REVIEW

Bio-chemo-mechanics of the thoracic aorta

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Abstract

The pathophysiology of thoracic aortic aneurysm and dissection is poorly understood, despite high mortality. An evidence review was conducted to examine the biomechanical, chemical and genetic factors involved in thoracic aortic pathology. The composition of connective tissue and smooth muscle cells can mediate important mechanical properties that allow the thoracic aorta to withstand and transmit pressures. Genetic syndromes can affect connective tissue and signalling proteins that interrupt smooth muscle function, leading to tissue failure. There are complex interplaying factors that maintain thoracic aortic function in health and are disrupted in disease, signifying an area for extensive research.

Key Words

- aorta
- vascular vessel
- shear stress
- biomechanics

Introduction

Thoracic aortic aneurysms and dissections (TAAD) are relatively less common when compared with other cardiovascular diseases, but can result in significant mortality and morbidity if managed inappropriately (1). Mortality of untreated dissections can approach 50% if no intervention is initiated within 48 hours (2). Aneurysms can be classified according to type (saccularor fusiform) and location (thoracic, thoracoabdominal or abdominal). They can lead to rupture or dissection - however, it is important to note that the majority of dissections do not have a pre-existing aneurysm (3). There is a wide spectrum of thoracic aortic aneurysmal disease, r summarised in Table 1.

Thoracic aortic aneurysms (TAA) may show significant variation in rate of growth and flow dynamics. There are several hypotheses suggested for this difference, ranging from embryonic origin to modelling of collagen (4). The risk factors that govern development of aneurysms and dissections are multifactorial, including hypertension and several genetic conditions. The pathophysiology of TAAD is poorly understood and attributed to several influences, involving a complex interplay between mechanical forces exerted by biological structure in the healthy and diseased thoracic aorta.

This literature review will explore evidence surrounding the genetic, biological and mechanical aspects of the thoracic aorta in health and disease to provide an understanding of how these factors may influence the development of TAAD. Deeper understanding of this area could guide more comprehensive models of risk stratification, enhance programmes for early detection and inform clinical decision-making.

Biology of the thoracic aorta

The thoracic aorta is a composite tube encompassing three distinct layers: the intima, media, and adventitia, as illustrated in Fig. 1 (5). The intima lines the lumen of the aorta and is comprised of a single layer of endothelial cells

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Table 1 Spectrum of thoracic aortic aneurysmal disease.

Forms of TAA	Characteristics	Examples
Degenerative	Most common form of TAA Weakening of connective tissue and tunica media Includes cystic medial necrosis and elastin degradation	
Genetic syndrome	Defects in elastin and collagen lead to maladaptive responses to increased wall stress	Marfan's syndrome, vascular Ehler's Danlos syndrome, Loey–Dietz syndrome, multisystemic smooth muscle dysfunction syndrome, Turner syndrome
Nonsyndromic	Single gene mutations that lead to defective production and function of vascular endothelial cells or smooth muscle cells	*FBN1*, *FOXE3*
Associations with bicuspid aortic valve disease	Leads to turbulent flow across it Leads to dilation of the aortic root and subsequent aneurysm formation	

that is anchored to the underlying basement membrane (6). Endothelial cells are responsible for producing signals to control vessel tone and produce enzymes that are important for immune function, blood clotting and platelet adhesion (7). The basement membrane of the tunica intima is a highly specialised extra cellular matrix network consisting primarily of collagen type IV, laminin, perlecan and heparan sulphate proteoglycan (8).

The tunica media mainly consists of elastin lamellae and smooth muscle cells and its role is to provide elasticity to the thoracic aorta (9). Elastin lamellae are networks of cross-linked elastin fibres which provide elastic energy storage for the vessel (10). Elastin fibres mainly consist of elastin and have various other microfibrillar proteins incorporated into the fibre (10). A notable microfibrillar protein is fibrillin, which interacts with other proteins to aid assembly, function, and long-term stability of the elastic fibres (10). Smooth muscle cells induce vasodilation and constriction. Heterogenous origins of smooth muscle cells have recently been reported in the thoracic aorta and provide a better insight into the variable susceptibilities to disease in different parts of the aorta. Sawada *et al.* demonstrated the different origin of smooth muscles cells between the ascending and descending thoracic aorta using genetically modified mice(11). Furthermore, the inner medial smooth muscle cells of the ascending aorta

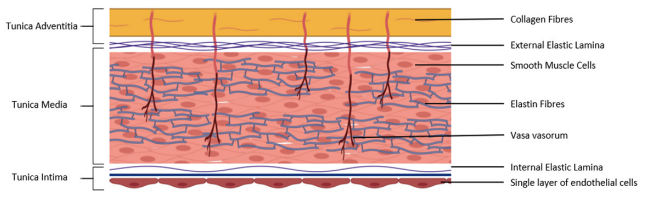

Figure 1
Layers of the thoracic aorta.

are derived from the second heart field while the outer medial cells are derived from cardiac neural crest (11). Conversely, the smooth muscle cells of the descending aorta are derived from single origin of somites, which are formed from the paraxial mesoderm (11). This could help explain the increased susceptibility to aneurysm in the ascending aorta compared to the descending aorta (12). However, actual functional differences due to the different origin warrant further research. The thickness of the tunica media is greatest in the thoracic aorta and decreases along the vessel. This is because elastin is greatest in the thoracic aorta and decreases further along distally from the heart, as a greater elastic energy storage is required to counter the stronger pulse closer to the heart (13). Therefore, the thoracic aorta is more susceptible to defects in extracellular matrix synthesis compared to distal regions of the aorta. The wall thickness-to-lumen diameter ratio remains constant as the lumen also decreases in diameter along the aorta (6).

The adventitia mainly comprises of fibroblasts, fibrocytes and bundles of collagen, which are supported by an external elastic lamina and together provide tensile strength. The vasa vasorum is woven into the adventitia and supplies oxygen and nutrients to the outer regions of the thoracic aorta. Recent evidence has suggested that the vasa vasorum of the thoracic aorta penetrates much deeper into the vessel wall compared to the distal aorta. Tonar *et al.* demonstrated the vasa vasorum density is higher in the tunica media and penetrates deeper towards the lumen in the thoracic aorta as compared to the abdominal aorta in porcine tissue (14). Furthermore, Federspiel *et al.* used immunohistochemical staining and confirmed these findings in human thoracic aorta (15). Collagen primarily provides tensile strength and in the adventitia collagen types I and III predominate (16).

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Collagen is arranged in a circumferential alignment, so that the unstressed tissues of collagen fibres are embedded in a wavy form in the soft ground matrix (16). Tensile strength makes the adventitia less stiff than the media, preventing overstretching and rupture (16).

All three layers create a dynamic vessel capable of withstanding large hemodynamic forces, which are most prominent in the thoracic aorta. Emerging evidence has suggested that the cells of the thoracic aorta are plastic and able to transform into other types of cells. Sandison *et al.* used prolonged time-lapse imaging to illustrate that vascular smooth muscle cells (VSMC) transitioned into non-contractile migratory macrophage-like cells (17). This could aid the understanding of certain pathology in the thoracic aorta which will be discussed later in the review.

Chemical pathways underlying thoracic aortic physiology

The smooth muscle cell contractile unit is composed of actin-containing thin filament and myosin thick filaments, along with regulatory proteins such as tropomyosin. The actin of the thin filament is a smooth muscle specific isoform which is encoded by the *ACTA2* gene (18). The thick filament consists of a hexametric molecule composed of two myosin heavy chains, two essential light chains and two regulatory light chains. Smooth muscle cells contract mainly due to an increase in intracellular Ca^{2+} which is induced by neural, hormonal, and local factors (18). Intracellular Ca^{2+} binds to the protein Calmodulin forming a complex, which in turn binds to myosin light chain kinase to activate it (18). Active myosin light chain kinase phosphorylates the regulatory light chain of the myosin complex, which activates the actin-dependent ATPase activity of the myosin globular motor head and results in contraction (18). VSMC is mainly initiated by a decrease in intracellular Ca^{2+}, which dissociates the Ca^{2+}/Calmodulin complexes. However, this does not result in complete relaxation and instead maintains basal tone. This is an energy efficient state as cross-bridges are maintained (19).

Transforming growth factor-β (TGFB) is an important cytokine that has a vital role in the development and maintenance of the vascular extracellular matrix. TGFB is generally secreted in its inactive form where it is anchored with fibrillin-1 to form a large latent complex. Microfibrils (mainly fibrillin-1) regulate the bioavailability and local activity of TGFB. Activated TGFB stimulates the phosphorylation of receptor-regulated Smad protein, which regulates transcription of genes responsible for extracellular matrix synthesis and stabilisation. TGFB signalling has also been associated with extracellular matrix degradation through the upregulation of metalloproteinase-2 and metalloproteinase-9. Recent evidence has shown that TGFB appears to have a greater role in extracellular matrix synthesis compared to degradation. Furthermore, the pathways involving extracellular matrix degradation through metalloproteinase-2 have also been shown to promote extracellular matrix synthesis. Shen *et al.* identified a dual role of metalloproteinase-2 in mice and also showed increased susceptibility to TAA due to metalloproteinase-2 deficiency (20). This shows that TGFB is essential in maintaining extracellular matrix stability and the defects in this signalling pathway are most prominent in the thoracic aorta as it has the greatest amount of extracellular matrix. However, dysregulation of TGFB signalling had divergent results, with both a protective and harmful role demonstrated in thoracic aorta pathology. Increased levels of TGFB have been associated with aggravating thoracic aorta pathology, as direct neutralization of TGF-B using antibodies showed reduced dilation in the ascending aorta (21). Interestingly, TGFB appears to exert different roles in the different cell types. Angelov *et al.* demonstrated that smooth muscle specific but not systemic inhibition of TGFB significantly increased the risk of TAA in angiotensin-II infused mice (22). This suggests that smooth muscle cell TGFB provide a protective effect on the vessel wall, and this action is possibly due to the previously established role of TGFB to stimulate VSMC proliferation (23).

Mechanics of the thoracic aorta

In order to understand the physical factors that lead to the formation of TAAD, it is important to understand mechanics of the thoracic aorta in health. Aortic tissue has several key physical properties that allow it to accommodate the pressures relayed through ventricular systole.

First, it has a non-linear stress–strain relationship at higher load levels, possibly mediated by collagen fibres (Fig. 2). Lower load levels demonstrate a nearly linear relationship between these two domains, mediated by elastin (24). Stress can be within the longitudinal or circular axis. There has been an observed difference in longitudinal stress along the path of the thoracic aorta, highest around the aortic arch and declining along the descending aorta. Secondly, aortic tissue has been demonstrated to increase

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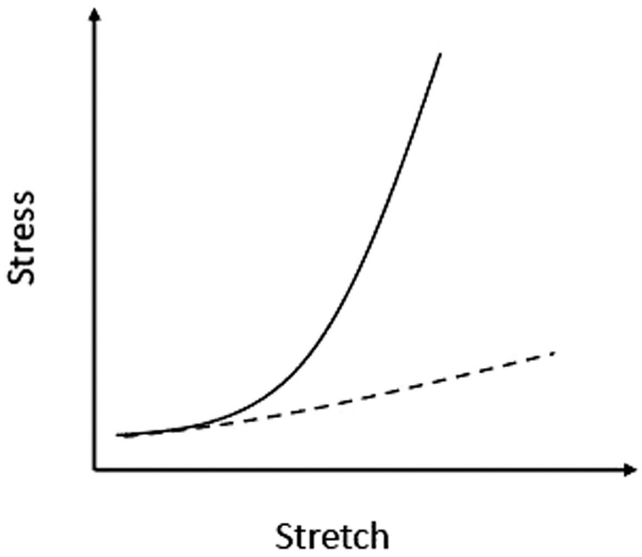

Figure 2
Stress–strain relationships in the thoracic aorta. The solid line depicts the natural relationship modelled *in vivo*. The dotted line depicts the relationship when collagen content is reduced.

in stiffness with increasing load. These properties may be exerted due to glycosaminoglycans (GAG), as research in porcine tissue treated with GAG removal showed quicker rates of stiffening in response to escalating load (25). Tissue from the thoracic aorta is pseudoelastic, in that there are different stress–strain patterns during loading and unloading. The difference can be reduced by repeating this process (i.e. conditioning tissue), however, it is suggested that this property is not demonstrated by human aortic tissue *in vivo* (26).

Aneurysmal tissue has several physical properties that are different to healthy aortic tissue. It has been demonstrated that aneurysmal specimens are stiffer in the longitudinal and circumferential dimensions compared to controls (27), however, this is inconsistent across the evidence base (28, 29). Strength and stiffness may be more pronounced circumferentially (29), possibly associated with increased deposition of collagen fibres in this direction (30). It is also suggested that there is concomitant decrease in elastin (31).

Physical forces aside from longitudinal and circumferential stress may play a part in aortic tissue remodelling. Combining *ex vivo* data with computational models, Witzenburg *et al*. demonstrated very low strength of porcine ascending aortas to radial shear, particularly in response to repeated loading (32). This could suggest an overlooked aspect of dissection.

Ability of the aorta to store and deploy energy is key to transmitting pressure from the left ventricle and driving perfusion to tissues. This property can be examined through tensile testing. Evidence suggests that a quick rate of energy loss is associated with failure of aortic tissue to withstand stress, predisposing it to dissection and aneurysms (33). The content and orientation of elastin in murine aortic tissue was found to be a strong predictor of energy storage (34). However, this finding was not replicated in a study comparing diseased murine tissue to controls (35).

The best example of these processes in action involve aneurysms caused by bicuspid aortic valve disease. Bicuspid valves differ from their counterparts with regard to number of leaflets (two vs three) and annular geometry (oval vs circular) (36). These alterations can lead to uneven sheer stress of systolic blood flow, which predisposes to aortic dilation and aneurysm formation at the root (37).

While *ex vivo* testing provides important information and context to link biological components with mechanical properties, inconsistencies in the evidence base suggest multiple factors may be responsible for aortic tissue failure. Furthermore, *in vivo* testing combined with computational fluid dynamics may be more beneficial for risk stratification and clinical decision making.

Genetic predisposition to thoracic aorta disease

TAA and TAD can be caused by syndromic and non-syndromic genetic factors.

Genetic syndromes

Marfan syndrome (MFS) is an autosomal dominant connective tissues disorder caused by mutations in the *FBN1* gene, which codes for fibrillin-1. Fibrillin-1 is a significant component of the extracellular matrix, hence Marfan's syndrome has been associated with an increased risk in thoracic aortic disease. Furthermore, deficiency in fibrillin-1 leads to the dysregulation of TGFB expression, which was thought to be the cause of thoracic aorta malformation. However, as described earlier the precise role of TGFB is controversial, and Marfan's syndrome has not been associated with an increased expression of bioactive TGFB (38). Nolasca *et al.* recently identified another potential mechanism to explain the impaired smooth muscle force observed in Marfan's syndrome (39). Furthermore, VSMC of MFS mice demonstrated a phenotype switch to mesenchymal-like cells, which

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resulted in impaired traction forces and a dampened force response to stiffer substrates (39). This further affirms the plasticity of the cells in the thoracic wall and its contributions to vascular disease.

Vascular Ehlers–Danlos syndrome (EDS) is another connective tissue disorder commonly associated with thoracic aorta disease. EDS type IV is an autosomal dominant pathology that is caused by a defective type III procollagen gene (*COL3A1*) that primarily affects the ECM of the heart and vasculature (40). Type III collagen predominates in the tunica adventitia, hence defective synthesis leads to increased fragility of the vessel, which is most prominent in the thoracic aorta. MRI measurements of the ascending aorta of EDS patients revealed a small incidence of enlarged ascending aortas without the formation of aortic aneurysms (41). Overall, the mutant type III collagen reduces stiffness of the adventitia and leads to widening of the aorta.

Loey–Dietz syndrome (LDS) is an autosomal dominant connective tissue disease that shares features with MFS and EDS. There are five types (types 1–5), caused by mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2* and *TGFB3*, respectively (42). Although autosomal dominant, at least 75% of patients have a de novo mutation and are the first in their family to manifest the disease (42). These mutations interfere with cell signalling pathways modulated by TGFB (discussed earlier). Patients with LDS present with aneurysms of the aorta which are particularly susceptible to dissection and the only available therapy is surgical treatment and regular surveillance.

Non-syndromic genetic predisposition

Non-syndromic causes of TAAD are confined to the aorta and do not have other systemic abnormalities. Non-syndromic causes account for 95% of all TAADs and can be further subdivided into familial and non-familial (also known as sporadic) (43). Familial non-syndromic TAADs refers to the instance when one or more family member is also diagnosed with TAAD (44). Research continues to identify genetic causes of familial TAADs, as 21% of patients have a positive family history of the condition. Interestingly, 21% appears to be an underestimate as many family members do not undergo the routine imaging to identify non-symptomatic aneurysms (43). In contrast, it was previously thought that sporadic non-syndromic TAADs are solely degenerative mediated. However, recent research suggests that there is also an underlying genetic cause in sporadic non-syndromic TAADs most likely due to variably penetrant gene expression (45).

ACTA2 encodes an isoform specific to SMC of α-actin, which polymerises to form thin filaments of the contractile unit. Mutations in *ACTA2* disrupts the amino acid arrangement in the subdomains of the actin, which alters the gross structure of the actin monomer. This leads to dysfunctional contraction of SMCs, manifesting as multisystemic smooth muscle dysfunction syndrome, which contributes to the pathogenesis of TAAD (40). Furthermore, Lu *et al.* demonstrated that the structurally altered actin monomer showed impaired interaction with myosin, unstable filament formations and an increase the number of actin monomer (46). The multiple defects observed suggest that mutant actin will decrease contractility of SMC in response to pulse pressure. Hence, *ACTA2* mutations have the most pronounced effect in the thoracic aorta which is sensitive to pulse pressure and requires a highly responsive vessel wall.

Multifactorial origin of thoracic aortic disease

There is a complex interplay between biological, mechanical and genetic factors that may cause thoracic aortic disease. The composition of aortic tissue provides it with inherent physical factors that allow it to accommodate and transmit pressures from the left ventricular outflow tract and maintain perfusion to the whole body. This is governed by chemical signalling and the function of these proteins are influenced by genetic factors.

Stress across aortic walls is conventionally thought to be exerted longitudinally and circumferentially. The relationship has been demonstrated to be non-linear, particularly at higher load levels. Longitudinal stress may differ more markedly than circumferential along the course of the thoracic aorta, and this is related to the reduction in elastin deposition along its length. The orientation of collagen fibres may also play an important role in stiffness and the stress–strain relationship of aortic tissue. Genetic disorders such as EDS interfere with the synthesis of collagen, which affects the ability of the thoracic aorta to withstand large pressures and predispose it to aneurysms and dissections due to wall weakness.

SMC play an integral role in the dynamic response to change in pressures within the thoracic aorta and they are sensitive to neural input. Modulating the stress–strain relationship, loading and unloading is critical to ensure integrity of the vessel and maintain perfusion. Mutations in components such as actin and myosin have been demonstrated *in vivo* to reduce contractility of these cells.

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The factors governing genetic syndromes such as abnormal elastin, tone and signalling can lead to maladaptive mechanotransduction which ultimately lead to a failure in aortic tissue to cope with wall stress. Since the genetic basis of TAAD is poorly understood, there are likely numerous genetic defects that affect smooth muscle cells, collagen and elastin to alter the strength and durability of tissue.

Most studies investigating thoracic aorta physiology usually analyse only one factor such as cell phenotype, which makes examining the interplay between all bio-chemo-mechanical factors difficult. However, there are a few experiments which have studied at least two factors and provide some insight on the combined effect of these factors. For example, Yamashiro *et al.* analysed solid mechanics in the context of extracellular matrix changes and determined that loss of elastic fibres in the thoracic wall leads to dysfunction in the mechanosensing of SMC (47). Atkins *et al.* investigated the effect of disruption in haemodynamics and its influence on the structure of the vessel wall. The porcine models demonstrated that disruptions in fluid dynamics influence chemical pathways, such as metalloproteinase 2, and directly mediatemedial degradation which contributes to TAA formation (48). These limited studies provide an insight on how the bio-chemo-mechanics factor are vital in normal physiology and that disruption in one can affect other factors and contribute to disease.

It is worth noting that the most prominent risk factor noted in patients with aneurysm or dissection is hypertension, highlighting the influence of lifestyle factors and interplay with biological and mechanical factors that affect integrity of the aorta. Bersi *et al.* examined the extracellular matrix and biomechanical difference of the thoracic aorta in hypertensive mice models to understand the varying susceptibility to disease in different sections of the aorta (49). The hypertensive models demonstrated disrupted intrinsic material stiffness in the intra mural cells of the ascending aorta, which leads to aneurysmal dilation. Additionally, the descending aorta showed excess fibrosis due to mechanical stress-initiated and inflammation-driven remodelling.

Screening programmes

There are no formal screening programmes for TAAs, possibly due to relative infrequency. A systematic review examined the evidence on the utility of screening for TAA in patients with giant cell arteritis. They reported significantly increased risk in these patients compared to controls. However, up to 5–10 patients would need imaging to detect a previously unknown aneurysm or dissection (50). Research investigating the value of genetic screening in patients with TAA or TAD found nearly a quarter had mutations of unknown significance in the 21 gene panel set (48).

Screening programmes may be of limited clinical utility in the general population but may be of use in at-risk patients. Additionally, deciding on an appropriate modality that is sensitive, specific and cost-effective is crucial to the success of any prospective programme. Commonly used imaging techniques (such as ultrasound) could be employed to track the strain in TAAs and aortic tissue stiffness, which have been subsequently validated (49, 50). Emerging technologies include 4D ultrasound, which can estimate strain using time-resolved 3D images. They have been used to good effect in estimating animal aortic aneurysm strain (51). Further research is needed to ensure an accessible, sensitive technique is chosen to enable creation of a feasible screening programme.

A major issue faced by clinicians in the management of TAAD is the capacity to determine which patient with an aneurysm will dissect or rupture. Currently, aortic diameter is measured to predict the aneurysm risk, however, it fails to detect all potential TAADs even in patient with a family history of TAAD (52). This emphasizes the need to find new biomarkers to help stratify risk in patients with a TAA. A recent study identified that elevated and persistent levels CRP, IL6 and TNF were as associated with progression of TAAD. The changing pattern of CRP could potentially be used as a marker of diagnosis and prophylactic treatment of complications (53).

Future research

There is a plethora of studies exploring one factor to assess its mechanism on the context of the thoracic aorta. Future studies should aim to combine the results of different experiments in a multifactorial computational model to assess the bio-chemo-mechanics of the thoracic aorta. Current studies only usually only focus on one factor, such as mechanics or biology and do not provide insight on how they rely on each other and contribute towards the pathological mechanism of thoracic disease. Additionally, bio-chemo-mechanical role of other components of the thoracic aorta also require further attention. For example, the role of proteoglycan in disease progression in the thoracic aorta is unclear and warrants further investigation, as they appear to be important in

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the signalling pathways of the thoracic aorta (50). TGFB is another yet controversial cytokine as its signalling pathway in disease has provided divergent results. Hence, future research should also aim to use more robust methods to investigate the role of TGFB. For example, many studies in the past have used pSmad 2 as a surrogate marker of TGFB. However, this has its own caveats as other pathways independent of TGFB have also shown to activate SMAD2 (36). Therefore, careful experimental designs and objective interpretation are required for future studies to tackle the wide range of disparities.

At present, clinical prediction of the risk of aneurysmal rupture is confined to aortic diameter. This metric is unreliable and shows great variation between individuals, therefore there is a need to determine biomarkers that are correlated with aneurysmal growth and risk of rupture. This will allow appropriate risk factor stratification and more accurate clinical decision making.

Summary and conclusion

Thoracic aortic aneurysms and dissections are serious albeit rare diseases that can result in high mortality if not detected and managed appropriately. The pathophysiology is poorly understood and has several factors in play. Smooth muscle cells and the composition of collagen and elastin helps mediate key mechanical properties that allow the thoracic aorta to withstand and transmit large pressures, however, remodelling is poor and dysfunctional processes can lead to tissue failure. Genetic syndromes can lead to defects in signalling proteins responsible for muscle contraction or connective tissue composition, thereby leading to inherent weakness. The impact of hypertension (which has genetic and environmental influences) is considerable in development of TAA and TADs, highlighting the need for research that considers multiple factors in studying pathophysiology.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

S I and A R conducted the literature search, wrote the first draft of the manuscript, was involved in editing and formatting the final manuscript. A H conceived the review, supervised data collection and writing of the manuscript.

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