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Review

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Risk of aortic dissection in patients with ascending aorta aneurysm: a new biological, morphological, and biomechanical network behind the aortic diameter

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Abstract

Thoracic aortic aneurysm represents a deadly condition, particularly when it evolves into rupture and dissection. Proper surgical timing is the key to positively influencing the survival of patients with this pathology. According to the most recent guidelines, ascending aorta size ≥ 55 mm and a rate of growth ≥ 0.5 cm per year are the most important factors for surgical indication. Nevertheless, a lot of evidence show that aortic ruptures and dissections might occur also in small size ascending aorta. In this review, we sought to analyze a new biological and morphological network behind the aortic diameter that need to be considered in order to identify the portion of patients with thoracic aortic aneurysm who are at increased risk of aortic complications, despite current aortic guidelines not advising surgical intervention in this group.

Keywords: Ascending aorta aneurysm; ascending aorta size; aortic dissection; genetic risk factors; morphological aspects; surgical indication for aortic repair

INTRODUCTION

The two most widespread diseases of the thoracic aorta are aneurysms (TAA) and dissections (TAD)[1]. In the United States, TAA is the 18th most common cause of death. TAA has an incidence rate of 10 cases per 100,000 patients per year and a prevalence of 0.16% to 0.34% in the general population[2,3]. Men are more like to have TAA compared to women; however, women tend to develop worse clinical outcomes and have an increased risk of TAD[4]. It is important to closely monitor TAA patients. At the same time, optimal surgical timing is crucial to improve survival. Cardiac surgery aims to prevent TAD or rupture of the aneurysm[5]. As a predictor of adverse aneurysmal outcomes, aortic diameter is still the most used criteria[6-9]. However, several studies have found that in a particular group of patients, complications may occur at smaller aortic sizes than we would predict[10-12]. In our opinion, it is necessary to investigate other parameters that better identify these high risk TAA patients for which earlier surgical intervention is necessary and at smaller aortic size[13]. The aim of this review is to analyze the biological, morphological, and biomechanical network as a potential useful tool to detect TAA subjects at higher risk of complications behind the diameter.

Role of the ascending aorta diameter in predicting acute aortic dissection

The in-hospital mortality rate of TAD is nearly 30%[14]. Until now, the only prevention is monitoring of the ascending aorta dilation and performing prophylactic surgical replacement. Although hypertension and specific genetic syndromes are well known risk factors of TAD, it is still difficult to predict this deadly condition with accuracy[15,16]. Current guidelines recommended surgery when the ascending aorta size reaches 5.5 cm for non-syndromic patients and 4.5 cm in syndromic patients[17]. However, data from the International Registry of Acute Aortic Dissections[18] showed that aortas could dissect at smaller sizes than that advocated in the guidelines. Among 591 type A TAD, 59% occurred at sizes less than 5.5 cm and 40% occurred at < 5.0 cm. These data correspond with our center's experience. Among 326 patients treated for Type A TAD in our Cardiac Surgery Department from April 2005 to March 2018, 212 patients had a maximal diameter less than 5.5 cm[19]. Svensson *et al.*[20] showed that 12.5% of 40 bicuspid aortic valve (BAV) patients with TAD had aortic sizes < 5 cm at the time of surgery. The same aortic diameter has been detected in Marfan population. In addition, several studies have showed that the aortic diameter before TAD is much smaller than after TAD. In experimental studies of human and porcine cadaver specimens, Williams *et al.*[21] showed that the onset of TAD caused a significant increasing of the aortic diameter (140%) in relationship to the hydrostatic pressure and to the percentage of the dissected aortic wall. Neri *et al.*[22] calculated pre-dissection aortic size from surgical specimens withdrawn from 220 individuals who underwent surgery for acute type A TAD. Using a specific explant technique, they performed cylinders of fresh aortic tissue and measured the inner layer of the true aortic lumen in the absence of perfusion pressure. The median ascending aorta size was 41.4 mm for the entire cohort. These authors concluded that that only 10% of the study population had aneurysms before TAD onset. It is very important to remember that looking only at the number of people operated for TAD with small diameter is not sufficient to determine the relative risk of TAD at sizes < 5.5 cm. That number has to be put into context by knowing how many people at those smaller diameters exist so that an actual risk can be determined. Accordingly, Paruchuri *et al.*[23] calculated the relative risk of TAD at sizes < 5.5 cm by analyzing both the number of occurring dissections (numerator) and the population at risk at each aortic size (denominator). They found that in the general population a large percentage of subjects (79.2%) had an aortic diameter < 3.5 cm and only the 0.22% of subjects had an aortic diameter ≥ 4.5 cm. Yet, while the majority of TAD may occur at aortic diameters below the surgical threshold, it is also true that the vast majority of aortas within this population are considerably smaller than this threshold. Thus, the true statistical risk of TAD at small aortic diameters may well be negligible given the anticipated enormous patient pool in the small aortic size range. However, there is a group of patients in which TAD may occur at smaller aortic sizes than the guidelines predicted. This questions the true prognostic value of the absolute aortic diameter and emphasizes the need for optimal timing of surgical intervention, especially in those patients under surveillance who do not meet

established size criteria for surgery but may still be at significant risk of TAD. Accordingly, Davies *et al.*[24] showed in 2006 that indexing absolute aortic diameter to anthropometric measurements provides individualized risk classification in patients with TAA. These authors introduced the concept of aortic size index (ASI), defined as aortic size/body surface area, as a predictor of aortic dissection, rupture, and death. In particular, they termed low risk patients as those with an ASI ≤ 2.05 cm/m^2. Moreover, weight fluctuates throughout the lifespan and can be deliberately influenced. Unlike weight, height does not change during adult life. Therefore, height-based relative aortic measures may be a more reliable long-term predictor of risk. For this reason, Zafar *et al.*[25] in 2018 introduced the concept of aortic height index (AHI), defined as aortic size/height; and they assessed that AHI is as good as the ASI for risk stratification. They defined low risk patients those with an AHI ≤ 2.43 cm/m. In addition, Acharya *et al.*[26] introduced the concept of *aortic area/height ratio* (IAAs) that was calculated indexing the aortic area (π x aortic radius^2) to the patient height and correlating it with the absolute aortic diameter. According these authors, a IAAs > 10 cm^2/m could be considered the limit for early and proactive surgery to prevent TAD.

New evidences behind the diameter

Beside the aortic diameter, there is need to analyze other aspect of TAA that could better identify patients in which aortic complications might occur at smaller aortic sizes than guidelines predict. In our opinion, there are specific biological, morphological, and biomechanical markers of early rupture and dissection that must be investigated in order to prevent deadly complication. In particular, in this review we focused our attention on: (1) specific gene mutations that confer an increased risk for adverse outcomes, even at small or normal aortic size; (2) histomorphological change and the quality of the aortic wall at the time of the operation; (3) morphological markers of rupture and dissection in aortic root and ascending aorta; and (4) flow abnormalities and the aortic wall shear stress.

Genetic features of thoracic aorta aneurysms

Recent progress in the understanding the pathophysiology of TAA have produced evidence suggesting different molecular pathways and their genetic variants as potentiaL biomarkers of TAD, which might be applied into TAA clinical management in order to prevent deadly complications[27-29]. These specific gene mutations are reported to induce an increased risk for adverse outcomes, even at small or normal aortic size[30,31]. The most interesting aspect is that this genetic risk is characteristic not only of syndromic patients but also of non-syndromic patients [Figure 1]. The three main genetic syndrome associated with TAA are: Marfan syndrome[32] (mutations in the fibrillin-1 gene) [Figure 2]; Ehlers-Danlos syndrome[33] (mutations in COL3A1), and Loeys-Dietz syndrome (mutations in TGFβR1 or TGFβR2)[34]. It has been recognized that aortic dissection in Marfan syndrome patients can occur also at smaller sizes, therefore we recommend early intervention. The non-syndromic TAA are divided into sporadic TAA and familial TAA. In familial TAA, one or more family members are affected by TAA. Sporadic TAA is characterized by sudden onset and no family history of aneurysm. On the other hands, many genes have been associated to familial TAA[35] [Figure 3]. Interestingly, recent evidences showed that the immune system and inflammatory related genes have an important role in the onset and progression of sporadic TAAs even at small aortic sizes. Among these inflammatory mediators, the Toll-like receptor 4 (TLR-4) is one of the most important player[36-38]. The activation of TLR-4-mediated signaling pathway, both on endothelial cells (ED) and vascular smooth muscle cells (VSMCs)[39,40], could determine the deregulation of angiotensin converting enzyme (ACE)[41-43], nitric oxide (NO)[44], metalloproteinases (MMP)[45-48] associated with endothelium dysfunction, extracellular matrix remodeling, and chronic inflammation causing medial degeneration in sporadic TAA [Figure 4]. Evans *et al.*[49] discovered that the interaction between TLR-4 and NO is one of the most important mechanisms by which aorta-derived mesenchymal progenitor cells activate the immune and inflammatory cells. The increasing inflammation induces sporadic TAA onset and progression. Li *et al.*[50] reported the importance of TLR-4-mediated signaling pathway in regulating the metalloproteinases-9 (MMP-9) expression in human aortic smooth muscle cells. Increased MMP-2 and

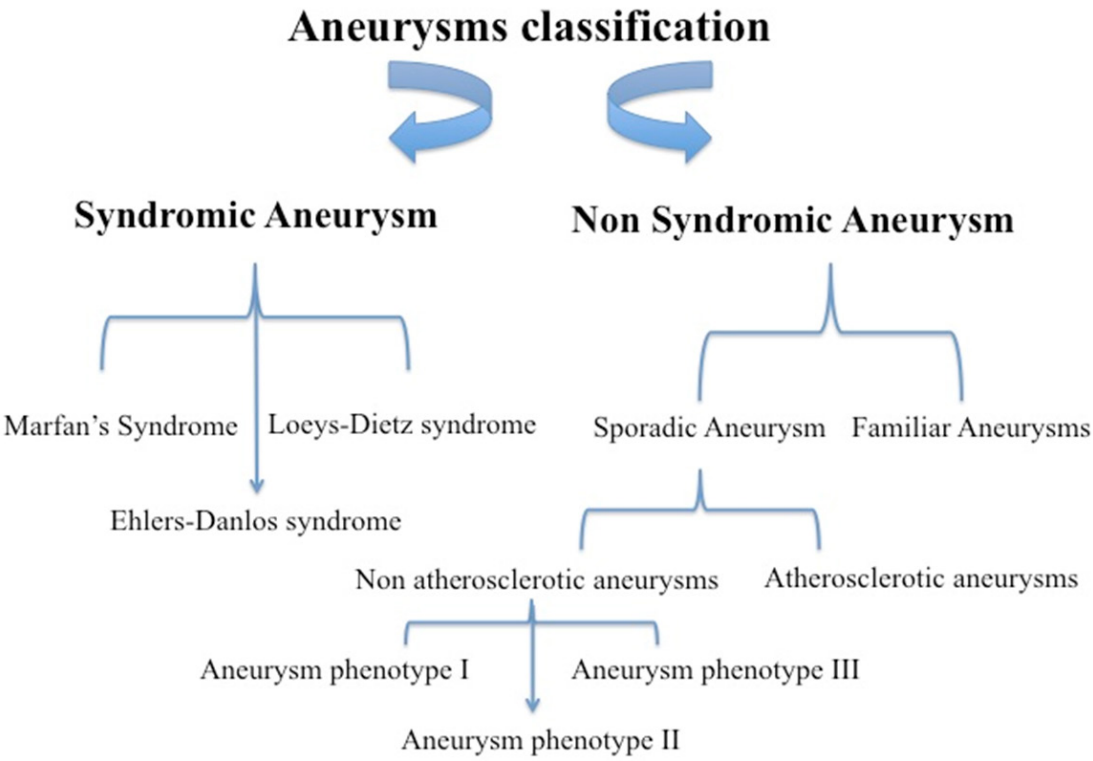

Figure 1. Aneurysm classification

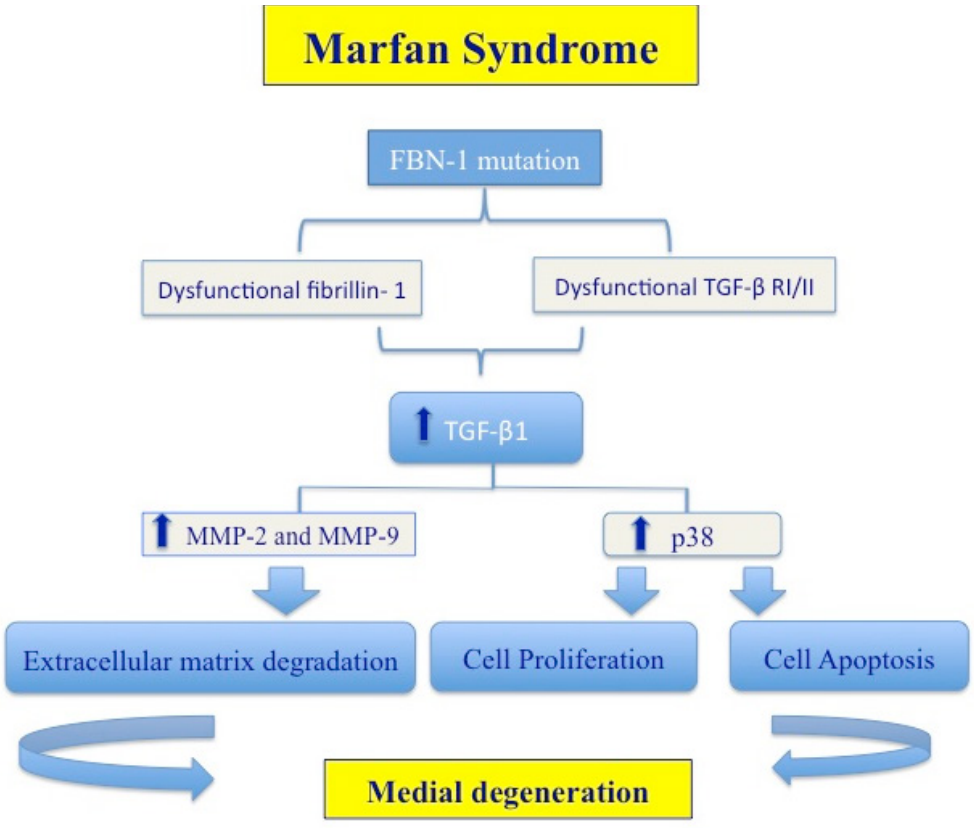

Figure 2. Marfan syndrome pathogenesis and related genes

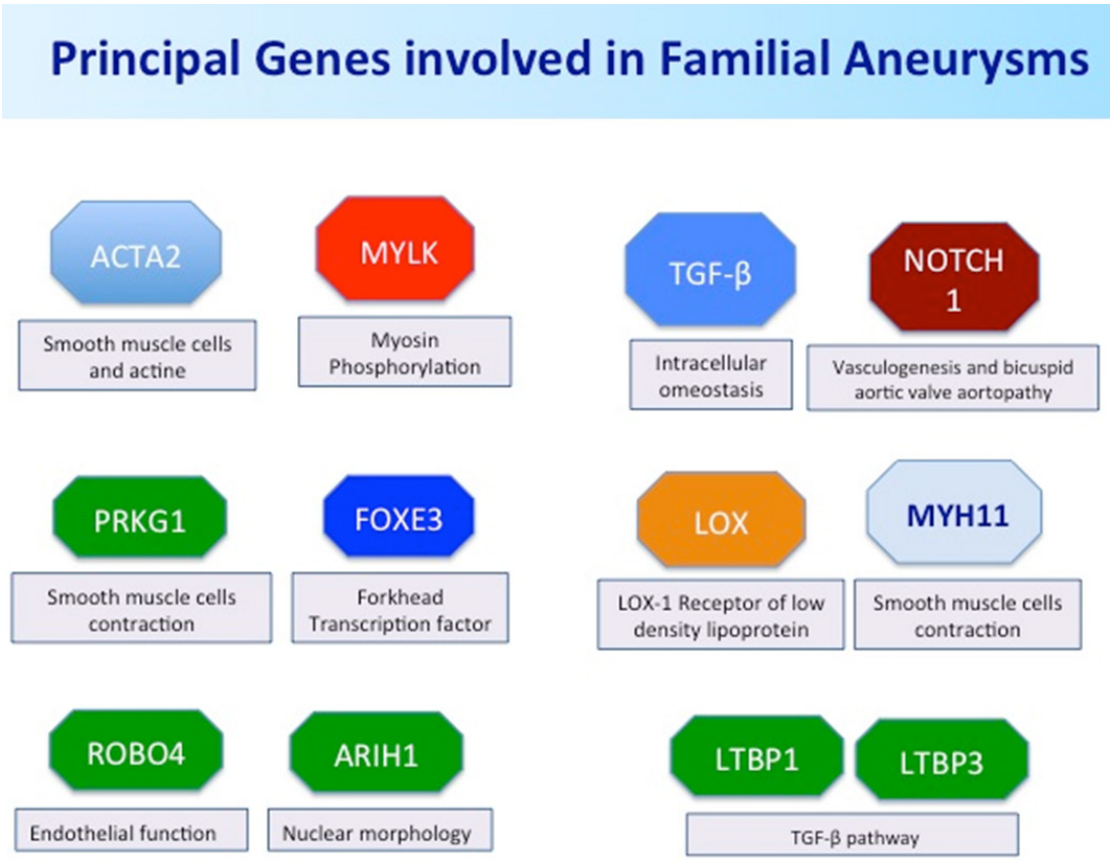

Figure 3. Principal genes involved in familial aneurysms

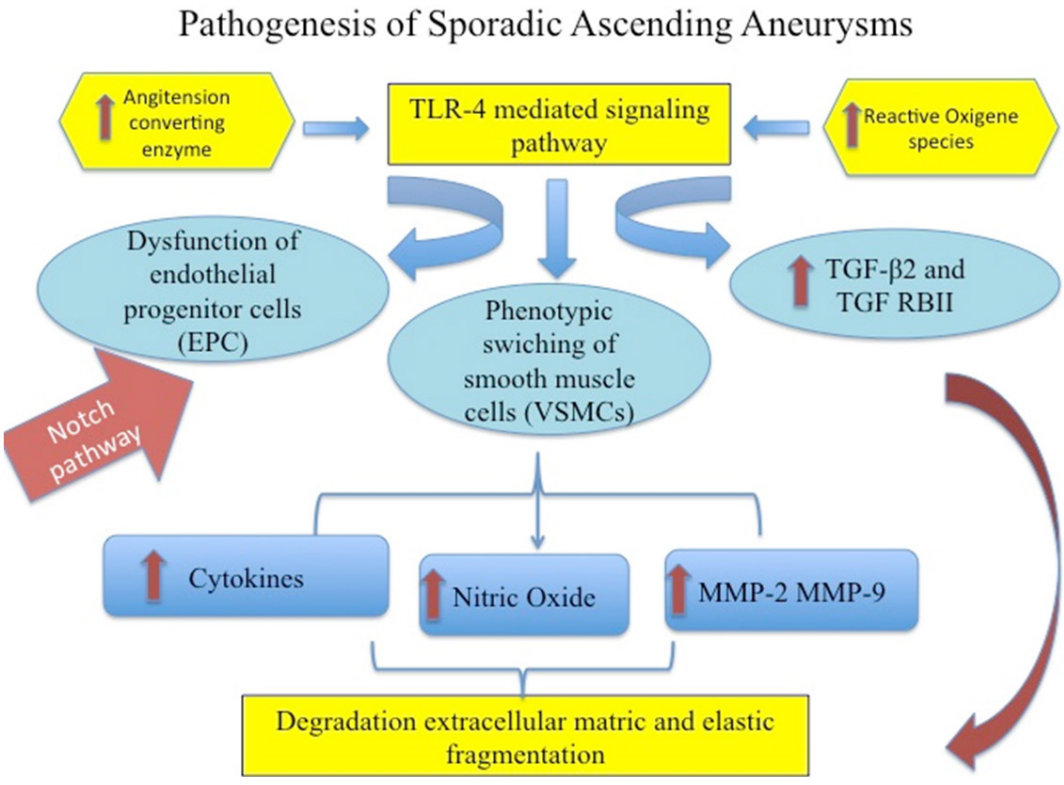

Figure 4. Sporadic ascending aneurysm pathogenesis and related genes

MMP-9 expression induced an increase in proteolysis in TAA and TAD as compared to the normal aorta. Finally, the TLR-4-mediated pathways seems to influence the activity of two important genes involved in the onset and progression of TAA: transforming growth factor-β (TGF-β)[51] and Notch[52,53]. Different roles of TGF-β pathways in tissue remodeling mechanisms have been reported in both syndromic and sporadic TAA. The activation of TGF-β results in an increase in extracellular matrix degradation through MMPs activation and multiple cytokines upregulation including interleukin-10. Additionally, a loss of function of the TGF-β receptors (TGFBR1 and TGFBR2) has been associated with both familial syndromic and non-syndromic TAAs. Furthermore, mutations in Notch gene homolog 1 (Notch1) and Notch1 pathway, typically associated to TAA patients with BAV, seem to regulate TGF-β cascade. In the aorta, the Notch pathway appears to regulate the differentiation of vascular smooth muscle cells, the most representative cells involved in aneurysmatic pathology. Finally, a very recent study[54] revealed the important role of the phosphodiesterase 5A (PDE5) gene mutation in human aorta and thoracic aortic aneurysms. Affected aortas showed lower levels of all the PDE5A isoforms compared to control aortas. Because PDE5 is expressed early during human aorta development, the study revealed an association between PDE5 gene mutation and anomalous aortic development.

Impact of histopathological changes in thoracic aortic diseases and genetic biomarkers of risk

One of the most important aspect to consider in order to optimize surgical indications in TAD is the severity of medial degeneration of the aortic media and, consequently, the fragility of the aortic wall. Previously, we observed that the severity of aortic media degeneration in TAD and TAAs are not related to the diameter of the aneurysm[55-58]. In atherosclerotic degenerative aneurysms (ADA), the grade of medial degenerative lesions was balanced to the grade of substitutive medial fibrosis. In contrast, in non-atherosclerotic degenerative aneurysm (NADA) and TAD, medial fibrosis was absent or of grade I. The relative absence of restorative fibrosis should predispose patients to aortic rupture. In particular, our study showed that TAD has the same histological and immunohistochemical features as NADA phenotype III: elevated medial cystic degeneration without replacement fibrosis, with plurifocal medial apoptosis, and strong collagenase concentration. Additionally, NADA phenotype III showed a very fragile aortic wall at the time of the operation. The morphological identity of the medial lesions observed both in NADA phenotype III and in the samples of patients with TAD, could be considered the precursor - and consequently the optimal biomarker - of the dissection, regardless of the diameter of the aneurysm or valve disorder. This evidence agree with recent studies that showed that up-regulation of metalloproteinases, related to inflammatory processes or genetic aspects, might affect the formation of TAA and TADs[59].

In order to identify patients with small to moderate sized aneurysms and at high risk of developing TAD, Balistreri *et al.*[55] investigated the genetic biomarkers specific for TAA phenotype III. Investigations were made into the potential role of 10 common and functional single nucleotide polymorphisms (SNPs) of the following genes: CCR5 (C-C chemokine receptor 5), TLR4 (toll like receptor 4), MMP-9 (metalloproteinase-9), MMP-2 (metalloproteinase-2), ACE (angiotensin-converting enzyme), and eNOS (endothelial nitric oxide synthase). Indeed, highly significant associations were observed between -786T/C eNOS, D/I ACE, and -735C/T MMP-2 SNPs and the risk of TAD. The presence of these genotypes may induce the development of this disease through different mechanisms [Figure 5]. A relationship between ACE gene SNPs and arterial hypertension has been demonstrated in different populations. At the same time, chronic systemic hypertension is considered to be the most common predisposing factor for TAD, with unfavorable effects on the vascular system such as cellular apoptosis, the production of reactive oxygen species, and vascular matrix MMP synthesis (particularly of MMP-2 and -9). In addition, it is known that molecules such as NO are involved in several pathways for the maintenance and regulation of a healthy intimal endothelium. Different SNPs of the eNOS enzyme have been found to vary in the expression and tissue levels of NO. In particular, -786 T/C eNOS reduced the transcriptional activity by around 50%, leading to a reduction in eNOS tissue endothelium levels that may result in reduced NO

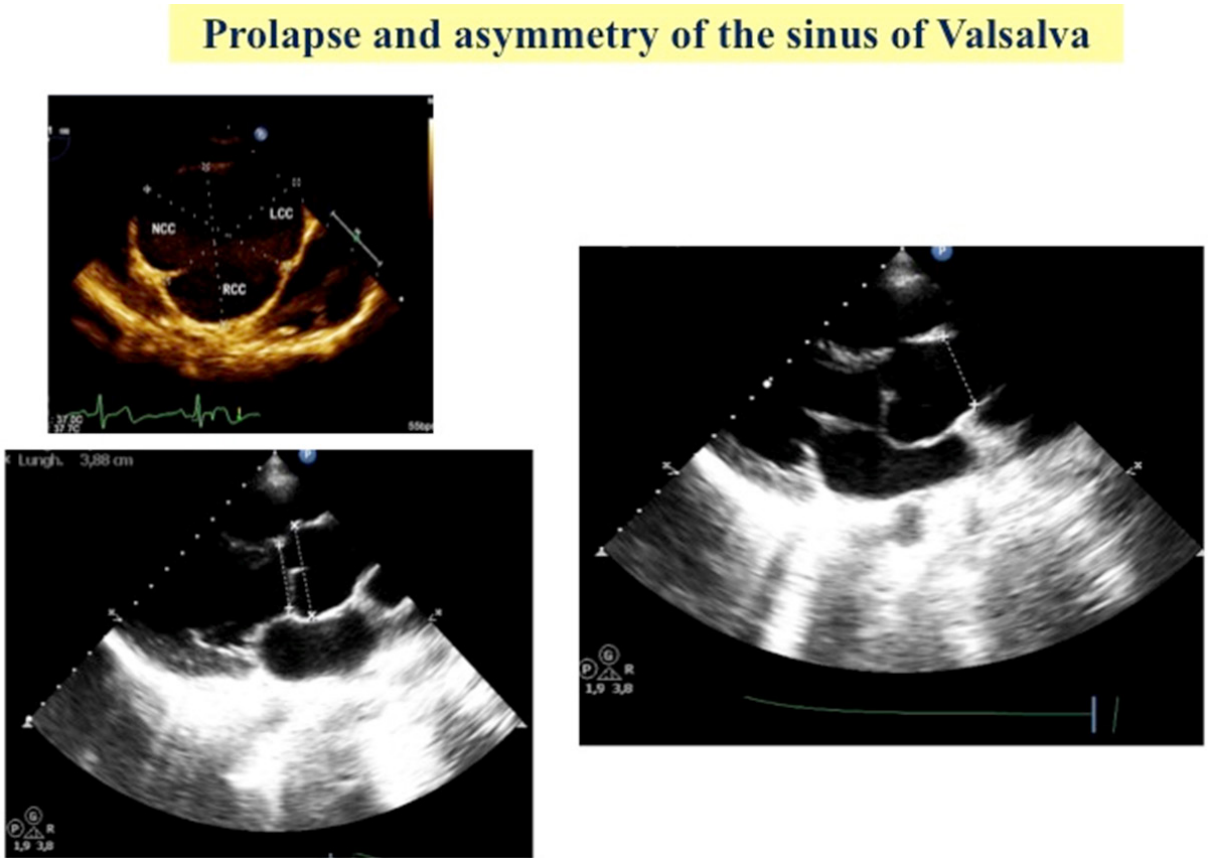

Figure 5. Prolapse and asymmetry of the sinus of Valsalva

production and consequently endothelial dysfunction and activation of the stretch pathway with the release of molecules, such as MMPs. Furthermore, a strong relationship between hypertension and increased and altered activity of MMPs (particularly MMP-2 and -9) and aortic wall remodeling has been reported. Among these, -735C7T MMP-2 SNP is associated with a threefold increase in MMP-2 levels and seem to be associated with hypertension, aortic remodeling, and aortic fragility, and consequently with aortic diseases such as aneurysm and dissection. Hence, the determination of D/D ACE, -735 T/T MMP-2, and -786 T/T eNOS genotypes might contribute to a prediction of the development of TAD in patients with S-TAA, independent of the aneurysm size.

Morphological markers of rupture and dissection in ascending aorta aneurysm

Beside the genetic and morphological aspect, in our opinion, there are specific morphological markers of rupture and dissection in TAA that is necessary to consider for surgical indication beyond the diameter. This reflection arises from our single operator surgical experience. From December 2003 to January 2020, a surgeon in our Cardiac Unit performed 320 Bentall de Bono operations (254 isolated procedure; 66 cases Bentall procedure associated with other cardiac surgery). We treated both sporadic aneurysms (287 patients) and syndromic aneurysms (33 patients). The in-hospital mortality for isolated procedure was 1% (from 2003 to 2014) and 0.8% (from 2015 to 2020). The in-hospital mortality for combined procedure was 3% (from 2003 to 2014) and 2.8% (from 2015 to 2020). In all these cases, our surgical indication was based not only on the diameter (≥ 5.0 cm for sporadic TAA and ≥ 4.5 for syndromic TAA) but also on certain morphological aspects such us: prolapse and asymmetry of sinus of Valsalva (mostly the non-coronary sinus) [Figure 5]; asymmetric ascending aorta dilatation [Figure 6]; aortic-ventricle disjunction [Figure 7]; arising of the epiaortic vessels from the convexity of the ascending aorta; ascending aorta length[60]; aortic volume.

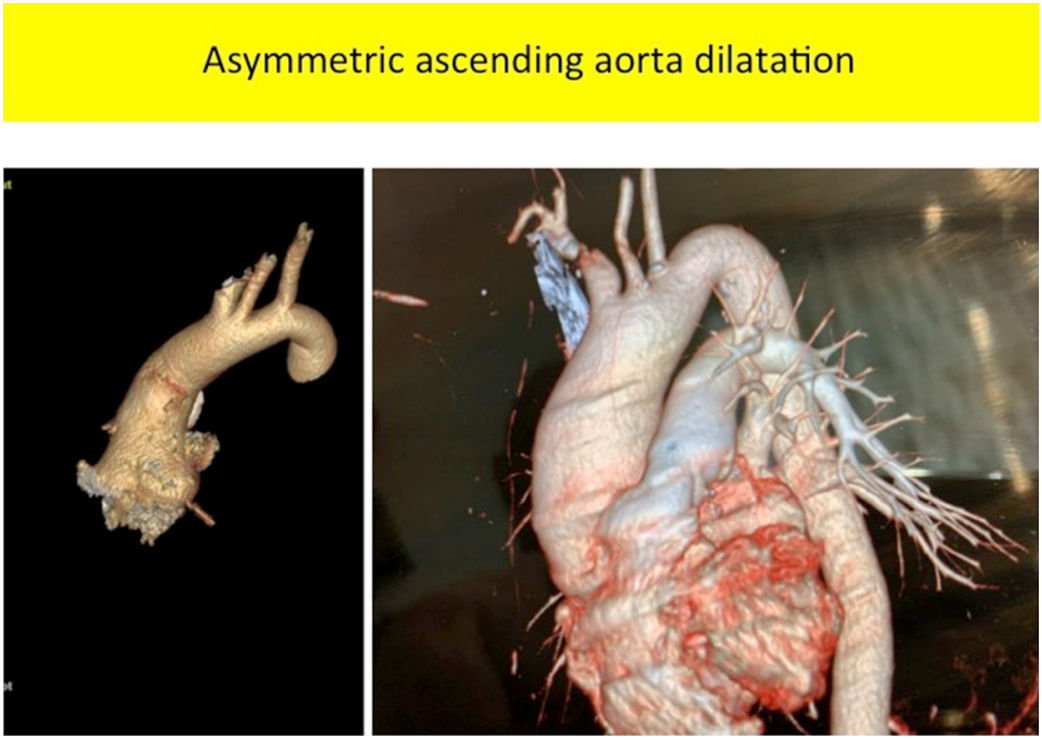

Figure 6. Asymmetric ascending aorta dilatation

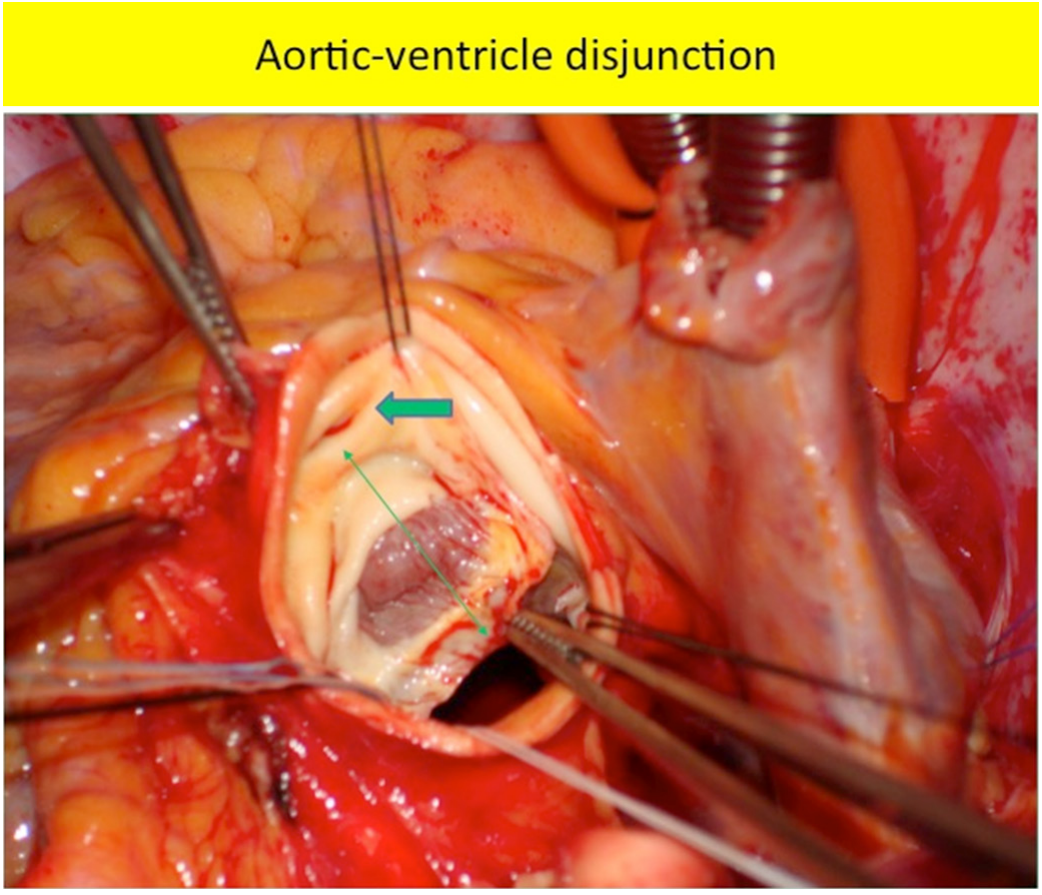

Figure 7. Aortic-ventricle disjunction

In a recent and interesting paper, Wu *et al.*[61] focused the attention on the longitudinal changes of the TAA. They measured the *ascending aortic length* (AAL) from the aortic annulus to the origin of the innominate artery using CT scan images. Interestingly, an AAL of ≥ 13 cm was associated with almost 5-fold higher average of aortic adverse events. In addition, Heuts *et al.*[62] assessed that measurements of aortic volume and length have superior diagnostic accuracy compared with the maximal diameter and could improve the timely identification of patients at risk for TAD.

However, we are aware that to validate our opinion and to confirm the importance of these morphological parameter for surgical indication, a multicentric study is needed.

Flow abnormalities and shear stress

Finally, other important aspects to consider are flow abnormalities and wall shear stress (WSS) in TAA. Beside the genetic aspects, hemodynamic factors play a crucial role in TAA onset and progression through the endothelial dysfunction[63]. Endothelial cells, in fact, line the lumen of blood vessels and they are at the interface between hemodynamic forces and vascular wall biology. Endothelial cells transduce mechanical and biological signals from blood flow into intracellular signals cascades through a process called mechanotransduction[64] which leads to inflammation and pathological conditions such as aneurysm and dissection. The endothelial dysfunction induces a switch in phenotype of smooth muscle cells and fibroblasts. These cells start to synthesize metalloproteinases and inflammatory pathways involved in the elastic fragmentation and medial degeneration causing aneurysm and finally dissection.

Several studies have been focused on WSS related to BAV patients with aortopathy. Barker *et al.*[65] found that WSS in the ascending aorta of patients with BAV was significantly elevated compared to healthy volunteers. Different phenotypes of BAV have been described according the cusps fusion (right-left; non-coronary left; non-coronary right) associated with different grade of WSS. In particular, BAV with fusion of the right and non-coronary cusps (non-coronary right phenotype) seems to have to higher WSS and a greater risk of TAD[66]. Additionally, it is evident that the WSS distribution is different according the BAV phenotype. Mahadevia *et al.*[67] described elevated WSS in the right-anterior wall of the ascending aorta for right-left BAV phenotype, and right-posterior wall for non-coronary right BAV phenotype. In all cases of BAV associated with aortopathy, the WSS is higher at the greater curvature of the ascending aorta. Accordingly, Della Corte *et al.*[68] found that medial degeneration was more severe in this region. Furthermore, Guzzardi *et al.*[69] has shown a direct association between WSS and histological alteration of the aortic wall in TAA patients. BAV patients undergoing ascending aorta replacement had pre-operative WSS mapping. In particular, they showed high levels of TGFβ-1, MMP-1, MMP-2, and MMP-3 in high WSS regions causing severe elastic fiber degeneration and extracellular matrix degradation, two important mechanisms underlying TAA progression and TAD onset[70]. This may be the explanation why some patients with aortic size below current intervention criteria develop acute aortic complications.

CLINICAL PRACTICE

Many different options are available to be used as criteria for determining when to operate on patients with aortic aneurysm, but it remains to be seen which ones will be most predictive of TAD. The identification of TAA patients with a high risk of TAD is very difficult in clinical practice. In the evaluation of TAA patient, we thought that the quantification of the absolute aortic diameter is not enough to decide the optimal surgical timing. It is necessary to perform specific and multiple evaluations. First of all, the absolute aortic diameter to anthropometric measurements are needed to calculate the ASI, AHI, and IAAs. At the same time, it is necessary to perform an imaging analysis of the TAA to identify markers of rupture and dissection in the aortic root and ascending aorta (e.g., prolapse and asymmetry of sinus of Valsalva, asymmetric ascending aorta dilatation, aortic-ventricle disjunction, and arising of the epiaortic vessels from the convexity of the ascending aorta). Yet, it is necessary to evaluate the aortic length and the aortic

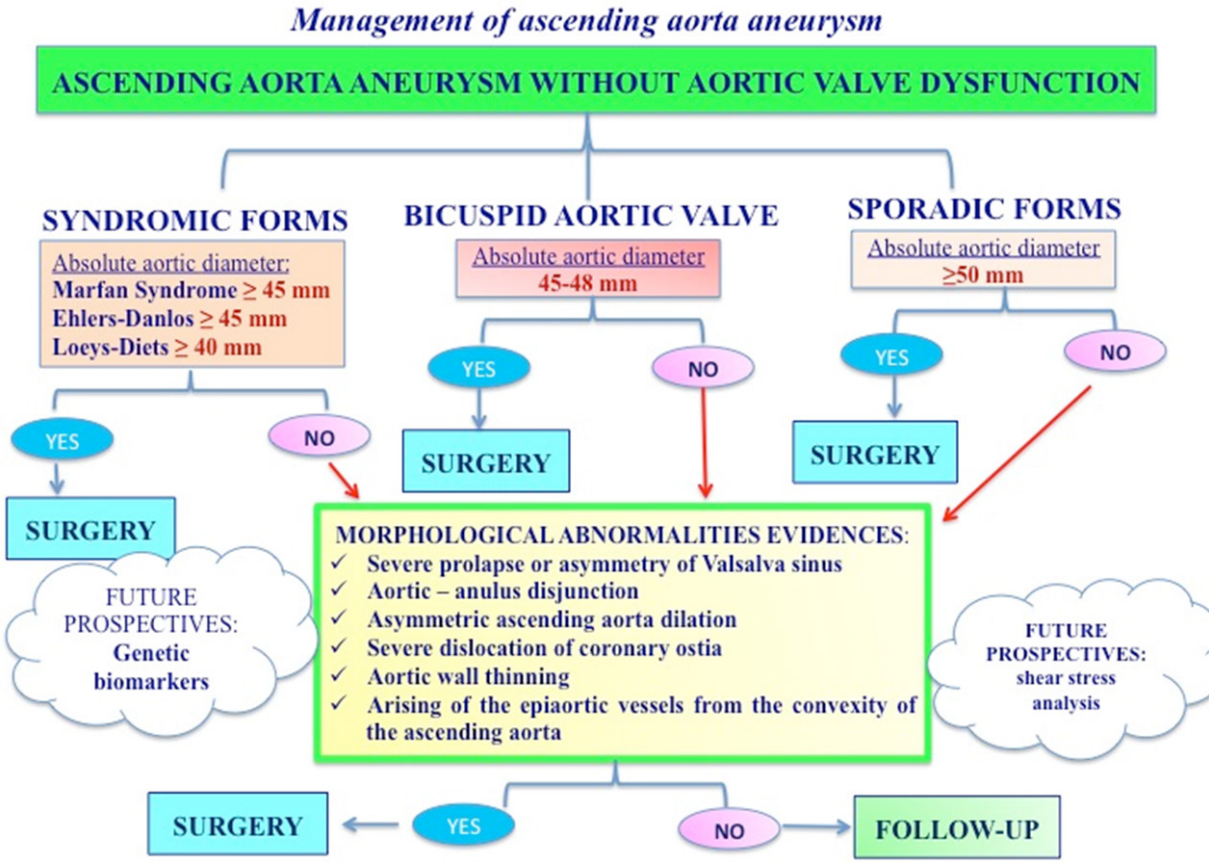

Figure 8. Management of patient with ascending aorta aneurysm without aortic valve dysfunction (Flow Chart). If surgery is indicated for the aortic valve disease, ascending aorta/ aortic root replacement must be performed according with morphological abnormalities despite the aortic size

volume. The morphological analysis could be integrated with a biomechanical evaluation using MRI or positron emission tomography. Finally, the patient evaluation must be completed performing a blood test in order to identify a particular genetic risk profile (*D/D ACE, -735 T/T MMP-2, or -786 T/T eNOS*) that could confer a particular phenotype of aneurysm (phenotype III) to non-syndromic patients and that phenotype evolves earlier to rupture or dissection despite he small diameter of the aorta. In these cases, surgeons should consider operating earlier and at smaller diameter [Figure 8]. Further studies comparing the predictive value of these many parameters would be necessary to help us decide which ones should be used in regular clinical practice.

CONCLUSION

The decision-making process of treatment in thoracic aortic aneurysms of the ascending aorta is complex, both as regards to the timing of the intervention and the treatment strategy. From the clinician's point of view, it is important to balance the risks of vigilant waiting with respect to preventive surgery and choosing a surgical treatment strategy that translates into the least number of early and late events. Preventive surgery of the aorta on the basis of the aortic size alone remains controversial among the patient population without known risk factors for dissection. Other markers, including histopathological phenotypes, genetic factors, morphological aspects, and flow abnormalities should be used as an appropriate surgical indication to prevent catastrophic complications.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Pisano C, Balistreri CR, Ruvolo G

Perfomal data acquisition, as well as provided administrative, technical, and material support: Nardi P, Altieri C, Bertoldo F, Buioni D, Ferrante MS, Asta L, Trombetti D

Availability of data and materials

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Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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