General Thoracic and Cardiovascular Surgery (2019) 67:1–11
https://doi.org/10.1007/s11748-017-0874-x

SPECIAL EDITION

Controversies in Surgery for Thoracic Aorta

Thoracic aortic aneurysm: unlocking the "silent killer" secrets

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Received: 30 June 2017 / Accepted: 21 November 2017 / Published online: 4 December 2017

Abstract

Thoracic aortic aneurysm (TAA) is an increasingly recognized condition that is often diagnosed incidentally. This review discusses ten of the most relevant epidemiological and clinical secrets of this disease; (1) the difference in pathogenesis between ascending and descending TAAs. TAAs at these two sites act as different diseases, which is related to the different embryologic origins of the ascending and descending aorta. (2) The familial pattern and genetics of thoracic aneurysms. Syndromic TAAs only explain 5% of the pattern of inheritance. (3) The effect of female sex on TAA growth and outcome. Females have been found to have worse outcomes compared to males. (4) Guilt by Association. TAAs are associated with abdominal aortic aneurysms, intracranial aneurysms, bicuspid aortic valve, and inflammatory disorders. (5) Natural history of TAAs. Important findings have been made regarding the expansion rate (in relation to familial pattern, location and size), and also regarding the risk of rupture or dissection. (6) The aortic size paradox. Size only is not a sufficient predictor of risk of dissection. (7) Biomarker void. Although many serum biomarkers have been studied, imaging remains the only reliable method for diagnosis and follow-up. (8) Indications for repair. Decisions are made depending on symptoms, location, size, and familial patterns. (9) Types of repair. Both open and endovascular repair options are available for certain TAAs. (10) Medical treatment. The efficacy of prescribing beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers remains dubious.

Keywords Thoracic aortic aneurysm · Aortic dissection · Biomarkers · Natural history · Medical management · Genetics · Indications for treatment

Introduction

Thoracic aortic aneurysm (TAA) is a subtle, indolent and dangerous disease. It takes its time but in the end it often strikes hard, just like a "silent killer". Because they seldom produce symptoms, thoracic aortic aneurysms (TAAs) can go unnoticed to the point that they produce dreadful complications [1]. As many as 21% of patients who suffer acute aortic events (including dissection and rupture) die at home before receiving medical attention [2, 3]. Together with abdominal aortic aneurysms (AAAs), TAAs are considered the 17th most common cause of death in individuals aged more than 65 years, [4] being the primary cause of 10,073 deaths, and a contributing cause in more than 16,415 deaths in the United States in 2012 [5].

But even silent killers leave evidence and have their own patterns that can be traced. The study of the natural history of TAAs gives us a weapon against this serious disease. In this review, we explore ten "secrets" that have impacted the understanding and management of TAAs. We aim to shed light on some clinical considerations and challenges that physicians face with the diagnosis, course, and natural history of TAAs.

We are dealing with two different diseases

Aneurysmal diseases of the thoracic aorta comprise two different categories, with ascending and descending aneurysms

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acting as substantially different diseases. This analysis fits a concept that aneurysm disease divides itself into two distinct entities at the ligamentum arteriosum: above the ligament is one disease and below the ligament is another. Proximal to the ligamentum, the disease is nonarteriosclerotic, whereas arteriosclerosis is abundant distal to it [6]. These differences may be related to the separate embryologic origins of ascending and descending aortic vascular smooth muscle cells (VSMCs), which are responsible for secreting many of the proteolytic factors associated with aneurysm formation, such as matrix metalloproteinase (MMP) and plasmin [7–9]. The ascending aorta and great vessel VSMCs arise from neural crest cells, whereas the descending aortic VSMCs arise from the paraxial mesoderm [10]. The aortic valve on the other hand arises from the lateral plate mesoderm,[10] and abnormalities of the aortic valve (eg: bicuspid aortic valve) have been found to be highly associated with coarctation of the aorta, suggesting that the abnormal aortic tissue may extend into the distal arch or proximal descending aorta [11, 12].

A difference in extensibility between the ascending and descending aorta has been shown as well. De Beaufort et al. have found that extensibility and longitudinal strain were most pronounced in the ascending aorta compared to the descending aorta [13].

It runs in the family

TAA is a familial disease that almost uniformly follows an autosomal dominant mode of inheritance, albeit with reduced penetrance and variable expressivity [14, 15]. Marfan syndrome and other connective tissue disorders such as Ehlers–Danlos syndrome, Loeys–Dietz syndrome and Turner syndrome are well established causes of TAA; nevertheless, they are only responsible for about 5% of TAAs and only explain a small portion of the familial pattern [6]. Patients who have heritable thoracic aortic disease but do not meet strict criteria for known connective tissue syndromes, are grouped as non-syndromic (ns-TAA) [14]. Robertson et al. demonstrated that up to one in six patients undergoing aortic surgery have features of heritable ns-TAAD, frequently presenting with aortic dissection [16]. It is worth mentioning that there is a significant overlap between syndromic and ns-TAAD because the same gene mutation can cause syndromic features in one family member, while not completing the full syndrome in others [17, 18].

The precise molecular genetics of TAAs are being clarified. For instance, mutations in the FBN*1* gene that encodes the Fibrillin-1 protein are mainly associated with Marfan syndrome. Mutations in genes encoding collagen (COL3A1) and elastin (ELN) also affect the matrix stabilization and can lead to weakening of the aortic wall [19]. Another set of genes encoding various components of the transforming growth factor beta (TGF-β) signaling cascade (TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, SMAD3 and SKI) produce TGF-β vasculopathies, and they are associated with Loeys–Dietz syndrome. Genes that encode components of the smooth muscle contractile apparatus (ACTA2, MYH11, MYLK, and PRKG1) produce smooth muscle contraction vasculopathies [19–21]. Loeys et al. have found that mutations in either TGFBR1 or TGFBR2 predispose patients to aggressive and widespread vascular disease [22].

It was found that approximately 30% families with heritable thoracic aortic diseases (HTAD) who do not have a clinical diagnosis of Marfan syndrome or another syndrome have a causative pathogenic variant in one of the known HTAD-related genes [18]. New pathologic and suspicious genetic variants are being discovered regularly, as whole exome sequencing (WES) proliferates in TAA patients and their family members [23]. A summary of genes and their categories, correlated to a simplified illustration of aortic dimensions for prophylactic surgical intervention, can be found in Fig. 1.

Women with TAA do poorly

TAAs seem to behave differently accoring to gender. A 5 cm aneurysm in a small sized female is certainly more threatening than the same aneurysm in a 6-foot well-built male athelete. But other than body size factors, female sex has been found to affect the growth rate and outcomes of thoracic aneurysms. In a study with 805 TAA patients, Davies et al. found that females had significantly higher rates of dissection ($P=0.005$) and lower 5-year event-free survival (90.3 and 84.3% versus 99.1 and 94.4%) despite inclusion of BSA in the analysis [24]. In another study, with 523 acute type A aortic dissection (AD) patients who underwent surgery, intramural hematoma (IMH) patients were significantly older (64 versus 56.8, $P<0.001$) and more commonly female (39 versus 26%, $P=0.01$). [25] With regards to growth, Cheung et al. found that TAA growth rates are greater in women than men (1.19 ± 1.15 mm/year in women and 0.59 ± 0.66 mm/year in men, ($P=0.02$) [26, 27]).

Female gender also accounts for the poorer outcomes seen with this disease. A recent study showed that females with Type B AD presented at a later age and were more likely to undergo thoracic endovascular aortic repair (TEVAR) and to have a perioperative cardiac event with open repair [28]. Another retrospective study of 2574 patients who underwent endovascular repair, of which 40% were women, found that female patients had a higher 30-day mortality (5.4 versus 3.3%; $P<0.01$). Females also had worse long-term survival and higher mortality at 1 year (9.8 versus 6.3%; $P<0.01$) even after adjusting for differences in age and comorbidities [29].

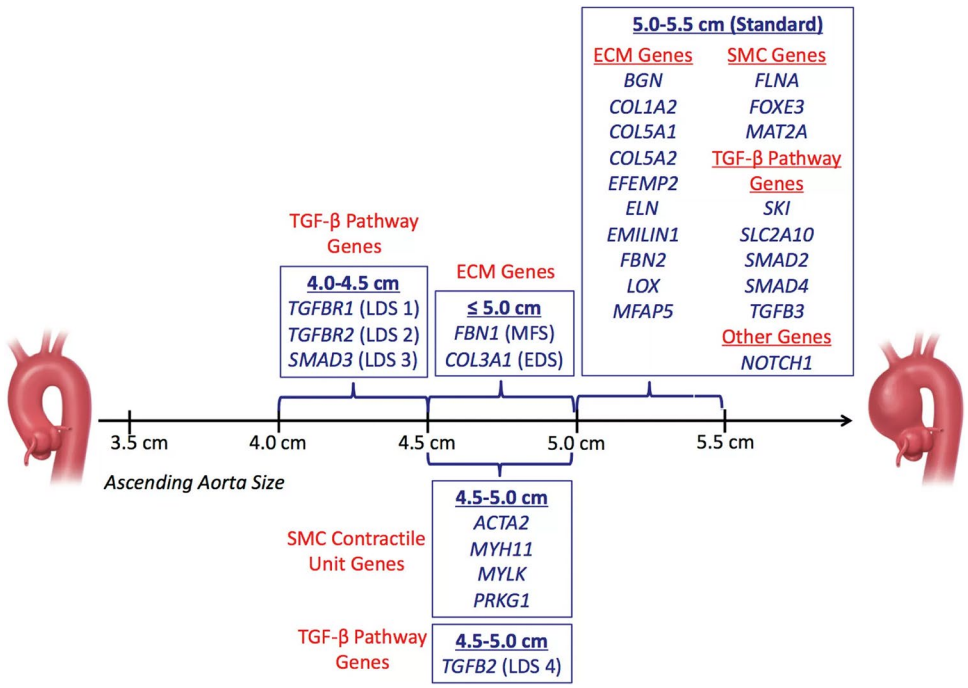

Fig. 1 Simplified schematic illustration of ascending aorta dimensions for prophylactic surgical intervention divided by gene category: extracellular matrix genes, smooth muscle cells contractile unit and metabolism genes, and TGF-β signaling pathway genes (Reprinted with permission from Brownstein et al. [23])

"Guilt by Association"

Another important secret is the association between TAAs and other medical conditions, which has been termed "Guilt by Association" [30] (Fig. 2). There is a strong association among thoracic aortic aneurysms and the presence of aneurysms at different anatomic locations. A high prevalence of ascending aortic dilation was noticed in patients with AAA [31]. In a retrospective study with 1942 patients with AAAs who were evaluated by echocardiography, more than 50% of patients had concurrent ascending aortic dilation [31]. Another association was noted in a radiologic study of 212 patients with a TAA, in which 9% of them were found to harbor intracranial aneurysms (ICAs) [32]. More recent studies have been conducted on the relationship between renal cysts and TAAs [33].

TAAs are also associated with inflammatory disorders. In one prospective study of 788 patients requiring surgery for thoracic aortic disease (aneurysm or dissection), 39 aneurysms (4.9%) were due to histologically proven aortitis, with the largest percentage attributable to giant cell arteritis (30 patients) [34]. Other inflammatory causes including Takayasu aortits, Bechet's disease and temporal arteritis were also noted.

One very important clinical correlation exists between TAA and bicuspid aortic valve (BAV). In persons with BAV, the aortic root and ascending aorta are significantly larger [35]. Ascending aortic dilation occurs more frequently and at a younger age in patients with BAV than it does in patients with normal trileaflet aortic valves (TAV) [11]. In a prospective study with 115 patients with BAV, Avadhani et al. found that there was an accelerated annual rate of ascending aortic growth of 0.47 cm/year (compared to the normal 0.1 cm/year in the average patient) [36].

BAV is the most common congenital cardiac anomaly, occurring in 1.37% of the population,[5] with some studies suggesting an autosomal dominant pattern of inheritance [37, 38]. The accompanying aortic dilatation increases the liability for dissection and rupture [39]. Ergo, it is important to follow the aorta closely once BAV has been diagnosed [11]. In a recent study, Girdauskas et al. found that the functional parameters of the aortic root, such as the systolic trans-valvular flow or BAV cusp fusion pattern, may be used to predict the severity of aortopathy in patients with BAV stenosis and can be useful in predicting future risk of aortic disease in such patients [40].

Recently, it was found that bovine aortic arch (BA) was significantly more common in patients with thoracic aortic disease than in the general population. In a retrospective study, reviewing CT and/or MRI scans of 612 patients with TAAD and 844 patients without TAAD, 26.3% of the patients with TAAD had concomitant BA, compared to 16.4% of the patients without TAAD ($P < 0.001$). The aortic expansion rate was 0.29 cm/year in the BA group and 0.09 cm/year in the non-BA group ($P = 0.004$) [41].

The natural history of TAA (its "playbook" is becoming known)

Little was known about the natural course of TAAs until the mid 1990s, when focused studies described the natural

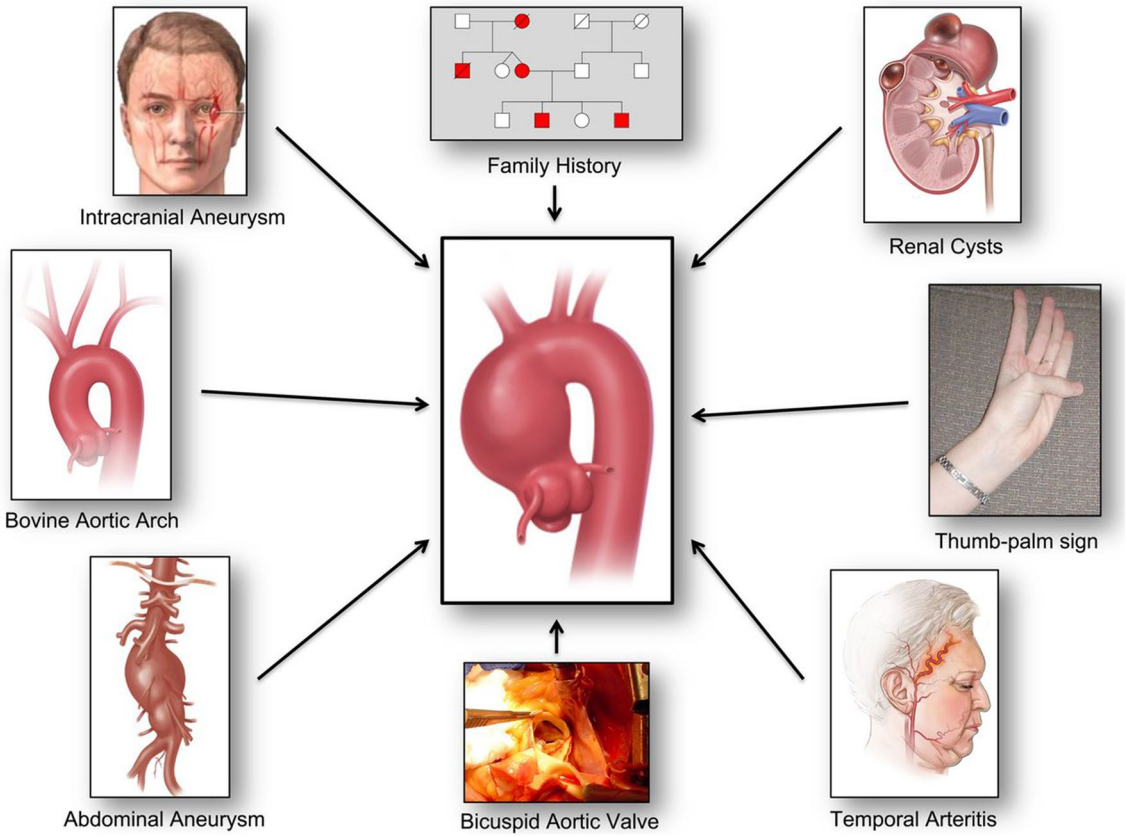

Fig. 2 An illustration of conditions associated with thoracic aortic aneurysm (Reprinted with permission from Elefteriades et al. [30])

history and unveiled the appropriate size criteria for repair before complications occur [42, 43].

In general, degenerative ascending TAAs have an average expansion rate of 0.1 cm/year, whereas descending TAAs expand by about 0.3 cm/year [42–44]. Patients with Familial TAAs have a more rapid expansion rate of about 0.2 cm/year, and syndromic TAAs can expand even more rapidly [14, 17]. This rapid expansion rate also applies to aneurysms associated with BAV which can expand by up to 0.2 cm/year [45, 46]. Marfan syndrome is associated with expansion rates up to 0.3 cm/year and TAAs associated with the particularly aggressive Loeys–Dietz syndrome can expand very rapidly at up to 1.0 cm/year [14, 22].

Aside from the familial pattern, the anatomic location of the aneurysm is also correlated with the rate of expansion. In a series of 87 patients who underwent serial CT or MRI (with a 6-month interval between scans), aneurysms located within the mid-descending aorta were associated with the most rapid expansion, while those in the ascending aorta had the slowest rate, despite having a larger initial diameter [47].

Size of the aneurysm has also been associated with the expansion rate [17]. Dapunt et al. have found that the rate of expansion for aneurysms > 5.0 cm in diameter was about 0.8 cm/year, but about 0.2 cm/year for aneurysms ≤5.0 cm [48]. However, these studies face the limitation of not taking the etiology and the location into account. Recently, Yiu et al. retrospectively studied 45 patients with arch aneurysms and found that aneurysm size > 6.5 cm was significantly associated with faster growth rate and predicted rupture risk, which may have implications in selection of patients for surgery [49].

Aneurysm morphology, i.e., whether the aneurysm is saccular or fusiform, may affect expansion rate as well. In one study, the expansion rate of saccular aneurysms that were followed was 0.28 ± 0.29 cm/year (mean follow-up 23.2 ± 19.0 months).

The most important aspect of the natural history concerns the risk of rupture or dissection. The most important risk factor predicting rupture of TAAs is the diameter but the location of the aneurysm is important as well [50]. There is a significant increase in the risk of rupture or dissection for a diameter greater than 6.0 cm for an ascending TAA and 7.0 cm for a descending TAA [42, 51].

As the aorta dilates, it loses its elasticity and becomes a stiff tube, reaching critical levels by a diameter of 6 cm for the ascending aorta, and 7 cm for the descending aorta. (Fig. 3) Extra danger accrues in high blood pressure situations (such as exercise or emotion) because the aortic wall

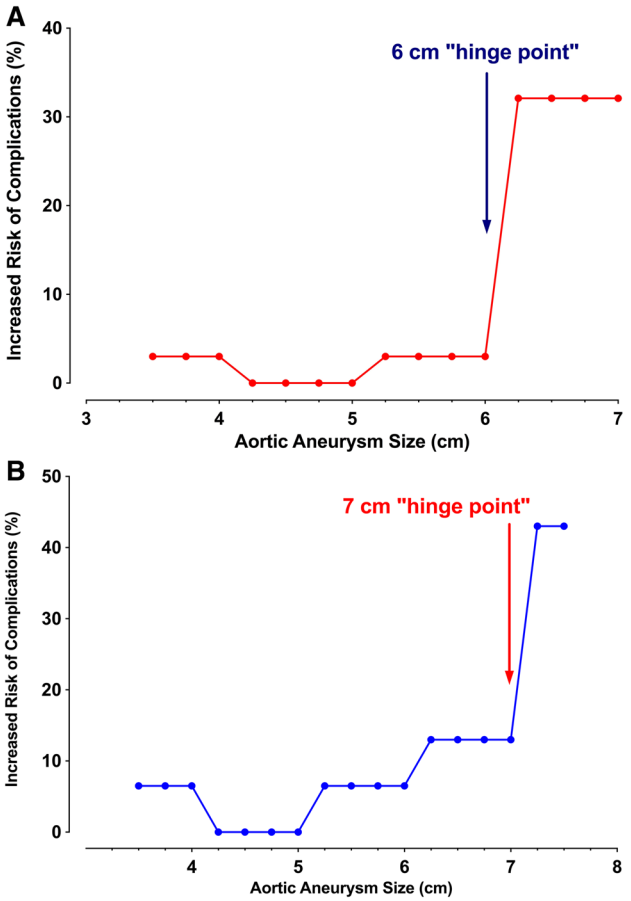

Fig. 3 Depiction of "hinge points" for lifetime natural history complications at various sizes of the aorta. The Y-axis lists the probability of complication; complication refers to rupture or dissection. The X-axis shows aneurysm size. **a** The ascending aorta. **b** The descending aorta. (Modified with permission from Coady et al. [42])

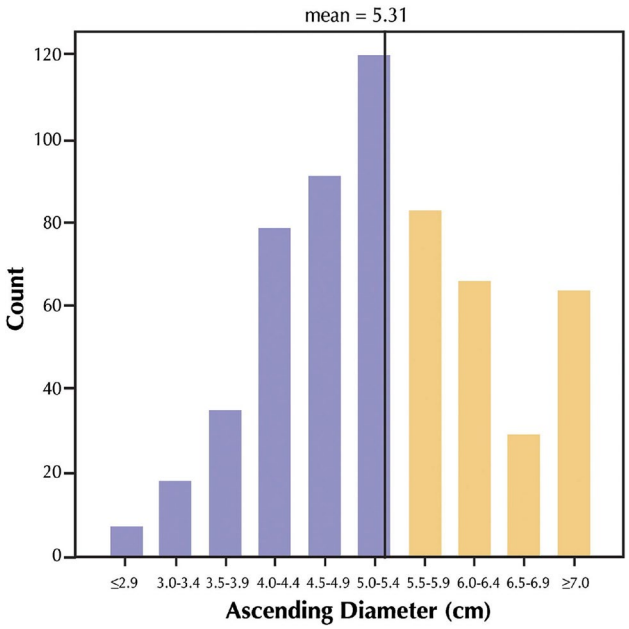

Fig. 4 Distribution of aortic size at time of presentation with Type A aortic dissection (cm). Purple bars indicated 59% of patients with diameters < 5.5 cm. (Reprinted with permission from Elefteriades and Farkas et al. [6])

stress generated can exceed the tensile strength of the aorta and lead to disastrous complications [42, 52].

The aortic size paradox

Although size is the most important risk factor, it has been demonstrated that it is not a sufficient marker to predict dissection. Among patients with acute type A aortic dissection registered in the International Registry of Acute Aortic Dissection (IRAD), Pape et al. found that the aortic diameter at presentation was < 5.5 cm in the majority of cases, with 40% presenting with a diameter < 5.0 cm. The mean diameter was 5.3 cm and the median was 5.0 cm with a wide distribution (2–10 cm) [53] (Fig. 4). Nearly 60% of patients had diameters less than 5.5 cm, which is the current threshold for elective repair. Interestingly, 51% of patients had none of the known risk factors (hypertension, Marfan syndrome, or BAV) for aortic dissection. Therefore, more risk predictors are needed to further shape the guidelines of management [6, 24].

However, this database faces the limitation of not taking the population at risk into account, by obtaining information from a referral hospital basis rather than a community population basis, with consequent inherent potential for misleading statistics. Further analysis was conducted to calculate the relative risk of aortic dissection at sizes < 5.5 cm, analyzing both the number of occurring dissections (numerator) and the population at risk at each aortic size (denominator), confirming that although dissections do occur at small sizes, patients with large aortas are at a 6000-fold higher risk of experiencing aortic dissection (Fig. 5). Thus, we can say that the aortic size paradox was resolved by extra-IRAD population base information, and traditional criteria for intervention are vindicated [54, 55].

Biomarker void

There is a need for useful serologic biomarkers that can detect TAA in asymptomatic patients and that can predict aortic dissection or rupture before, not after, they happen [56].

D-dimer level has been suggested as a biomarker, as it very effectively detects thrombus formation in the aortic lumen. D-dimer is extremely sensitive, and we strongly recommend that it be used liberally in emergency department. However, D-dimer is very nonspecific, and many diseases

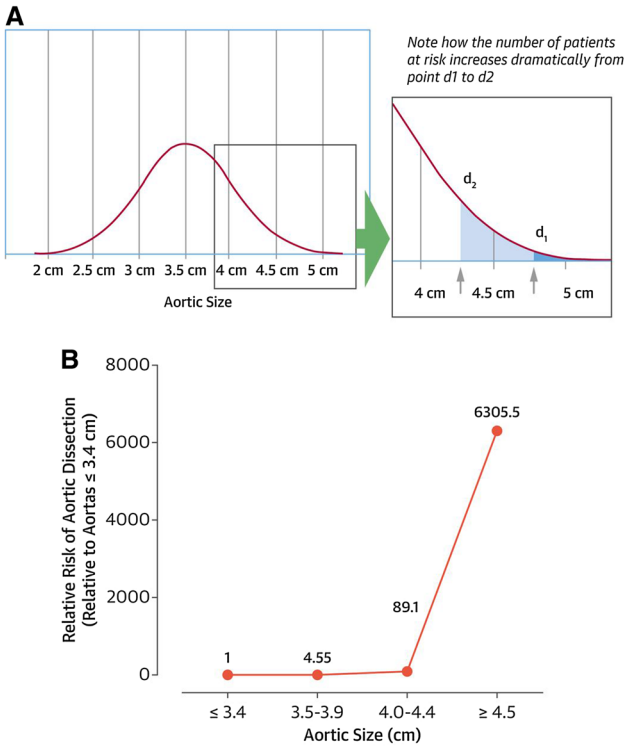

Fig. 5 The international registry of acute aortic dissection (IRAD) demonstration of the "paradox" that many aortic dissections occur at small aortic sizes exemplifies this issue. **a** The population at risk increases dramatically moving leftward from the right "tail" of the bell curve. At small aortic sizes, a huge population is at risk; therefore, although dissections do occur, the relative risk is very low compared with the huge "at-risk" population. **b** The relative risk is > 6000-fold higher for large aortas than for small ones. This vindicates traditional intervention criteria. (Panel **a**—modified with permission from Reprinted with permission from Elefteriades and Farkas [6]. Panel **b**—reprinted with permission from Paruchuri et al. [54])

can increase its level in the blood [57]. Other serum markers, such as matrix metalloproteinases (MMPs), have been advocated because they can degrade extracellular matrix proteins and have been found to play a significant role in the pathogenesis of aneurysms [58]. However, due to paucity of evidence regarding MMPs, they cannot yet be implemented in clinical practice. Other biomarkers such as cytokines, lipoproteins, homocysteine and TGF-β, have been suggested as well, but none of these have been proven reliable, and further studies are needed [56, 59].

Currently, and with recent advances in molecular imaging, there has been an increased focus on other imaging modalities for TAA, including PET and SPECT, which have the potential for clinical translation and application [60]. Sakalihasan et al. have shown that the PET scans "light up" in active vulnerable aneurysms; this may prove to be a reliable predictor of impending rupture [61].

Indications for surgical repair

Major cardiovascular society guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), Society of Thoracic Surgery (STS) and the American Association for Thoracic Surgery (AATS) recommend the repair for all symptomatic TAA (ruptured, dissected, causing pain). In contrast, repair of asymptomatic TAAs is not recommended until the risk of rupture or other complications exceeds the risks associated with repair [62–66].

As mentioned, the aorta loses its distensibility at a size of 6 cm (vide supra), so it is prudent to consider elective repair before it reaches this dangerous size. Elective repair of ascending TAA is recommended for aortic diameter > 5.5 cm, and elective repair of descending TAA is recommended for a diameter > 6.5 cm [42, 43, 50]. Clearly, these are not absolute measures and should be personalized according to many factors, such as the patient's body size, family history of aortic dissection, rapid aneurysmal growth (> 5 mm/year) and general comorbidities.

Taking body size into account, smaller sized patients should have different thresholds for repair. Studies have suggested using an indexing method to help correct for body size. Using that index, elective ascending aortic repair is recommended before the aortic size index (aortic diameter [cm] divided by body surface area [m]) reaches 2.75 cm/m [24]. Kälsch found out that BSA is an independent factor associated with increased aortic diameter and suggested a cut-off point for aneurysmal aortic diameter at the 95th percentile [67]. Another method to account for body size suggests that, for cases of Marfan syndrome, it may be reasonable to perform elective aortic root replacement for patients with an ascending aortic area (cm^2) to height (m) ratio of 10 [68].

The presence of genetic or familial conditions such as Marfan syndrome should modify the indications for elective repair. For asymptomatic patients with Marfan syndrome or other syndromic TAAs, elective repair is warranted for aortic root diameter ≥ 5.0 cm. Repair at a diameter < 5.0 cm is suggested for patients with progressive aortic incompetence, rapid expansion by > 5 mm/year, or family history of dissection or rupture [62, 63, 66]. For more aggressive syndromic TAAD such as Loeys–Dietz syndrome, repair is considered at a diameter ≥ 4.5 cm [69].

For asymptomatic patients with BAV, repair is warranted at a diameter > 5.5 cm but for those with a family history of dissection or rapid expansion, repair is warranted at a smaller diameter (from 5 to 5.5 cm) [62, 70]. Repair at an even smaller diameter (> 4.5 cm) can be considered in those with severe aortic stenosis or regurgitation [71]. A summary of indications for repair can be found in (Fig. 1). A very recent study has shown vividly the devastating prognosis once a first dissection has occurred in a family: The odds ration (OR) for dissection in other family members with

TAA increases 2.7-fold. In such a scenario, prophylactic aortic replacement maybe warranted regardless of the size of the aneurysm [72].

Open or endovascular repair?

Thoracic aneurysm repair was first performed in the 1950s [73], and since then, surgical techniques have evolved with remarkable survival rates [74]. The importance of determining the diameter criteria for repair emerges from the huge difference in outcome between elective and emergent repair. Emergent repair is associated with higher perioperative morbidity and mortality, with studies showing up to 44% 30-day mortality in patients with severe medical comorbidities [75]. On the other hand, elective repair in experienced centers can produce much better outcomes. In a recent study with 3309 patients, Coselli et al. estimated that the postoperative survival was 83.5 ± 0.7% at 1 year, 63.6 ± 0.9% at 5 years, 36.8 ± 1.0% at 10 years, and 18.3 ± 0.9% at 15 years [76].

Ascending TAA is managed with an open surgical approach with median-sternotomy using cardiopulmonary bypass, often requiring aortic root replacement and coronary artery reimplantation [77]. For patients with trileaflet aortic valve or with BAV, the valve can often be spared or repaired at the time of surgery [78]. There has been recent debate regarding whether replacement of smaller diameter aortas should be performed simultaneously in patients who are already undergoing aortic valve replacement or who have risk factors for complications (eg: family history of dissection) [79, 80].

Descending TAA can be repaired with an open or endovascular approach [81], or a combination of the two (hybrid repair) [82]. The endovascular approach has been associated with less perioperative morbidity and mortality at the "expense" of less durability [83, 84]. The choice of approach ought to be personalized according to the patient's aneurysm etiology and preoperative risk profile [62].

At this time, there is no standard treatment for endovascular repair of ascending aortic aneurysms but there have been several trials to develop a single endovascular device for simultaneous aortic valve replacement and ascending aortic repair [85].

Medical treatment

Current practice guidelines for patients who do not meet the criteria for surgical correction include cardiovascular risk reduction with smoking cessation, antihypertensive therapy, and the use of statins and beta blockers [86–88]. Nevertheless, there has been conflicting evidence about the efficacy of medical treatment of TAAs.

Regarding beta blockers, they decrease the inotropic state of the heart and the shear stress and impact force of blood ejected into the aorta. Although their use has gathered some experimental support only in Marfan patients, [89–91] it is biologically plausible to attempt using them in non-Marfan patients as well. For patients with BAV, guidelines on the treatment of valvular disease suggest ß-blockers for those with an ascending TAA (diameter greater than 4.0 cm) who are not candidates for surgical correction and who do not have aortic regurgitation (Class IIa) [71]. Recently, objective analyses have strongly questioned the benefits ß-blockers [92].

Other antihypertensive medications have been studied as well. Experimental research has shown the role of the renin–angiotensin–aldosterone system (RAAS) in aneurysm formation [93–95]. However, conflicting evidence has been found regarding the use of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi) in patients with TAA [92].

It was found that ACEi may decrease SMC apoptosis, [96] and ARBs may be of benefit in decreasing aneurysm expansion by antagonizing TGF-ß [97, 98]. Lacro et al. found promising results indicating that Angiotensin II can increase the expression of MMP-2 via AT1 receptor and ERK1/2 signaling pathways in human SMCs and suggested that antagonists of AT1R and ERK1/2 may be useful for treating TAAs [99].

In a small cohort study with 18 young patients with Marfan syndrome and aortic root dilation, ARB therapy significantly reduced the rate of aortic expansion [from 3.54 ± 2.87 mm/year during previous medical therapy to 0.46 ± 0.62 mm/year during ARB therapy ($P < 0.001$)] [98]. Another randomized trial reported no benefit of an ARB (losartan) over a beta-blocker (atenolol) with respect to the rate of aortic-root dilation in patients with Marfan syndrome who were followed over a 3 years period [100]. One way to look at this study is that losartan is as effective as atenolol in the treatment of patients with Marfan syndrome, yet this interpretation is based on the premise that beta blockers are an effective treatment to start with.

Statins have been mostly studied in the context of AAA [101]. Statin therapy may provide a protective effect in patients with AAA by inhibiting matrix metalloproteinases (MMPs) and plasminogen activator [102]. In one retrospective review of TAA patients, mortality rates were lower among those taking statins compared with those who were not (20 versus 3%) [84]. It is fair to say that TAA currently lacks well-proven suppressive medical therapy that can halt aneurysm growth and prevent rupture. Patients' lives are only saved by diagnosis, monitoring and timely surgical intervention.

Doxycycline has also been studied for AAA as an inhibitor of MMPs [101]. The non-invasive treatment of abdominal aortic aneurysm clinical trial (N-TA3CT) is

currently ongoing in the USA to investigate the role of doxycycline in AAA treatment.

Conclusion

Thoracic aortic aneurysm can be subtle in presentation until dreadful complications occur, which is why it can be termed as a "silent killer". TAAs act as two different diseases with complex pathogenesis involving different embryologic and molecular factors. TAA has been found to be a familial disease with a predominantly autosomal dominant inheritance. Faster growth rates and poorer clinical outcomes have been noted in the female sex. There has been an increased clarification of the natural history of TAAs (expansion rates and size at rupture or dissection), however, we need better predictors, beyond absolute size, for the future. Until now, serum biomarkers are not reliable, therefore, imaging remains the means to diagnose and follow TAAs, selecting patients who are candidates for repair based on size and symptoms. Options of management include open or endovascular surgical repair, or conservative medical management. Substantial doubts persist regarding the efficacy of medical treatment. Although medical and surgical science has made substantial strides in "Reading the playbook" of TAA, much more remains to be elucidated regarding this indolent but virulent disease [103, 104].

Compliance with ethical standards

Conflict of interest All authors declares that they have no conflict of interest.

Sources of funding None.

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