dedifferentiation, exemplified by the marked expression of c-Kit, phosphorylated-c-Kit and HIF1α, the dilated BAV group was comparable to only a subgroup of the non-dilated BAV (BAb) was significantly distinct. This difference between the dilated BAV and BAb was also noted clinically in commissure position.

Conclusion: All BAVs show a less well differentiated aortic wall as compared to TAV. Using a panel of molecular tissue markers the non-dilated BAV can be divided in a susceptible (BAb) and a non-susceptible (BAa) group for aortic dilation.

Similarity in the dilated BAV and BAb was also noted clinically in commissure position.

Conclusion: All BAVs show a less well differentiated aortic wall as compared to TAV. Using a panel of molecular tissue markers the non-dilated BAV can be divided in a susceptible (BAb) and a non-susceptible (BAa) group for aortic dilation.

**SCIENTIFIC PROGRAM**

**Saturday September 13**

**The treatment of Type B dissection**

Rachel Clough
Guy’s and St Thomas’ NHS Foundation Trust and King’s College London, London, United Kingdom

Aortic dissection is associated with significant morbidity and mortality [1]. Computed tomography is usually used for rapid radiological evaluation, replacing catheter-based angiography as the most commonly used pre- and post-operative imaging modality for the aorta [2]. Functional imaging methods such as magnetic resonance (MR) have evolved considerably in

![Figure 1](https://example.com/image1.png)

**Figure 1.** These are mesh plots of the velocity of blood flow in the true and false lumens at different timepoints in the cardiac cycle. Red demonstrates high velocity and blue low velocity flow.

![Figure 2](https://example.com/image2.png)

**Figure 2.** These are four dimensional phase contrast MR images. Helical flow evolves over time and is shown with the large white arrow. The true and false lumens are indicated by the red and white arrows respectively.
 recent years and are able to provide clinically relevant information regarding the anatomy, and underlying haemodynamics and biomechanics [3-5]. (Figure 1, Figure 2). These features can be used for accurate diagnosis, risk stratification and selection of the appropriate treatment for individual patients [6-8]. Advanced MR image acquisition expertise and equipment is becoming available at a growing number of institutions worldwide and this will greatly enhance existing imaging and treatment strategies for patients with aortic dissection.

References

The new criteria of risk in clinically silent type B dissection
Falko Tillwich
Rostock, Germany

Acute aortic dissection is a multi-faceted disease often associated with fatal outcome. The common denominator of aortic dissection is disruption of the media layer of the aorta with possible complications like sidebranch compromise malperfusion, neurological impairment, pericardial tamponade and cardiogenic shock depending on location and expansion of the dissection. An undelayed diagnostic and therapeutic management are key to successful treatment.

Patients with acute aortic dissection often present with a variety of symptoms. Prognosis is clearly related to undelayed and appropriate individualized treatment depending on the absence or presence of complications in addition to a variety of early signs of impending complications.

Genetics and pathology of bicuspid aortic valves

Comparative biology of progressive dilatation (aneurysm) versus acute intraparietal rupture (dissection) of the human ascending aorta
Jean-Baptiste Michel
Inserm Unit 1148, Paris, France

Whatever their etiologies, monogenic disease, associated to bicuspid aortic valves, or degenerative, all TAAs and dissections share common pathophysiological pathways involving proteolysis of insoluble extracellular matrix [1], allowing dilation and finally rupture [2]. The arterial wall of conductance arteries is structured as a spatial multi-layered tissue: endothelium, media and adventitia from inside to outside, in which all the interstitial signalling are unidirectional from inside to outside (convection) as a teleonomic consequence of specie’s evolution [3]. Analysis of interactions between outwardly convected plasma proteins within the arterial wall components has never been studied in TAA. Since plasminogen-derived plasmin is a serine protease able to injury adhesive glycoproteins of the extracellular matrix, to release TGF-beta of its storage sites and to activate MMP’s proforms, we have recently focused on the ability of plasminogen:
- to produce active plasmin during outward convection through TAA walls [4],
- by interaction with vascular Smooth Muscle Cell (vSMC) [5],
- to degrade fibronectin and fibrillin [6],
- to provoke pericellular proteolysis and vSMC anoikis [7],
- to release TGF-beta [8],
- to be inhibited by Protease Nexin-1(PN-1) expressed by vSMC [9] – a Smad2-dependent tissue serpin expression [10],
- to be cleared as a Plasmin/PN-1 complex by vSMC in human TAA.

Therefore plasmin activation could be an interesting target for functional diagnostic and therapeutic option in TAAs and dissections.

References

Novel flow-mediated gene expression signature in patients with bicuspid aortic valve
Per Eriksson
Atherosclerosis Research Unit, Center for Molecular Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Bicuspid aortic valve (BAV) is the far most common congenital disorder of the aortic valve and is believed to result from abnormal cusp formation during valvulogenesis. It has been estimated that BAV is present in 1–2% of the population. The presence of BAV predisposes for progressive dilatation of the ascending aorta and thereby constitutes an increased risk of aortic aneurysm that can eventually lead to fatal rupture or dissection of the aorta. The prevalence of aortic dilatation (thoracic aortic aneurysm,
BAV is a common disorder (1–2% population) with a high risk of aortic valve deterioration and ascending aorta dilatation. TTE is usually the primary imaging technique for diagnosing BAV and it is usually adequate to assess the aortic root and proximal ascending aorta. Visualization of the mild-distal ascending aorta, the most frequent dilated segment in BAV, may be difficult in adults, and MRI or CT is an option.

Yearly TTE surveillance is recommended in patients with a diameter >40 mm and a baseline MRI or CT scan can be indicated. If there are no significant disparities between measurements, TTE will be use to follow-up valvular dysfunction and ascending aorta dilatation until the diameter reaches 45 mm. In cases with significant disparities (>3 mm) due to difficulties in the visualization of the tubular part of the ascending aorta or asymmetry in the aortic root, annual MRI or CT is mandatory. Surgery is recommended when the aorta reaches a diameter of 55 mm, or 50 mm when there are risk factors. A growth rate of the aorta diameter >3 mm/y, correctly measured, in end-diastole, side by side, using the same imaging technique, should also be considered an indication for surgical treatment.

In cases with non-standard body-size, indexation of diameters by BSA is recommended. An index value >30 mm/m² can be accepted as a recommended cut-off value for surgical indication. Valvular dysfunction should be followed-up just as other valvular diseases are.

After surgery, depending on the type: supracoronary replacement with/without aortic valve surgery, Bentall’s procedure or only valvular repair, imaging control by TTE/TOE should be performed before discharge and a TTE annually from then on. In cases with an ascending aorta diameter >45 mm MRI or CT should be performed every 2-3 years. When the aorta diameter is over 50 mm these imaging test are indicated annually. The maximum diameter to indicate a reintervention is not well established (55 mm-60 mm) and should be decided considering the age, risk factors and comorbidities.

An aortic index 35 mm/m² or a annual growth rate >5 mm are also taken into account for surgical reintervention indication.

References

Aortic dimensions in patients with bicuspid and tricuspid aortic valves
Anders Franco-Cereceda
Karolinska University Hospital, Stockholm, Sweden

The prevalence of bicuspid aortic valve (BAV) is 1–2% making it the most common cardiac malformation. BAV is associated with valve disease (stenosis or regurgitation) and aortic disease (dilatation/aneurysm or dissection). It has been estimated that more than 50% of BAV individuals will develop indications for surgery.

In surgical cohorts approximately 50% of patients subjected to isolated aortic valve surgery have a BAV while in combined aortic valve disease and ascending aortic dilatation, more than 75% of the patients have a BAV. Annular ectasia/root dilatation is similarly common in BAV and tricuspid aortic valve (TAV) while mid-ascending aortic dilatation is predominantly found in BAV. Aortic valve stenosis combined with aortic dilatation is almost exclusively associated with BAV while patients with aortic valve regurgitation and aortic dilatation usually have a TAV. Thus, the terminology “post-stenotic dilatation” may be misleading giving the extreme scarcity in TAV stenosis. Increased severity of valve stenosis in BAV and valve regurgitation in BAV and TAV is associated with smaller degree of aortic dilatation. Interestingly, ascending aortic dilatation and coronary artery disease is very rare regardless of valve phenotype. In patients undergoing ascending aortic surgery, the dimensions of the remaining aorta are consistently smaller in BAV than TAV patients.

Based on these findings, knowledge of clinical presentation may guide in surgical strategies and decision making, and allow for adequate and correct follow-up of patients with BAV- and TAV-associated valve and aortic disease.

Controversies in clinical management of bicuspid aortic valve disease

Pre-operative and post-operative follow-up of BAV and its complications
Arturo Evangelista
Hospital Vall D. Hebron, Barcelona, Spain

...
Imaging flow alterations in BAV aortopathy

Malenka Bissell
University of Oxford, Oxford, United Kingdom

Recent advanced in cardiovascular magnetic resonance imaging have allowed identification of new potential imaging biomarkers in bicuspid aortic valve disease.

It is now becoming apparent that helical flow pattern in the ascending aorta at least contribute in part to the ascending aortic dilatation and may be used for risk stratification in the future. These flow alterations can be imaged directly by visualising the blood flow in 3 dimensions (4Dflow) and many promising parameters can be calculated from these including rotational flow, wall shear stress and flow angle.

Aortic dissection in BAV patients: the IRAD experience and beyond

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Characteristics of Acute Aortic Dissection in Patients with Bicuspid Aortic Valve: Insights from the IRAD Registry.

Background: Bicuspid aortic valve (BAV) is a congenital condition that predisposes patients to ascending aortic aneurysm and dissection. We aimed to characterize patients with acute aortic dissection (AAD) and BAV to improve our understanding of this disease.

Methods and results: We examined 3393 AAD patients enrolled in the International Registry of Acute Aortic Dissection. Among 113 patients with BAV (3.3%), 93 (82.3%) presented with type A AAD while 20 (17.7%) had type B AAD. Compared to tricuspid aortic valve (TAV) patients, those with BAV were younger (mean age: 53.6 ± 16.3 vs. 63.5 ± 13.5 years; p < 0.001). BAV patients demonstrated more known aortic aneurysms (25.5% vs. 13.1%; p < 0.001) and prior aortic valve replacement (14.7% vs. 3.1%; p < 0.001). Compared to the TAV population, AAD in BAV patients more frequently involved the aortic root (46.2% vs. 34.7%; p = 0.016) and/or arch vessels (41.6% vs. 28.6%; p = 0.014). Furthermore, these patients demonstrated less extension to the abdominal aorta (28.6% vs. 44.6%, p = 0.002). In addition, BAV subjects were more likely to present with larger aortas (Sinuses of Valsalva: 5.0 ± 3.9 cm, p < 0.001; ascending: 5.3 ± 4.5 cm, p < 0.001), and aortic valve insufficiency (52.1% vs. 39.3%; p = 0.013). Consequently, BAV patients more frequently underwent aortic valve (56.8% vs. 21.7%; p < 0.001) and/or root (66.7% vs. 28.4%; p < 0.001) replacement. Despite their younger age, BAV patients did not show superior hospital survival rates (80.5% vs. 86.7%; p = 0.096).

Conclusions: AAD BAV patients present with distinct morphological and clinical characteristics. These findings may expand our understanding of this aortic malformation and improve management.

References
Controversies in Surgery for BAV Aortopathy

Alessandro Della Corte
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The clinical and basic research on bicuspid aortic valve (BAV) and associated aortopathy is an exponentially expanding field. Nevertheless, the current knowledge of BAV, particularly its causes, pathogenetic mechanisms, and pre-clinical history, is probably more limited than generally believed. These persistent gaps of knowledge have affected the surgical treatment of BAV aortopathy with both a lack of guiding criteria for treatment individualization and important divergences in practice among the different surgeons and centers. BAV aortopathy today is over-treated in a proportion of patients undergoing valve surgery with a mildly or moderately dilated aorta, by the addition of aortic resection procedures that are generally at low-risk but may not be really needed. Another proportion of BAV patients may be exposed to a significant risk of acute aortic complications that can go overlooked, in the absence of an overt aortic dilatation at the time of aortic valve surgery.

The official recommendations for surgical indication in BAV aortopathy have remarkably changed over the last few years. Akin to the indications for aortic surgery, the criteria for the extent of resection are also currently subject to wide variations according to the individual surgeon or center’s policies. However, no other stratification criteria than the aortic diameter are today considered in the surgical decision making process. Does the aortic diameter need to be integrated into a more complex system of stratification including other risk markers, so that its relative weight in guiding the indications can vary case by case according to other prognostic factors? The accumulating body of literature, trying to suggest which the other risk markers could be, will be appraised in this lecture: beside the already available phenotypic markers, also markers of altered aortic function and/or abnormal aortic flow and even possibly circulating biomarkers are currently being focused on in research.

Future research on BAV will need to be of multidisciplinary and translational nature, research objectives should be pursued taking into adequate account the heterogeneity and complexity of the disease and within multi-specialty, multi-center registries, so that, ultimately, the surgical approach to BAV aortopathy will hopefully be based on the concepts of phenotypic and genotypic stratification and treatment individualization.
therapy after implantation of the On-X mechanical valve prosthesis rather than the currently recommended societal guidelines.

Methods: In the PROACT trial, patients requiring aortic (AVR) or mitral valve replacement (MVR) were randomized to receive either lowest dose warfarin (AVR HR) test INR 1.5–2.0 and MVR test INR 2.0–2.5 or to continue standard dose warfarin therapy (control INR 2.0–3.0 AVR and 2.5–3.5 MVR). The low risk (LR) AVR group was randomized between an aspirin / clopidogrel regimen and standard dose warfarin, three months after surgery, INR was adjusted by home monitoring and a daily aspirin was given to all patients. Adverse events were independently adjudicated according to the AATS/STS guidelines for valve studies.

Results: 749 AVR patients were randomized into control (378) and treatment (371) groups between September 2006 and February 2013. These groups break down to test – 185 HR, 90 LR and 96 MVR; later, a hemiarch with a novel, valved ascending aortic prosthesis. In early cases, urgent 11 (18%) and elective 36 (59%); one in-hospital death 13 days postoperatively. There was one intraoperative death (emergent attempted salvage of an acutely ruptured dissection); one in-hospital death 13 days postop.

Conclusions: INR may be maintained in the range of 1.5–2.0 in AVR patients after implantation of the On-X bileaflet mechanical prosthesis. In combination with low-dose aspirin, this therapy resulted in significantly lower risk of bleeding than customary INR 2.0–3.0, without significant increase in TE.

OnX valve conduit: from table-made to off-the-shelf, a single surgeon experience
Marc Gerdisch
Franciscan St. Francis Heart Center, Indianapolis, United States

Objective: To evaluate the performance of a novel, valved ascending aortic prosthesis for replacement of the aortic root with or without the ascending aorta and/or hemiarch in patients with aortic valve (AV) disease of heterogenous etiology.

Methods: Charts were reviewed for all patients who underwent replacement of the aortic root with or without the ascending aorta and/or hemiarch with a novel, valved ascending aortic prosthesis. In early cases, the prosthesis was hand-fabricated by sewing an On-X mechanical aortic heart valve (On-X Life Technologies, Austin, TX) to a Valsalva graft; later, a commercially available, prefabricated, valved ascending aortic prosthesis (On-X) was used. All operations were performed by a single surgeon (MWG).

Results: Between May 2008 and June 2014, 62 consecutive patients underwent the procedure. Baseline characteristics and risk factors are detailed in Table 1. The first 14 patients received the hand-fabricated pros-
eratively (supermorbid obese patient with emergent preoperative AV endocarditis, septic emboli, ARF, and acute MI with cardiogenic shock); and one in-hospital death 32 days postoperatively (s/p emergent operation for infected prosthetic AV, MV, and PPM). Two late deaths occurred: one 4 months postoperatively from a recurring pseudomonas infection of a PPM combined with AV/MV endocarditis; and one sudden death 20 months postoperatively from a suspected rupture of a descending aortic aneurysm. Long-term, patients show acceptable valve and hemodynamic function. In patients with preoperative AS, average gradients decreased from 39.1 ± 16.6 mmHg preoperatively to 10.0 ± 4.1 postoperatively (n = 30). There was one late reoperation to repair a periarteric leak following a redo-AVR/MVR replacement in a patient with history of intravenous drug abuse and double prosthetic valve endocarditis. There was 1 lower-extremity thrombotic event, 1 TIA in a patient with subtherapeutic INR, and no incidence of stroke.

Conclusions: In this small series, the novel valved ascending aortic prosthesis yielded acceptable results when used for aortic root, ascending aorta, and proximal arch replacement, without an apparent elevated risk of complications.

Short communications from selected papers

Aortic complications in bicuspid aortic valve and marfan syndrome: a histologic comparison
Nimrat Grewal1, Romy Franken1, Barbara J.M. Mulder1, Marie-José Goumans2, Johannes H.N. Lindeman2, Monique R.M. Jongbloed2, Marco C. DeRuiter2, Robert J.M. Klautz2, Robert E. Poelmann2, Ad J.C. Bogers3, Adriana C. Gittenberger-de Groot2
1Academic Medical Center, Amsterdam, The Netherlands;
2Leiden University Medical Center, Leiden, The Netherlands

Objective: Patients with bicuspid aortic valve (BAV) and Marfan syndrome (MFS) have an increased susceptibility for development of ascending aorta dilation and dissection compared to persons with a tricuspid aortic valve (TAV). In this study we compared the histopathological substrate of their aortopathy, in order to demonstrate intrinsic defects and to elucidate pathways of a distinct clinical course.

Methods: Ascending aorta wall biopsies were divided in five groups: BAV (n = 36) and TAV (n = 23) both without and with (>44 mm) dilation and non-dilated MFS (n = 8). General histologic features and expression of vascular smooth muscle cell maturation markers were investigated. Furthermore expression of fibrillin-1 known to be mutated in MFS was also studied.

Results: In most aspects MFS was comparable to BAV showing a less differentiated media of the aortic wall with significantly lower expression of alpha smooth muscle actin, SM22alpha, smoothelin and lamin A/C. The fibrillin-1 level was decreased in all BAVs and MFS as compared to the TAV. Unlike TAV, MFS and BAV further did not exhibit markers for degeneration and ageing like inflammation and progerin expression. However similar to the TAV, MFS showed medial cytolytic necrosis and degradation of the elastic lamellae, which was not seen in BAV.

Conclusions: In MFS a fibrillin-1 deficiency accompanies immaturity of the aortic wall like in BAV. This is ameliorated in MFS by the genetic mutation leading to also structurally abnormal fibrillin-1 explaining a multiple hit theory, which leads to severe aortopathy at a younger age in MFS.

New approach in the treatment of aneurysm of Sinus of Valsalva
Andranik Petrosyan, Patrice Bergeron
Department of Thoracic and Cardiovascular Surgery, Clinique “Residence du Parc”, Marseille, France

Objective: is to reduce the operation time and the risks of complications related of coronaries’ implantation in high risk population by using a new approach and a new technique of treatment of aortic aneurysm in sinus of Valsalva segment.

Methods: Were selected and operated 15 patients (11 male), mean age 81 ± 8.2 years old, with aortic dilatation in sinus of Valsalva (the mean diameter 50.5 ± 7.38 mm) without aortic annulus dilatation. The major criteria of selection were the dilatation of non-coronary and right coronary cusps of the sinus of Valsalva, with intact left-coronary cusp. Surgical steps included the resection of dilated non-coronary cusp, then dilated aorta 1 cm above of right and left coronary arteries orifices. Next step was a duplication of the aortic wall by polypropylene suture in the middle of right-coronary cusp by reducing the surface approximately equal to unchanged left-coronary cusp. The suture was started from outside to inside and from the end of sinus of Valsalva (sino- tubular junction side) to the annulus of aorta by stopping 1-1.5 mm above of the annulus. The running type of suture was used. With the same stitch and same needle was doubled the suture by coming back to the end of sinus of Valsalva: finishing the node in outside of aorta. A tailored Dacron tube was used to

Figure 1. CT scanner of dilated non-coronary and right coronary side and not dilated left coronary side of sinus of Valsalva.

Figure 2. The reconstruction on picture of the suture on the right coronary side of SV (view from outside).
replace the resected aorta according to David technique. The mean cardiopulmonary bypass time and cross-clamp time were 96 ± 19.4 and 73.4 ± 11.1 minutes respectively. Results: The maximum follow-up was 30 months, mean 12 months. There were no death and stroke in perioperative and early post-operative periods. In one case patient presented low cardiac output syndrome and long cardiopulmonary bypass was needed (140 minutes). One case of TIA was detected. Late complications include one aortic arch dilatation, one left-coronary cusp dilatation, one infective endocarditis of aortic native valve at 18th months and one death at 10th month of follow-up. During the re-operation for infective endocarditis the full visual revision of aortic wall, the added suture of the right coronary cusp and the right coronary orifice revealed the presence of the suture, not involvement in infective endocarditis, no thrombus on the suture, no distortion of the aorta, no occlusion or kinking in right coronary

**Table 1. Preoperative characteristic of 15 patients**

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11 (73.3)</td>
<td>1 (6.6) History of previous coma</td>
</tr>
<tr>
<td>Female</td>
<td>4 (26.6)</td>
<td>2 (13.3) Syncpe</td>
</tr>
<tr>
<td>Diabetic</td>
<td>2 (13.3)</td>
<td>1 (6.6) Pulmonary embolism</td>
</tr>
<tr>
<td>CKD</td>
<td>4 (26.6)</td>
<td>2 (13.3) Epilepsy</td>
</tr>
<tr>
<td>HTN</td>
<td>8 (53.3)</td>
<td>5 (33.3) Thrombo-phlebitis</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5 (33.3)</td>
<td>1 (6.6) History of rheumatism</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (13.3)</td>
<td>1 (6.6) Pericarditis</td>
</tr>
<tr>
<td>Smoker</td>
<td>5 (33.3)</td>
<td>1 (6.6) Previous AVR</td>
</tr>
<tr>
<td>COPD</td>
<td>3 (20)</td>
<td>1 (6.6) Previous PCI</td>
</tr>
<tr>
<td>Carotid severe stenosis</td>
<td>2 (13.3)</td>
<td>1 (6.6) Intramural hematoma</td>
</tr>
<tr>
<td>TIA</td>
<td>2 (13.3)</td>
<td>1 (6.6) Stroke</td>
</tr>
</tbody>
</table>


**Table 2. Preoperative data**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Mm (mean) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Valsalva dilatation</td>
<td>15</td>
<td>100</td>
<td>50.5 ± 7.38</td>
</tr>
<tr>
<td>Ascending aorta dilatation</td>
<td>11</td>
<td>74.8</td>
<td>53.5 ± 16.7</td>
</tr>
<tr>
<td>Atypical placement of right coronary artery orifice</td>
<td>4</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>4</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency (sever and moderate)</td>
<td>8</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (mean)</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD - standard deviation.

**Table 3. Perioperative data**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Time minutes (mean) ± SD</th>
<th>Mm (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>10</td>
<td>66.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral cannulation</td>
<td>5</td>
<td>33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECC</td>
<td>15</td>
<td>100</td>
<td>96 ± 19.4</td>
<td></td>
</tr>
<tr>
<td>Cross clamp</td>
<td>15</td>
<td>100</td>
<td>73.4 ± 11.1</td>
<td></td>
</tr>
<tr>
<td>Dacron tube</td>
<td>15</td>
<td>100</td>
<td>30 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

*ECC - Extracorporeal circulation, AVR - aortic valve replacement, SD - standard deviation.

**Table 4. Postoperative complications**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection of sternum</td>
<td>1</td>
<td>6.66</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td>6.66</td>
</tr>
<tr>
<td>Arch dilatation</td>
<td>1</td>
<td>6.66</td>
</tr>
<tr>
<td>Left coronary cusp dilatation</td>
<td>1</td>
<td>6.66</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>6.66</td>
</tr>
</tbody>
</table>
Impact of obesity on the risk of aortic dilatation in patients with bicuspid aortic valve
Marianna Buonocore, Ciro Bancone, Sabrina Manduca, Franco E. Covino, Marco V. Montibello, Giovanni Dialetto, Alessandro Della Corte
Dept of Cardiothoracic Sciences, Second University of Naples — Cardiac Surgery, V Monaldi Hospital, Naples, Italy

Introduction: The impact of obesity on the association between congenital bicuspid aortic valve (BAV) and ascending aorta dilatation is currently poorly defined.

Methods: By analysing a database containing anthropometric, echocardiographic and clinical information of 715 adult BAV patients, we assessed the relation between obesity and aortic diameter at both root and ascending level and between obesity and presence of aortic aneurysm (diameter ≥5 cm), also stratifying with respect to other factors affecting the aortic phenotype, including gender, hypertension, valve function, and cusp fusion pattern.

Results: Obesity was found, according to WHO definition, in 20% patients. The rate of obese patients increased from the third to the fifth decade of age, to remain stable thereafter (p < 0.001). Patients with a body mass index (BMI) ≥30 had a significantly greater mean diameter of the aorta at the ascending tract (4.4 ± 0.7 cm) compared to non-obese patients (4.1 ± 0.8 cm; p < 0.001), whereas aortic root diameter was only slightly larger (3.6 ± 0.6 cm versus 3.7 ± 0.5 cm; p = 0.10).

Figure 1. Obesity was an independent predictor of the ascending diameter in multivariable linear regression analysis (p = 0.004) and of ascending aortic aneurysm in multivariate logistic regression (OR 2.1; 95%CI 1.04–4.16; p = 0.035). The difference in ascending diameter was greater than predicted based on age differences, and obese patients showed no significant correlation between age and diameter unlike the other patients. When stratifying for gender, the difference in aortic diameter between obese and non-obese patients did not reach significance in the female subpopulation (p = 0.06). Obesity was significantly associated with hypertension (p = 0.005), however in non-hypertensive patients the association with larger ascending aorta was confirmed. The difference in ascending diameter between obese and non-obese patients was greater in the subgroup with normal valve function, also showing a stronger correlation of diameter with BMI (Figure 1). There was a significant association between obesity and aortic aneurysm (diameter ≥5 cm), both in the general cohort and in the subgroups with: right-noncoronary cusp fusion pattern (p = 0.007), normal blood pressure (p < 0.001), normal valve function (p = 0.002).
Conclusions: This is to our knowledge the first study observing a significant impact of BMI on the presence and severity of aortopathy in BAV patients. The obesity factor is likely to have complex interactions with other known modifiers of the aortic phenotype: this study suggested which BAV patient profiles could benefit more from dietary and medical interventions aiming at preventing or controlling BMI increase.

PARALLEL SESSION | Innovation in perfusion

COAGULATION MANAGEMENT
Update in coagulation management
Gregory Hans
CHU of Liege, Liege, Belgium

Coagulopathy is frequent after cardiothoracic surgery involving the use of cardiopulmonary bypass. It can lead to excessive bleeding, require the administration of allogenic blood products and adversely affect patients' outcome. The fact that worldwide 20% of allogenic blood products are transfused in the setting of cardiothoracic surgery further highlights the importance of this problem[1]. With respect to blood products utilization, the use of a transfusion protocol has been shown superior to transfusion based on clinical judgment alone[2]. Consequently, most hospitals have developed their own transfusion protocol for treating bleeding after cardiothoracic surgery. Many of these protocols rely on viscoelastic point-of-care tests like thromboelastometry to guide the administration of blood products. Specific tests for platelet aggregation also become increasingly popular and are particularly helpful in the assessment of patients treated with anti-platelet agents. Despite the broad availability of point-of-care tests, standard laboratory coagulation tests also remain useful. Preoperatively, they inform about the patient’s "coagulation" reserve. Fresh Frozen Plasma (FFP) and platelet concentrates (PC) have long been the cornerstones of treatment of postoperative bleeding. More recently, the critical importance of maintaining an adequate level of fibrinogen has been recognized[3]. Prothrombin complex concentrates, activated factor VII, factor XIII and desmopressin also appear in many transfusion algorithms although their exact place remains to be determined. There is little doubt that in the near future, these transfusion algorithms will be considered as part of an integrated and patient-centered approach aimed at reducing the need for transfusion and improving patient's outcome: here is the concept of patient blood management[4]. The patient's hematologic system is indeed increasingly recognized as a valuable resource of which a part is used during surgery. Transfusion can be avoided when the preoperative amount of red blood cells and clotting factors is such that the patient will be left with an acceptable amount of them after what he will have lost during surgery. Treating preoperative anemia, identifying and fixing preoperative clotting disturbances and adequately dealing with anti-platelet agents and anticoagulants preoperatively all contribute to increase the preoperative "reserve". Using blood sparing surgical techniques, anti-fibrinolytics and intraoperative cell salvage decrease the amount of net blood losses during surgery. Reducing unnecessary hemodilution and rationalizing intraoperative fluid therapy also contribute to reduce intraoperative anemia. Eventually, tailoring the transfusion trigger for red blood cells and rationalizing the administration of clotting factors are essential to avoid unnecessary transfusions. In this presentation, we will review some aspects of the management of excessive post-operative bleeding particularly relevant to patients undergoing major aortic surgery under cardiopulmonary bypass.

References

TEMPERATURE MANAGEMENT
Deep hypothermia: the gold standard?
John A. Elefteriades
Aortic Institute at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA

Effective cerebral protection remains a principle concern during aortic arch surgery. Deep hypothermic circulatory arrest (DHCA) has been entrenched as the primary neuroprotection mechanism since the 70s, as it slows injury-inducing pathways by limiting cerebral metabolism. However, excessive DHCA duration has been associated with poorer neurological outcomes, necessitating the adjunctive use of antegrade (ACP) and retrograde cerebral perfusion (RCP). ACP has superseded RCP as the preferred perfusion strategy as it most closely mimics physiological perfusion. Even with ACP, there exists uncertainty regarding several vital technical details, such as unilateral versus bilateral perfusion, flow rate and temperature, perfusion site, undue trauma to head vessels, and risks of embolization. We believe that for the vast majority of aortic arch operations, the simplicity and effectiveness of straight DHCA justify its sole use, without necessity for ACP or RCP perfusion adjuncts. This presentation offers a historical and clinical comparison of the DHCA with other techniques of cerebral protection. The safety of straight DHCA for up to 50 minutes of brain protection is documented with detailed neurocognitive testing results.

References

TEMPERATURE MANAGEMENT
Modern temperature management in aortic arch surgery
Maximilian Luehr, Friedrich-Wilhelm Mohr, Christian D. Etz
Department of Cardiac Surgery, Leipzig Heart Center, University of Leipzig, Leipzig, Germany

Arch surgery is undoubtedly among the most technically and strategically challenging endeavours in aortic surgery, requiring thorough understanding not only of cardiovascular physiology, but also in particular, of neurophysiology (cerebral and spinal cord), and is still associated with significant mortality and morbidity. In the late 1980s, when deep hypothermic circulatory arrest (HCA) had gained widespread acceptance as the standard approach for arch surgery, antegrade selective cerebral perfusion (SCP), as an adjunct to deep HCA, began its triumphal march, offering excellent neuroprotection and improved overall outcome. This encouraged the use of antegrade SCP in combination with steadily increasing body core temperatures-a trend culminating in the progressive advocacy of moderate-to-mild temperatures up to 35°C, and even normothermia. The impetus for progressive temperature elevation was the limitation of adverse effects of profound hypothermia and the most welcome side
effect of significantly shorter cooling and rewarming periods on cardio-pulmonary bypass (CPB), and thereby, potentially, the alleviation of the systemic inflammatory response and, in particular, the risk of severe postoperative bleeding (and other organ dysfunctions). The safe limits of prolonged distal circulatory arrest, particularly with regard to the ischaemic tolerance of the viscera and the spinal cord, have not yet been clearly defined. Adverse outcomes due to inappropriate temperature management (core temperatures too high for the required duration of distal arrest) are probably highly underreported. Complications historically associated with hypothermia, namely excessive bleeding, are possibly overestimated. Trading effective neuroprotection and excellent outcomes for the risk of prolonged 'warm' distal ischaemia might constitute a significant step back, jeopardizing visceral and, in particular, spinal cord integrity, with unpredictable consequences for long-term outcome and quality of life, particularly affecting those in need of more complex surgery or with previous neurological deficits.

VENTILATION MANAGEMENT
Prophylactic NIV: does it improve patient’s outcome?
Alastair Glossop
Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Noninvasive ventilation (NIV) is a form of respiratory support that has become an established treatment for acute respiratory failure (ARF) over the last 20 years, with mortality benefits demonstrated in patients with ARF due to COPD, cardiogenic pulmonary oedema and in the immunocompromised [1]. More recently it has been used prophylactically to prevent progression to respiratory failure in susceptible and high risk patient groups, including patients following major surgery. Development of respiratory failure in post operative patients is associated with a number of adverse patient outcomes including prolonged critical care and hospital stay, increased incidence of infective complications and - in certain patient groups - increased mortality.

The effects of using NIV to prevent respiratory complications following major vascular surgery have been studied in two large RCTs to date [2,3]. They concluded that the prophylactic use of NIV, compared to standard medical therapy, resulted in significant reductions in rates of hypoxaemic respiratory failure, respiratory complications and hospital length of stay. These findings have been replicated in several other patient groups at risk of developing respiratory complications following major surgery including abdominal [4], cardiac [5] and thoracic surgery [6]. In addition a recent meta analysis of studies suggested a mortality benefit with the use of NIV compared to standard medical therapy in general post operative populations [7].

Therefore the use of prophylactic NIV is associated with better outcomes for patients, with reduced morbidity and mortality demonstrated across a range of surgical specialties. The use of NIV is recommended in patients following major vascular procedures to reduce the risk of pulmonary complications that are associated with significant morbidity and worse patient outcomes.

References

VENTILATION MANAGEMENT
An innovative approach of CRF treatment: low flow CO2 removal
Philippe Morimont1, Julien Guiot1, Thomas Desaive2, Vincent Tchana-Sato1, Nathalie Janssen1, Aurelien Cagnina1, Simon Habran1, Dominique Hella1, Francine Blaffart1, Philippe Kohl1, Jean-Olivier Defraigne1, Bernard Lambermont1
1University Hospital of Liege, Liege, Belgium; 2University of Liege, Liege, Belgium

Introduction: As with any therapy, mechanical ventilation has side-effects, and may induce lung injury (ventilator-induced lung injury (VILI)) because of overdistention, repeated stretch to the alveoli and increased inflammatory mediators levels [1]. In order to reduce these deleterious effects, protective ventilation strategies have been developed. However, beneficial effects resulting from protective lung ventilation are counterbalanced by deleterious hemodynamic effects. Indeed, hypercapnia resulting from ventilation at lower tidal volume enhances pulmonary hypertension and is associated with right ventricular failure. In order to supplement or replace the lung function and to avoid ventilator-induced lung injury, gas exchange via an extracorporeal device has been developed. Such a device may make it possible to avoid mechanical ventilation altogether in selected patients. Extracorporeal membrane oxygenation (ECMO) allows blood oxygenation and carbon dioxide (CO2) removal but requires high blood flow and, as a result, placement of large cannulas. Less invasive veno-venous devices, called "low flow extracorporeal veno-venous CO2 removal therapy (ECCO2RT)", have been specifically designed for CO2 removal with high gas exchange efficiency at relatively low blood flow rates [2]. The aim of our study was to determine if ECCO2RT used at early stage of ARDS could have beneficial hemodynamic effects on pulmonary circulation and improve RV function.

Methods: Our study was performed on an experimental model of ARDS obtained in 8 pigs. After sedation, analgesia and endotracheal intubation via a cervical tracheostomy, the pigs were connected to a volume-cycled ventilator. A micromanometer-tipped catheter was inserted into the main pulmonary artery and into the left atrium. A conductance micromanometer-tipped catheter was inserted into the right ventricle. ARDS was obtained by repeated bronchoalveolar lavage (0.9% saline solution). Protective ventilation at lower tidal volume was then achieved. Animals were connected to a pump-driven extracorporeal membrane oxygenator (PALP, MAQUET, Germany) in order to achieve CO2 removal therapy.

Results: ARDS induced severe hypercapnic acidosis (PaCO2 = 82.5 ± 10.8 vs. 46.3 ± 10.7 mm Hg and pH = 7.14 ± 0.07 vs. 7.46 ± 0.07, p < 0.01). Systolic pulmonary artery pressure (PAPs) significantly increased from 27.4 ± 4.3 to 43.0 mm Hg, p < 0.01. After the PALP was started,

Figure 1. Effect of ECCO2RT on pulmonary arterial pressure PAP, systolic pulmonary arterial pressure.
acidity was corrected (pH = 7.39 ± 0.08) and normocarbia was maintained (PaCO2 = 41.9 ± 12.6 mm Hg, p < 0.01) despite protective ventilation (tidal volume = 6 vs. 10 mL/kg). At the same time, PAPs significantly decreased to 30.8 ± 5.0 mm Hg, p < 0.01.

Conclusions: Veno-venous removal therapy enabled protective ventilation while maintaining normocarbia during ARDS. CO2 removal decreased acidosis was corrected (pH = 7.39 ± 0.08) and normocarbia was maintained (PaCO2 = 41.9 ± 12.6 mm Hg, p < 0.01) despite protective ventilation (tidal volume = 6 vs. 10 mL/kg). At the same time, PAPs significantly decreased to 30.8 ± 5.0 mm Hg, p < 0.01.

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was reported. 42 patients gave a mean time from presentation to knife-to-skin (KTS) of 296 minutes (median 192.5, range 40–1410). 5 patients died intra-operatively. Overall survival to discharge was 40%, with a calculated mean P-possum predicted mortality of 68% and a mean Glasgow Aneurysm score of 95. Table 1 shows the break down of times to CT and times to theatre for the two distinct groups - those who survived versus those who died. Discussion: Limitations lie in the nature of the study (retrospective), missing notes and gaps in documentation. We extrapolated from our data however that patients who died had on the whole a much more rapid KTS time (median 135 minutes) when compared to those who survived (median 217 minutes). This is likely to be somewhat attributable to a heightened sense of urgency with patients who are inherently unstable. Interestingly despite a significant mean time to theatre, overall survival was higher than predicted by the P-possum score. (Tables for this abstract can be viewed in the PDF Abstract Book).

References

Evaluation of the multilayer flow modulator in aneurysm repair using porcine animal models
Sherif Sultan1,2, Edel P. Kavanagh2, Michel Bonneau3, Chantal Kang3, Antoine Alves4, Niamh Hynes2
1Western Vascular Institute, Galway, Ireland; 2Galway Clinic, Galway, Ireland; 3Centre de Recherche en Imagerie Interventionnelle, Jouy-en-Josas, France; 4Biomatech-NAMSA, Chasse-sur-Rhône, France

Purpose: To examine with porcine test animals whether the Multilayer Flow Modulator (Cardiatis, Isnes, Belgium) (Figure 1) can successfully treat abdominal aortic aneurysms (AAA) through intra-arterial hemodynamic modulation without substantial parent or small branch artery compromise.

Methods: The MFM was evaluated in 8 porcine test animals with AAA experimentally induced by grafted venous tissue. The planned study period was 1 month, at which point all animals were to be euthanized and explanted for final examination of devices and vessels. The MFM delivery system underwent a separate evaluation with planned deployment of 8 devices in 1 pig without an induced aneurysm.

Results: In the delivery system evaluation, navigation, placement, deployment, and withdrawal were without complication. In the evaluation of MFM performance in induced aneurysms, angiographic follow-up at 8 days showed 3 aneurysms reduced in size and 1 totally excluded. Collective examination upon final angiography and explantation showed an overall trend of reduction in aneurysm size. In 2 explants, the aneurysm opening was nearly occluded with thrombus and the venous graft wall had thickened significantly, suggesting an evolution into an arterial type vessel wall. No intimal hyperplasia was observed in any of the explants. The visceral arteries covered by the device remained patent, and the device was found to be adhering to the arterial wall with endothelialization clearly visible.

Conclusion: In this in vivo study, the MFM was implanted without intra-arterial compromise and aneurysms were stabilized while adequate blood flow was preserved to collateral arteries. Further studies are needed to assess the MFM.

Changes in thread design of the multilayer flow modulator and the effects on biocompatibility
Sherif Sultan1,2, Edel P. Kavanagh2, Michel Bonneau3, Chantal Kang3, Antoine Alves4, Niamh Hynes2
1Western Vascular Institute, Galway, Ireland; 2Galway Clinic, Galway, Ireland; 3Centre de Recherche en Imagerie Interventionnelle, Jouy-en-Josas, France; 4Biomatech-NAMSA, Chasse-sur-Rhone, France

The Multilayer Flow Modulator (MFM) (Cardiatis, Isnes, Belgium) is a self-expandable mesh of cobalt alloy wires used for the treatment of aortic aneurysms. We assessed the impact of design thread count and duration of implantation on the biocompatibility of the MFM in porcine animal models. Eight mini-piglets received 26 MFM (12 with 56 thread design, 14 with 80 or 96 threads) in iliac, carotid, and renal arteries. Animals were sacrificed/explanted at 1, 3, and 6 months, when histological and ultra-
structural analyses were conducted. The MFM was successfully deployed in 25 of 26 cases. The 56 thread devices were well tolerated locally and yielded fewer signs of inflammation and neointimal hyperplasia. Percentage stenosis was 16.9% ± 5.1% for the 56 thread devices versus 33.4% ± 10.2% for the 80–96 thread devices (p = 0.001) at 3 months, and 21.7% ± 9.9% for the 56 thread devices versus 33.6% ± 12.4% for the 80–96 thread devices (p = 0.004) at 6 months. The 5 devices selected for Scanning Electron Microscopy (SEM) examination were well deployed, integrated into the vessel wall and endothelialized (Figure 1), and had patent side branches. Further preclinical and clinical studies will extend assessment of the long-term safety and effectiveness of the MFM.

**Endothelization kinetics of multilayer versus single layer intra-arterial stents**

Sherif Sultan1,2, Edel P. Kavanagh2, Michel Bonneau3, Chantal Kang3, Antoine Alves4, Niamh Hynes2

1Western Vascular Institute, Galway, Ireland; 2Galway Clinic, Galway, Ireland; 3Centre de Recherche en Imagerie Interventionnelle, Jouy-en-Josas, France; 4Biomatech-NAMSA, Chasse-sur-Rhône, France

The multilayer flow modulator (Cardiatis, Isnes, Belgium) is a self-expandable mesh of braided cobalt alloy wires used for treatment of aortic aneurysms. Because the endothelialisation kinetics of the device are poorly understood, they were investigated and compared with those of two single-layer control stents in porcine animal models.

A total of 19 stents were implanted in the left and right iliac and carotid arteries of 5 adult pigs, with each animal receiving two multilayer flow modulator devices plus a balloon-expandable stainless steel stent and a self-expandable nitinol stent. An animal was sacrificed every week for up to five weeks for device explantation, at which time analyses were conducted on the explants and/or vessels by gross examination, histology, scanning electronic microscopy, and immunohistochemistry.

All 19 stents were successfully delivered. At 1 week, endothelialisation and neointimal covering were slightly more advanced for the multilayer flow modulator device than for the two control single-layer stents. For all devices, non-significant traces of inflammation or thrombosis were noted, and there were no signs of local intolerance. Through 5 weeks, the proximal and distal edges of the multilayer flow modulator device were often not fully integrated into the artery wall, indicating that the endothelialization process was not totally complete (Figure 1).

Overall, the multilayer flow modulator device was found to develop a thin layer of endothelial cells sooner and was associated with less significant neointimal development than the two single-layer control stents. At 1 and 2 weeks, surface cell proliferation confirmed the positive integration of the multilayer flow modulator device into vessels, with continuing neointimal development over the duration of the study.

**Off label use of Valiant graft for treatment of complete endograft migration with major endoleak**

I. Sharaf, I. Andraos, G. Rothenbacher, M. Storck

Karlsruhe Vascular and Endovascular Center, Karlsruhe City Hospital, Karlsruhe, Germany

**Background:** In this case report we describe the off label use of Valiant graft to treat endograft migration with major endoleak.

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Figure 1. Scanning electron microscopy showing endothelialization of the MFM.

Figure 2.
A 71-year-old Caucasian man with history of nephrectomy and paraaortic lymphadenectomy presented at approx. 15 years after their initial endovascular abdominal aortic aneurysm repair. He had separation of a proximal aortic cuff from a migrated main body device resulting in a type I endoleak. He was treated with an aortouniiliac endovascular graft with cross-over bypass from right to left common femoral artery.

An infrarenal aneurysm, originating 26 mm below the renal arteries with separation of a proximal aortic cuff from a migrated main body device, was revealed by means of CT and angiography (Fig.1-2). The maximum outer diameter of the aneurysm was 9 cm. It was decided that a thoracic aortic graft, with a cranial diameter of 40 mm and a length of 152 cm, should be implanted. The stent graft (Valiant, Medtronic, Minneapolis, USA) was inserted via a right femoral arteriotomy over an extra-stiff guidewire (Amplatz extra stiff, William Cook Europe, Bjaeverskov, Denmark). A Reliant® Ballon catheter was used to mold the two graft’s coaxial aortic segments. A patent aortouniiliac stent graft and absence of leakage was shown by means of postoperative angiography. There was technical success with no postoperative complications. On CT-angiography follow-up after 4 days shows subtotal obstruction of aortic stent and the cross-over graft (Fig.3-4). A transfemoral thrombectomy via right femoral approach was done. Finally a CT-angiography shows rest thrombosis in the Endograft that we decided to treat with oral anticoagulation (Marcumar®, active substance: Phenprocoumon) (Fig. 5).

Conclusion: To perform this technique, there must be a sufficient distance between the proximal landing zone and the flow divider of the migrated endograft to allow deployment. If applicable the treatment with Valiant thoracic endograft has advantages over the use of an open reconstruction upside from off label use due to its lower intra- and post-operative complications.

Conflict of Interest (COI): no conflict

Uptake of FDG detected by positron emission tomography in the abdominal aortic aneurysm is correlated with endoleaks and predicts the adverse outcome of AAA after endovascular aortic repair

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Endovascular aortic repair (EVAR) has been applied to abdominal aortic aneurysms (AAA) to decrease and prevent morbidity and mortality due to open surgery. However, this approach may lead to complications such as occurrence of endoleaks which may result in aneurysm rupture. Decisions for complementary treatment after EVAR to prevent aneurysm rupture are based on endoleak characterization and aortic diameter expansion. These two parameters are however not always predictive of rupture. Recent reports support the view that 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) provides unique information on cellular metabolic activity thought to drive aneurysm expansion and rupture [1]. We evaluated here if FDG/PET could predict the outcome of aneurysms repaired by endoprostheses.

A cohort of 56 AAA patients (55 male; mean age of 74.6 years), treated by EVAR, underwent one or several PET/CT before and/or after surgery with a total number of 108 examinations. When the PET was positive before EVAR, 50% of these patients presented symptoms, such as increasing diameter of the aneurysmal sac, while only 12.5% of PET0 patients were symptomatic. Furthermore, two patients PET+ before EVAR underwent conversion for open surgery for rapid growth and rupture with leaking. Such outcome did not occur among the PET0 patients. No significant difference in the occurrence of endoleak could be found between the two groups of patients. The circulating levels of MMPs inhibitors, TIMP1 and TIMP2, were negatively correlated to the level of FDG uptake measured before EVAR suggesting possible alterations of the extracellular matrix remodeling leading to instability of the wall in this group of patients. A positive FDG uptake occurring after EVAR was not correlated to the AAA diameter but 54% of these patients presented endoleaks versus 22% in PET0. The circulating level of IL6 was also correlated with this FDG uptake after EVAR. When comparing globally the group of patients presenting endoleaks to those without endoleak, significantly increased circulating levels of the fibrinolytic factors D-dimers, and of the inflammatory...
cytokine IL8 were observed whereas that of the collagenase MMP1 was largely decreased.

Altogether, these results suggest that PET positivity before EVAR might predict a negative outcome of the endoprosthetic repair and could represent a beneficial tool for patient management.

Reference


**Hemodynamic assessment of endoleak using time-resolved phase contrast magnetic resonance imaging**

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**Background:** Endoleak is defined as persistent blood flow within the aneurysm sac but outside the stent-graft [1] and reported to account for >45% of all post endovascular aortic aneurysm repair (EVAR) reintervention complications [2]. Computer tomography (CT) surveillance has been often performed for endoleak detection, but recently the superiority of magnetic resonance angiography (MRA) to detect endoleak has been reported [3–5]. More recently, time-resolved phase contrast magnetic resonance imaging (4D-Flow) has been introduced and demonstrated the utility in hemodynamic analysis of the heart, thoracic aorta, abdominal aorta, branch vessels of abdominal aorta, and intracranial vasculature [6–10]. The purpose of this study is to investigate the usefulness of 4D-flow for assessment of post-EVAR endoleak.

**Material and Methods:** From January 1, 2013 to April 30, 2014, MRA/4D-Flow and CT were performed in 24 patients within 10 days after EVAR in Hamamatsu University School of Medicine, Japan. MRA/4DFlow date set were transferred to a personal computer in DICOM format, and postprocessed with a flow analysis software (Flova, Renaissance Technology, Hamamatsu, Japan). Several sectional planes of the abdominal aorta, inferior mesenteric artery (IMA), and lumbar arteries (LAs) were selected and analysed.

**Results:** CT identified endoleaks in 12 patients (50%) and MRA/4D-flow identified endoleaks in 18 patients (75%). According to 4D-flow analysis, type I, II, III, IV endoleaks were 83.3, 75, 16.7, and 8.3%, respectively. 7 patients among the 18 patients with endoleak (38.9%) showed concomitant multiple types of endoleak. Hemodynamic analysis with 4D-flow demonstrated that type II endoleak could be further classified into the 3 distinct subtypes according to the flow patterns of the aortic side branches (fig.1). Type Ila endoleak is to-end-fro solitary leak in which branch vessels of abdominal aorta show periodical changes in blood flow direction from between retrograde and antegrade without connecting to any other branch arteries. Type IIb endoleak is inflow-and-outflow connection type leak in which there is a connection between the inflow and outflow aortic branches. Type IIc endoleak is one-way solitary flow type leak in which there is a leaking branch with continuous inflow or outflow, but there is no recognized counterpart.

**Conclusions:** Hemodynamic analysis using 4D-Flow provides more detailed information about endoleak. This novel modality helps to classify endoleaks and might be useful to decide strategy for treatment of endoleaks for preventing aneurysm rupture.

**Volume growth of abdominal aortic aneurysms is predictable and correlates with increasing biomechanical rupture risk.**

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**Introduction:** The growth of abdominal aortic aneurysm (AAA) diameter is unpredictable and the use of different measurements that could increase the accuracy is debated. Volume has been proposed as a more sensitive measurement of growth [1,2]. Finite element modeling (FEM)-derived peak wall stress (PWS) and the maximal wall stress/wall strength ratio, called peak wall rupture risk (PWR) has previously been shown to be
superior to diameter at predicting rupture [3,4]. In this study, we wanted to test whether growth of AAA volume is predictable and how it correlates with biomechanics as estimated by FEM.

**Methods:** Forty-one patients (9 women, 32 men) with baseline AAA diameters of 40-60 mm and two computed tomography angiographies (CTA) performed within 8–17 months were retrospectively identified. Digital 3D models of the AAAs were reconstructed from all CTAs and the models were subsequently subjected to FEM. Annual rates of geometric growth and biomechanical rupture change were calculated from the differences in geometry, PWS and PWRR between CTAs. Correlation was determined by Spearman’s rank and predictability was assessed with receiver operating characteristic (ROC) curves.

**Results:** Mean growth rates for diameter and volume were 3.1 mm (12%) and 21 cm³ (14%) per year, respectively. As expected, baseline diameter correlated with baseline volume ($r = 0.71$, $p < 0.0001$) and diameter growth rate correlated with volume growth rate ($r = 0.35$, $p = 0.0002$). However, in our small cohort with limited range of AAA diameters, diameter growth could not be predicted by baseline diameter ($r = 0.22$, $p = 0.33$, ROC area $< 0.65$, $p > 0.17$). On the other hand, volume growth was predicted by baseline volume ($r = 0.56$, $p = 0.00014$, ROC area $> 0.82$, $p < 0.0020$). Volume growth correlated with increasing PWS/PWRR in whole sample ($r > 0.3$, $p < 0.05$) and in aneurysms with growth rate higher than the sample median ($r > 0.5$, $p < 0.018$), whereas diameter growth did not (whole: $r < 0.2$, $p > 0.29$; > median: $r < 0.3$, $p > 0.25$).

**Conclusions:** Volume growth was predictable from baseline measurements and correlated with increasing biomechanical rupture risk, in contrast to diameter growth. These results support other recent reports on the possible increased accuracy in growth and rupture risk estimations by considering the volume of the aorta rather than only its maximum diameter.

References

**Simultaneous orthotopic liver transplantation with abdominal aortic aneurysm repair**

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**Introduction:** Concomitant abdominal aortic aneurysms (AAA) and liver cirrhosis that need surgical treatment are rare. There are still controversies regarding the timing of AAA repair and liver transplantation as well as optimal treatment of AAA [1]. However, it has been observed that these aneurysms expand more rapidly in transplant recipients than in non-transplant individuals [2]. Furthermore, transplant patients show higher rates of AAA ruptures with the considerable risk for surgery-related ischemic injury [3].

**Case presentation:** We present a case of a 70-year-old white male presented with end-stage liver disease secondary to chronic hepatitis C with a solitary hepatocellular carcinoma measuring 5 cm in a right liver lobe. A 6.7 cm abdominal aortic aneurysm (AAA) was also discovered during preoperative evaluation. The decision was made to perform an orthotopic liver transplantation with simultaneous aneurysm repair. The patient was initially explored through median laparotomy. The liver transplant was performed first with the liver graft prepared on the back table in the standard fashion. The liver graft was transplanted using “piggy-back” technique with end-to-side caval and end-to-end portal vein anastomosis. The arterial anastomosis was performed with end-to-end anastomosis between the donor proper hepatic artery and the recipient common hepatic artery. The bile duct anastomosis was performed with an end-to-end anastomosis. Midline incision was extended to the pubis. After proximal and distal vascular control of infrarenal aorta, resection of AAA was performed and reconstruction with prosthetic Intervascular 22 mm with 3.0 Prolene in a running fashion. The patient remained well during 1-year follow up.

**Conclusion:** Although rare, in a patient with end-stage liver disease and AAA, a simultaneous liver transplantation and aneurysm repair represent the safest treatment solution.

References

**Long term results after retroperitoneal repair for AAA. Single center experience**

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**Introduction:** The increasing use of endovascular procedures has significantly reduced the number of open surgical repairs for abdominal aortic aneurysm (AAA). The retroperitoneal approach, less invasive than the transperitoneal approach, is characterized by better postoperative outcomes but is still less commonly performed [1]. The purpose of this study
was to describe the postoperative outcomes and survival rates after abdominal aortic aneurysm repair through the retroperitoneal approach.

**Methods:** A retrospective analysis from consecutive patients electively treated for AAA in our Unit from 1996 to 2011 was performed. In 280 cases the patients received endovascular repair (EVAR), whereas 560 underwent surgical treatment through either a transperitoneal (group TP: 193) or retroperitoneal approach (group RP: 367). The two groups were compared for postoperative outcomes and survival rates at 12 and 180 months after surgery. Oral feeding, mean length of hospital stay, stay in the ICU were shorter in the RP group. Respiratory and cardiac complications were higher in the TP group. 12 and 180 months survival rate in the RP group appeared significantly higher compared with the TP group. From 2008 an enhanced recovery protocol is being applied for all AAA patients undergoing retroperitoneal repair showing additional improvements in postoperative outcomes.

**Conclusions:** Surgical retroperitoneal approach has still a place in the repair of AAA. Application of enhanced recovery protocols may further contribute to improve postoperative outcomes in patients unsuitable for EVAR techniques. Surgical training and competence should be maintained in order to select the more appropriate therapy for each patient.

**Reference**


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**Endovascular treatment of type B aortic dissection with aortic coarctation**

**Arnaud Kerzmann, Anne-Catherine Lespagnard, Natzi Sakalihasan, Jean-Olivier Defraigne**

**CHU Sart-Tilman, Liege, Belgium**

**Introduction:** Uncomplicated Type B aortic dissection has traditionally been treated by medical therapy. Recently endovascular repair has been suggested as an alternative to get better anatomical remodeling of dissected aorta. Association of type B aortic dissection with coarctation is rare. We report one case of uncomplicated type B aortic dissection associated with isthmic coarctation and treated by stent-graft.

**Case report:** A 63-year-old man was admitted to our emergency room for sudden precordial pain irradiated in the shoulders and later in the epigastrium. He had past history of obesity and asymptomatic isthmic coarctation. Thoraco-abdominal computed tomography (CT) revealed uncomplicated acute type B aortic dissection emerging from the coarctation and ending at the diaphragm. The largest diameter of the descending aorta was measured at 60 mm. Antihypertensive treatment with clinical monitoring in intensive care unit was started. D-dimer level raised to 1286 μg/l. Positron emission tomography combined to CT detected strong 18F-FDG uptake into the dissection. Endovascular treatment was realized 17 days after dissection’s onset. Under general anesthesia and drainage of the cerebrospinal fluid, 2 stent-grafts were used to cover the coarctation and after dissection’s onset. Under general anesthesia and drainage of the cerebrospinal fluid, 2 stent-grafts were used to cover the coarctation and expansion and remodeling of the entry tear of uncomplicated type B aortic dissection by a stent-graft can lead to thrombosis of the false lumen, expansion and remodeling of the true lumen, and prevention of late complications. D-dimer level and uptake of 18F-FDG could be determinants of unfavorable outcome in uncomplicated acute type B aortic dissection. Endovascular treatment of type B aortic dissection complicating coarctation is feasible and safe. More follow-up and randomized studies are mandatory to prove the efficacy of such treatment.

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**Establishment of a new murine elastase-induced aneurysm model combined with transplantation**

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**Introduction:** The aim of our study was to develop a reproducible murine model of elastase-induced aneurysm combined with aortic transplantation.

**Methods:** Adult male mice (n = 6–9 per group) underwent infrarenal, orthotopic transplantation of the aorta treated with elastase or left untreated. Subsequently, both groups of mice were monitored by ultrasound until 7 weeks after grafting.

**Results:** Mice receiving an elastase-pretreated aorta developed aneurysms and exhibited a significantly increased diastolic vessel diameter compared to control grafted mice at 7 week after surgery (1.11 ± 0.10 mm vs. 0.75 ± 0.03 mm; p<0.001). Histopathological examination revealed disruption of medial elastin, an increase in collagen content and smooth muscle cells, and neointima formation in aneurysm grafts.

**Conclusions:** We developed a reproducible murine model of elastase-induced aneurysm combined with aortic transplantation. This model may be suitable to investigate aneurysm-specific inflammatory processes and for use in gene-targeted animals.

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**Figure 1.** Schematic presentation of the main steps of the procedure (A, D) Step 1: Mouse jugular catheter introduced through an aortotomy and secured with a silk tie. (B, E) Step 2: Aorta filled with saline containing type I porcine pancreatic elastase. (C, F, G) Step 3: Aortic transplantation using sleeve technique /F: Proximal anastomosis, G: Distal anastomosis/. (H) Aorta after transplantation.

**Reference**


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**Renal function following OSR and FEVAR of juxtarenal aortic aneurysms**

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Aim of the Study: The analysis of selected morphological features of infrarenal AAA in patients qualified for an invasive treatment in order to determine the feasibility and limitations of endovascular treatment and to outline directions of future development.

Material and Methods: The assessment of images from CT angiography of 100 patients qualified for the invasive treatment of infrarenal AAA was carried out. The average age of the patients was 69 years old. The maximum diameter of the aneurysm was 64 mm. The analysis of the images was performed using Osirix program with 3D-MPR mode. The morphology of the proximal neck was evaluated (diameter, length, angulation, shape, presence of thrombus and calcification) along with the diameter of the distal neck, diameters and course of common iliac arteries, iliac external and internal arteries. Optimal morphological criteria were defined as follows: proximal neck with cylindrical shape with calcification and thrombus, which do not exceed 50% of the neck circumference, diameter 18–28 mm, 15 mm in length and the angle between the aneurysm and the axis of the aorta < 60°, distal neck with a diameter ≥ 20 mm, distal landing zone of the common iliac arteries with a length of ≥ 10 mm and ≥ 20 mm in diameter, iliac external arteries with a diameter of ≥ 7 mm.

Results: Only 23% of the AAA met all the optimal morphological criteria. The most common deviations from the optimal criteria related to the morphology of the proximal neck was conical shape of the neck, the diameter > 28 mm, the angle between the aneurysm and the axis of the aorta > 60°, and also the distal landing zone of the common iliac arteries.

Conclusion: The majority of patients with infrarenal AAA who were qualified for invasive treatment do not meet the optimal criteria for endovascular treatment. The introduction of the systems capable of effective and durable endovascular treatment of AAA with conical, angulated, wide necks and wide common iliac arteries would extend the optimal morphological criteria.

Current morphological limitations of endovascular treatment of infrarenal abdominal aortic aneurysm
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Introduction: One of the most important factors determining the feasibility and success of endovascular treatment of infrarenal abdominal aortic aneurysm (AAA) is the fulfillment of certain morphological criteria. Morphological characteristics of AAA may differ in various populations of patients. Furthermore, currently there are several systems available for endovascular treatment of AAA with different morphological requirements.

Aim of the Study: The analysis of selected morphological features of infrarenal AAA in patients qualified for an invasive treatment in order to
Background: We have shown that elevating plasma high-density lipoproteins (HDLs) before aneurysm induction reduces AAA formation in the AngII-induced hypercholesterolemic mouse model [1]. Our further experiments will address the question of whether HDL elevation may be a therapeutic option.

Methods: Experiment 1. AAs were generated in Ang II-induced ApoE-deficient animals and following randomization to two groups animals received saline (sc) or rHDLs at 1(10 mg/kg) (sc) on alternate days for six weeks. MRI scans (4.7Ts) were obtained before and after treatment and the area (mm²) measured at the maximal area.

Experiment 2. Having generated AAAs in AngII-induced ApoE-deficient mice, following randomization one group received Adnull (an Adenoviral construct containing no additional gene) and the other group received AdA-I (an Adenoviral construct containing human ApoAI2). Mice were MRI scanned before and 4 weeks after injection to determine the effect of elevating HDLs in this manner. In addition, between group evaluation of maximal aortic area was evaluated using histological analysis.

Results: rHDL regresses Ang II induced aneurysm formation (Table 1). AdA-I increased the plasma concentration of human ApoA-I when compared to Adnull (1.872 ± 0.547 g/L vs 0.043 ± 0.001 g/L, n=5). Changes in size of aneurysm following AdA-I injection were inconclusive when measured using MRI; histological assessment is currently being completed.

Table 1.

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References


Long-term experience of surgery of TAAD type A in Ukraine

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Background: Present our approach and show results of surgical treatment of type A TAAD based of our experience.

Methods: 582 consecutive patients with type A TAAD were operated on from 1980 to 2014 in the our clinic (481 (82,6%) males). Their age ranged 20 – 78 years, mean 51,7 ± 9,2. Acute (subacute) dissection took place at 128 (86,5%) pts, chronic – in 20 (13,5%). The causes of aneurysms forming were: arterial hypertension, atherosclerosis – in 363 (62,4%); MS – 82 (14,1%); cystomedianecrosis – 67 (11,5%); BAV – 48 (8,2%); blunt aortic injury – in 8 (1,4%) cases, unknown – 11 (1,5%); lues – 3 (0,5%). In acute (subacute) stages of dissection we performed 453 (77,8%), others – 129 (22,2%) had chronic process. Main part of patients, 379 (65,1%) had type I, others 203 (34,1%) – type II according De Bakey classification. The preoperative status included: acute aortic valve insufficiency – 258 (44,3%); haemopericardium (heart tamponade) – 104 (17,9%); acute renal insufficiency – 57 (9,8%); multiorgan failure – 17 (2,9%) patients. All operations were performed with bypass, mild hypothermia (26-30°C), 192 (32,4%) patients with arch injury – deep hypothermia (18-20°DI and retrograde cerebral perfusion. We used: supracoronary grafting with valve resuspension – in 366 (62,9%) pts, Bentall-Bono operation in 210 (36,1%); other – 6 operation in 2 (1,0%), 18 (3,1%) patients received 1-3 CABS. Results: Mean blood loss after operation composed 504 ± 73,7 ml. Hemorrhage became the reoperation reason in 17 (2,9%) pts. Temporary neurological complications were observed in 18 (3,0%) pts. There was no difference in deep and mild hypothermia group. Permanent neurological complications composed 7 (1,2%) pts, but they weren’t observed completely since 2008. The postoperative 30 days mortality composed 12,7% on the all period and reduced up to 5,1% for the last 4 years; was slightly higher in acute dissection group, 13% and 11,6% in comparison. Conclusion: Obtained surgical experience, improvement of heart and brain protection in surgical treatment of dissecting aneurysms type A permitted to achieve hospital mortality 5,1%.

ApoA-I/HDL as diagnostic, prognostic and therapeutic biomarkers of abdominal aortic aneurysm

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Objective: Abdominal aortic aneurysm (AAA) evolution is unpredictable, so we aimed to identify biomarkers that could help in the prognosis as well as in finding potential therapeutic targets to slow AAA progression.

Approach and Results: A differential quantitative proteomic analysis of plasma proteins was performed in AAA patients at different stage of evolution [small AAA (aortic size = 3–5cm) vs large AAA (aortic size>5 cm)] by using iTRAQ labelling, high-throughput nano-LC-MS/MS and a novel multi-layered statistical model. Among the proteins identified, ApoA-I was decreased in large compared to small AAA patients. These results were validated by ELISA in plasma samples from small (n = 90) and large AAA (n = 26) patients [150(12–168) vs 135(113–144) mg/dl, respectively, p < 0.001]. As expected, ApoA-I levels strongly correlated with HDL concentration (r = 0.9, p < 0.001). ApoA-I/HDL levels showed a negative correlation with aortic size (r = –0.4, p < 0.01) and thrombus volume (r = –0.3, p < 0.01), which remained significant after adjusting for traditional risk factors. In a prospective study, HDL became a strong indepen-
dent predictor for aneurysmal growth rate in multiple linear regression analysis (n = 122, p = 0.008) and was significantly negatively associated with need for surgical repair (Adjusted HR: 0.18, 95% CI: 0.04–0.74, p = 0.018). Moreover, in a nationwide Danish registry, mean HDL concentration in large AAA patients (n = 6,560) was almost half of what was noticed in patients with aortoiliac occlusive disease (n = 23,496) (0.89 (2.99) mmol/l vs 1.59 (5.74) mmol/l, p < 0.001]. Finally, administration of an ApoA1 mimetic peptide decreased the mean aortic diameter of AAA in AngII-infused mice compared to those injected with saline (1.4 ± 0.1 vs 1.7 ± 0.2 mm at 28 days).

**Conclusion:** ApoA-I/HDL levels are negatively associated to AAA evolution. Therapies targeting HDL functionality could halt AAA formation.