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STATE-OF-THE-ART REVIEW

# Pathobiology of Aortic Aneurysms and Dissections

## Synthesis of Recent Investigations and Evolving Insights

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**ABSTRACT**

The pathobiology of aortic disease is linked to aortic region: atherosclerosis for abdominal aorta, primary medial degeneration or aortitis for ascending thoracic aorta, and all causes for descending thoracic aorta and thoracoabdominal lesions. The pathogenesis of aortic dissection involves damage of the outer media from impaired perfusion from dysfunctional vasa vasorum, formation of discrete foci of disrupted vascular smooth muscle cell-elastic fiber extension-contractile units, and imbalance of radial sheer stress across the aortic wall, thereby creating an intimal tear and linear dissection. Thoracic aortic aneurysms develop from the chronic progression of medial degeneration coupled with the weakening of the remodeled adventitia, allowing for aortic dilatation. Precipitating factors include hypertension and mutations of genes regulating the vascular smooth muscle cell-elastic fiber extension-contractile units. Criteria are presented for distinguishing genetic from acquired causes of thoracic aortic aneurysms and dissections, with important implications for therapeutic and surgical decisions in the care of these patients. (JACC Adv. 2025;4:101682) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In addition to atherosclerosis, the aorta, "the greatest artery," can develop several different types of aneurysms (diameter increase of at least 1.5 times normal), primary dissections (longitudinal split in the media), aneurysms complicated by dissections, and focal lesions, including intramural hematoma and penetrating aortic ulcer. These lesions are distinguished by their locations and extent and have chronic and acute clinical presentations (**Figure 1**, Supplemental Figures 1 to 3).[1-4]

This state-of-the-art review aims to present a comprehensive synthesis of the pathology and pathogenesis of aortic aneurysms and dissections based on integrating structural, functional, molecular, and genetic alterations present in the diseased aortic tissues.[5-8] Factors pointing to a genetic vs acquired etiology are identified with implications for diagnosis and management.

## DEVELOPMENTAL BIOLOGY AND FUNCTIONAL ANATOMY OF THE AORTA

Insight into the pathological basis of aortic diseases is provided by correlating light microscopic histopathology with less well-appreciated findings obtained by transmission and scanning electron microscopy.[9-14] The ascending aortic region, including the aortic arch up to the ligamentum arteriosum, is populated by a mosaic of vascular smooth muscle cells (VSMCs) and adventitial cells that are embryonically derived from

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**ABBREVIATIONS AND ACRONYMS**

**AAA** = abdominal aortic aneurysm

**AD** = aortic dissection

**BAV** = bicuspid aortic valve

**CMN** = cystic medial necrosis

**CMN/D** = cystic medial necrosis/degeneration

**ECM** = extracellular matrix

**EFE** = elastic fiber extensions

**EFL** = elastic fiber lamellae

**GAG** = glycosaminoglycans

**MD** = medial degeneration

**MEMA** = mucoid extracellular matrix accumulation

**MLU** = medial lamellar units

**TAAD** = thoracic aortic aneurysms and dissections

**TGF** = transforming growth factor

**VSMC** = vascular smooth muscle cell

**VSMC-EFE-CU** = vascular smooth muscle-elastic fiber extension-contractile unit

**HIGHLIGHTS**

- Aneurysms and dissections of the aorta are common disorders that can produce life-threatening complications due to compromise of end-organ perfusion and rupture.
- This review presents a comprehensive conception of the pathology and pathogenesis of aortic aneurysms and dissections based on correlations of genetic and molecular perturbations with the pathological changes in the diseased aortic tissues.
- Improved understanding of the pathology of these conditions has come from a systematic analysis of the histopathology using consensus criteria linked to correlation with alterations identified by transmission and scanning electron microscopy.

either the second heart field or the cardiac neural crest.[15] The descending thoracic and abdominal aorta are derived from the somite and splanchnic mesoderm. Endothelial cells are derived de novo from mesodermal precursors during angiogenesis.[16]

The aortic media comprises repeating medial lamellar units (MLU) with a characteristic microarchitecture characterized by: 1) 2 adjacent longitudinally oriented, large elastic fiber lamellae (EFL); 2) thin interconnecting elastic fibers that extend across the lamellae and make attachments to adjacent longitudinal EFL; 3) lateral elastic fiber extensions (EFE); 4) linkages of the EFE to VSMC formed by microfibrillar connections to focal adhesions (dense plaques) and connections of the dense plaques to the contractile filaments inside the VSMC; and 5) interdigitated collagen fibers (**Figure 2**).[9-14] These complexes form VSMC-EFE-contractile units (VSMC-EFE-CU) (**Figure 2**). Their function is regulated by transforming growth factor beta (TGFβ) and angiotensin II signaling pathways.[17-19]

The adventitia is the most complex and heterogeneous layer of the vessel wall.[20] The adventitia consists of an extracellular matrix (ECM) scaffold composed of abundant collagen fibers and interdigitating elastic fibers in the inner layer, fibroblasts, blood and lymphatic vessels, nerves, progenitor cells, immune cells, and, in the thoracic aorta, vasa vasorum.[20,21] The elastic elements in the aortic wall mediate elastic recoil and create a buffering capacity to maintain microvasculature perfusion (Windkessel effect).[19] The collagenous adventitia restrains the aorta from excessive extension and recoil.[22]

## DIFFERENTIAL EPIDEMIOLOGY AND PATHOLOGY OF AORTIC DISEASES

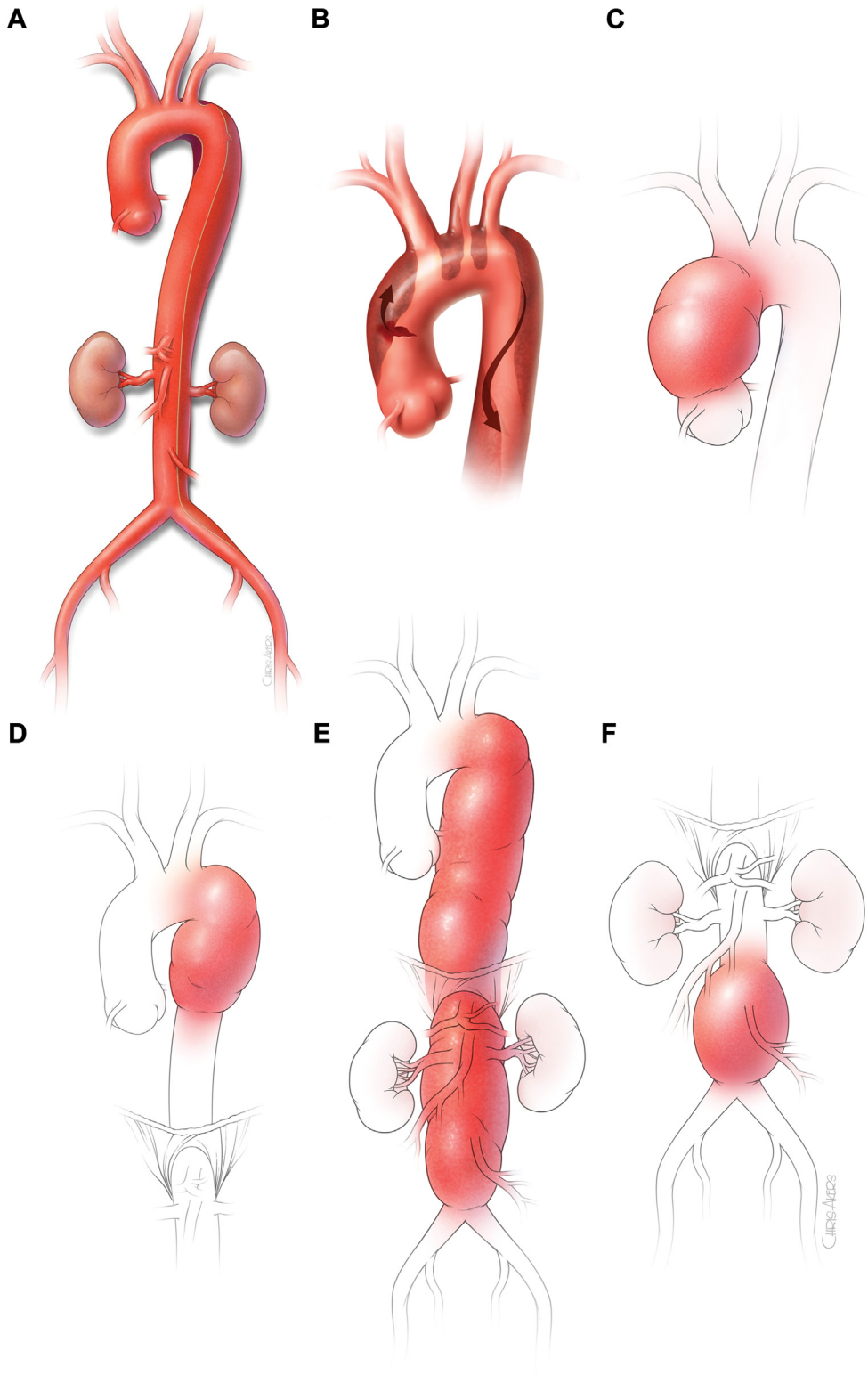
The pathogenesis of abdominal aortic aneurysms (AAA), often called atherosclerotic aneurysms, involves a propensity for atherogenesis combined with a genetic predisposition and marked inflammation leading to marked medial and adventitial damage (Supplemental Figure 2).[23,24] Genetic associations with AAA are positive family history in 20% of cases and high frequency of occurrence in twins.[20]

Patients with thoracic aortic aneurysms and dissections (TAAD) present as cases with apparent sporadic, acquired etiology or known heritable genetic etiology, designated as heritable thoracic aortic disease (**Table 1**). Less than 30% of all TAAD cases can be attributed to specific gene mutations, whereas more than 70% are sporadic.[5,6,18,25,26] The mutations are in genes that regulate components of the MLU (**Figure 3**). The ascending thoracic aorta and descending thoracic aorta are prone to different pathological processes. These are linked to different embryological origins of the VSMC populations in the 2 segments.[1-6,18,27] Ascending TAAD is characterized by pathologic alteration of the aortic media. Ascending TAAD has the highest incidence of established genetic aortopathy.[1-6,27] Descending thoracic aortic aneurysms and thoracoabdominal aortic aneurysms have multiple etiologies: atherosclerosis, aortitis, and medial degeneration (MD).[1-6]

## SYSTEMATIC PATHOLOGICAL ASSESSMENT OF MEDIAL DEGENERATION

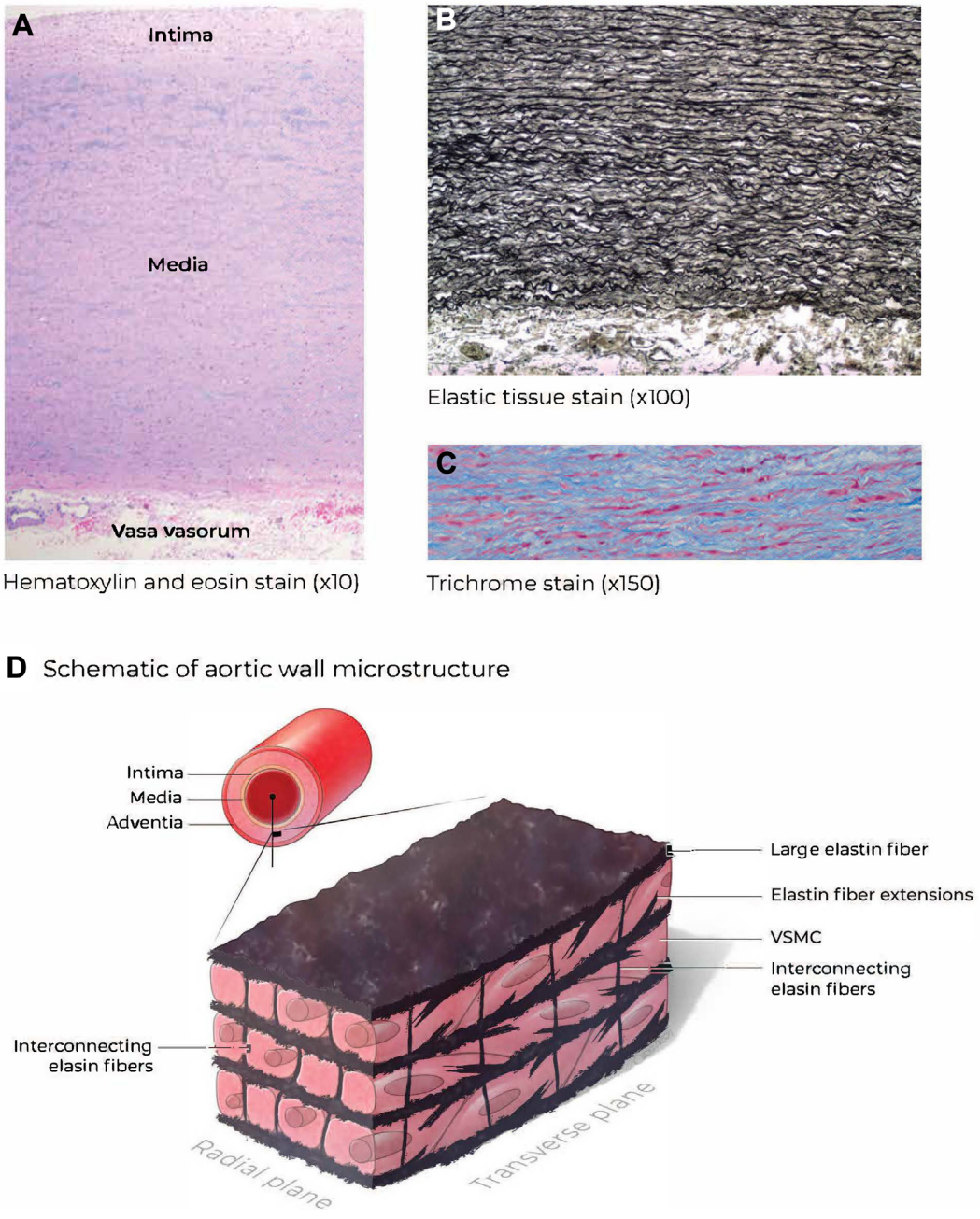
Since the original description by Erdheim in 1930, the terms cystic medial necrosis (CMN) and cystic medial designation have been used interchangeably to describe cystic histological foci with prominent pools of basophilic ground substance and absence of normal cellular elements.[8] Cystic medial necrosis/degeneration (CMN/D) was regarded as the primary pathological lesion associated with TAAD for decades. However, reported observations of minimal cystic change in many cases of aortic dissection (AD) raised doubts about the pathogenetic role of CMN/D and

**FIGURE 1** **Anatomic Types and Locations of Different Types of Aortic Dissections and Aneurysms**




(A) Type B aortic dissection begins in the distal aortic arch. (B) Type A aortic dissection begins in the proximal ascending aorta. (C) Ascending aortic aneurysm—annuloaortic ectasia. (D) Descending thoracic aortic aneurysm. (E) Thoracoabdominal aortic aneurysm, extent II. (F) Abdominal aortic aneurysm.

**FIGURE 2** **Aortic Wall Histology and Microstructure**




(A) The aortic wall has a thin intima, a thick media, and an adventitia with vasa vasorum. (B) The aortic media has an orderly arrangement and is composed of multiple medial lamellar units (MLU) delineated by adjacent elastic fibers. (C) The MLU also contains vascular smooth muscle cells (red) and collagen fibers (blue). (D) Schematic of aortic wall microstructure in radial and transverse planes. The microstructure forms functional VSMC-EFE-contractile units (VSMC-EFE-CU) oriented in a herringbone-like pattern allowing for optimal force generation and efficient mechanotransduction. Adapted with permission from Davis.[13] The article was published in Laboratory Investigation, Volume 68, Davis EC, Smooth Muscle Cell to Elastic Lamina Connections in Developing Mouse Aorta: Role in Aortic Medial Organization. pp 89 to 99, Copyright Elsevier, 1993. EFE = elastic fiber extension; VSMC = vascular smooth muscle.

**TABLE 1 Thoracic Aortic Aneurysms and Dissections (TAAD)**

| |
|---|
| Sporadic TAAD – 70%-80% |
| Heritable TAAD – 20%-30% (entities and associated mutated genes)[a] |
| Syndromic |
| Marfan (FBN1), vascular Ehlers-Danlos (COL3A1), Loeys-Dietz (TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3), other syndromic aortopathies |
| Nonsyndromic, familial (FTAAD) |
| ACTA2, MYH11, MYLK, PRKG1, MAT2A, MFAP5, FOXE3, THSD4, and FBN1 |
| Congenital conditions |
| BAV aortopathy – NOTCH1, TGFBR2, MAT2A, GATA4 and other genes<br>Autosomal dominant polycystic kidney disease – PKD1, PKD2<br>Turner syndrome – chromosome abnormality |

[a]Approximately 20% of TAA patients report a positive family history and, on account of extensive gene discovery efforts, approximately 30% of such cases can be explained by monogenic defects in more than 30 different genes.

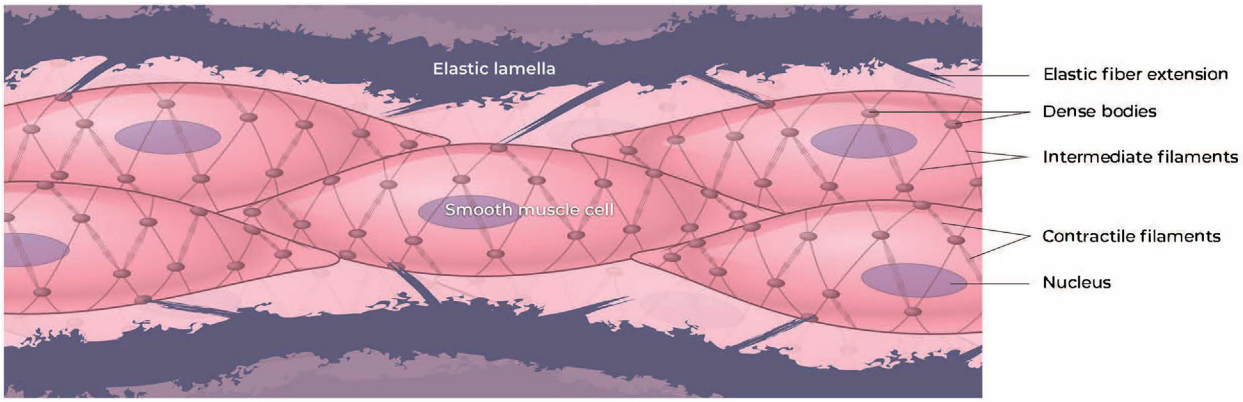
BAV = bicuspid aortic valve; SMAD = suppressor of mothers against decapentaplegic; TGFBR1 = TGFβ type 1 receptor; TGFBR2 = TGFβ type 2 receptor.

uncertainty as to the pathologic basis for AD and TAA formation.[8,28]

In 2015 to 16, the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology established consensus guidelines and criteria to provide a unified nomenclature for the histopathologic findings of the inflammatory and noninflammatory degenerative diseases of the aorta as well as a new diagnostic and grading scheme for MD (Supplemental Table 1, **Figures 4 and 5**).[7,8] A separate 11-point histopathological classification and scoring system has been developed specifically for AAA.[29]

The consensus scoring system, or similar systematic approach, has been adapted for research

**FIGURE 3 Genes Associated With Heritable Thoracic Aortic Aneurysms**

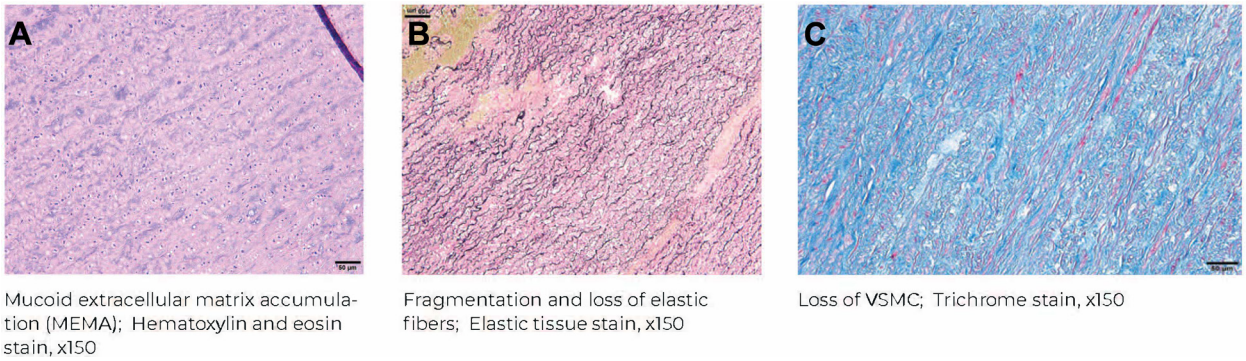



- **Smooth Muscle Cell (SMC) Contractile Apparatus**
  FOXE3, MYLK, PRKG1
- **Extracellular Matrix**
  COL1A1*, COL3A1, COL5A1*, LOX, MFAP5, PL001
- **TGFβ Signaling**
  TGFβ2*, TGFβ3*, TGFβR1*, TGFβR2*, SKI*, SMAD 2*, SMAD 3*
- **TGFβ Signaling + SMC Contractile Apparatus**
  ACTA2, MYH11
- **ECM + SMC Contractile Apparatus**
  FLNA*
- **ECM + TGFB Signaling**
  βCN*, FβN1
- **Other**
  MAT2A

* Syndromatic TAA

The genes control function of the extracellular matrix (ECM), TGFβ signaling, and the smooth muscle cell (SMC) contractile apparatus.TAA = thoracic aortic aneurysm; TGF = transforming growth factor.

**FIGURE 4 Prototypical Histopathological Alterations Seen With Medial Degeneration**




(A) Accumulation of basophilic pools of mucopolysaccharides (glycosaminoglycans), designated mucoid extracellular matrix accumulation (MEMA). (B) Fragmentation and loss of elastic fibers. (C) Loss of VSMC. In the trichrome stain, the sarcoplasm of the remaining VSMC stains red and the collagen blue. Abbreviation as in Figure 2.

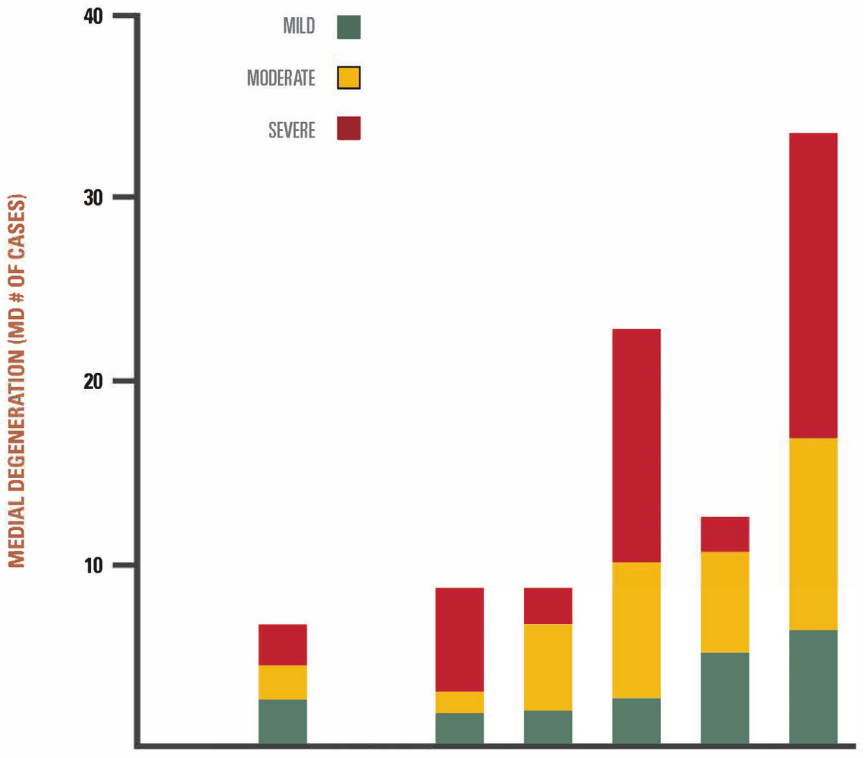
purposes at several centers, including ours.[30-47] The general findings from these studies are presented in Supplemental Table 2 and summarized in Supplemental Table 3.[30-47] Findings related to genetic arthropathies are summarized in **Table 2**.[32,46,48-50] Typically, ascending TAA and dissection are dominated by MD. Atherosclerosis is absent or focal and mild, with coexistent significant atherosclerosis and MD occurring less frequently. Waldron et al[27] have provided clinical evidence that patients with ascending TAAs are strongly protected from atherosclerotic disease. Concerning sex differences, despite its higher prevalence among men, women with TAAD have lower rates of treatment and surgical intervention and often have worse outcomes.[51] There is a correlation between higher MD scores and increased aortic diameter.[35] However, AD has often occurred in smaller aortas associated with high MD scores.[35,52] This important observation supports clinical decision-making and risk stratification of AD based on aortic size index or aortic height index rather than aortic dimensions alone.[3] Although bicuspid aortic valve (BAV) is linked to an aortopathy, MD scores are consistently lower in aortic specimens from BAV vs tricuspid aortic valve cases (Supplemental Table 2). However, the ascending thoracic aortic wall composition in BAV patients is distinctively different from normal with a thinner intimal layer, thinner EFL, prominent intralamellar mucoid extracellular matrix accumulation (MEMA), and fewer differentiated VSMCs.[53,54] Abnormal composition is the substrate for the propensity for ascending thoracic aortic dilatation and dissection associated with BAV.

## PATHOBIOLOGY OF AORTIC DISSECTION

Rates of occurrence of major risk factors for AD are as follows: hypertension 50% to 86%, obstructive sleep apnea 13%, BAV 2%, connective tissue disorder 10%, and aortic aneurysm 9%.[28] The pathological substrate for AD has long been the subject of confusion and controversy. A formal review of more recent studies (1980-onward) showed that: CMN/D of mild degree was seen with increasing age, and more frequently in patients with hypertension. CMN/D was present in only 8% to 19% of AD patients without Marfan syndrome, and of mild degree. CMN/D, usually of severe degree, was found in 40% to 82% of AD patients with Marfan syndrome (**Figure 6**).[28] Thus, overt cystic lesions of CMN/D cannot be the inciting universal cause of AD.

Recent studies have identified other pathological changes predisposing to AD. Low-grade chronic inflammation develops in the stressed aortic wall,[54] and leads to structural and functional alterations in the vasa vasorum, hypoperfusion and secondary microvascular angiogenesis in the outer media (**Figure 7**).[55,56] Dysfunction of the vasa vasorum predisposes to ischemic injury of the outer media.[55,56] This injury can induce loss of the small interconnecting elastic fibers, documented by scanning electron microscopy as the earliest demonstrable structural alteration of the media.[11,12,28] Transmission electron microscopic studies have identified additional multifocal fine structural alterations including focal defects in elastic fibers, loss of VSMC-elastic fiber connections, and VSMC alterations including loss

**FIGURE 5** Histopathological Grading of Medial Degeneration in 86 Cases of Proximal Thoracic Aortic Disease




| HEREDITARY/ SPORADIC | H | H | H | H | S | S | S | S |
|---|---|---|---|---|---|---|---|---|
| AD DISC/ AA NO DISC | AD | AD | AA | AA | AD | AD | AA | AA |
| BICUSPID AV/ TRICUSPID AV | BAV | TAV | BAV | TAV | BAV | TAV | BAV | TAV |
| MILD | 0 | 2 | 0 | 1 | 1 | 2 | 5 | 6 |
| MODERATE | 0 | 1 | 0 | 1 | 4 | 9 | 7 | 11 |
| SEVERE | 0 | 2 | 0 | 5 | 2 | 11 | 2 | 14 |

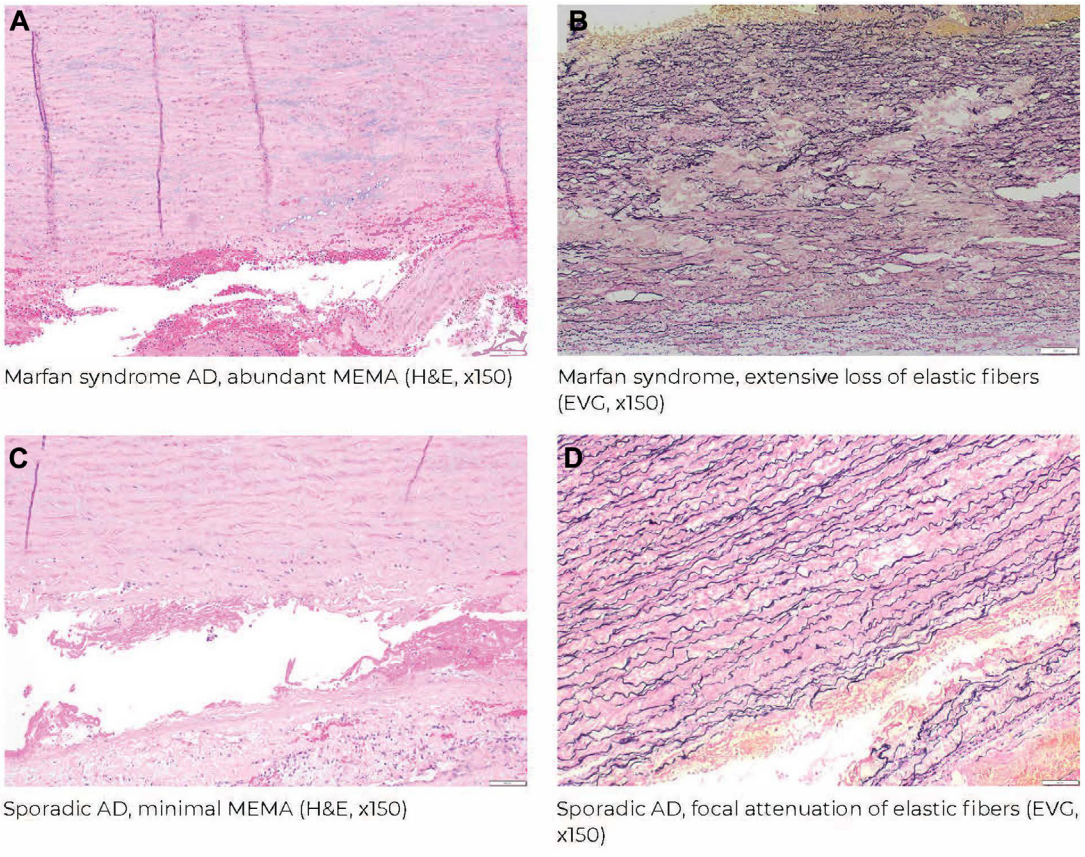
Overall medial degeneration is significantly greater in the hereditary vs the sporadic group ($P = 0.004$), including the extent of elastic fiber fragmentation ($P = 0.03$) and translamellar MEMA ($P = 0.04$). The medial degeneration score was not significantly different between patients with type A aortic dissection and with nondissected aortic aneurysms, but the medial degeneration score was significantly lower for patients with BAV than for patients with TAV ($P = 0.03$). From Buja LM et al.[46] Used under the terms of the Creative Commons Attribution-Non-Commercial License (CC BY-NC, https://creativecommons.org/licenses/by-nc/4.0/). AD = aortic dissection; BAV = bicuspid aortic valve; MEMA = mucoid extracellular matrix accumulation; TAV = tricuspid aortic valve.

**TABLE 2** Characteristic Findings in Cases of Documented HTAD

| |
|---|
| Overall medial degeneration is moderate to severe in most cases[46] |
| A characteristic of the Marfan aorta is extensive MEMA.[32,46] |
| Aortas with ACTA 2 and MYH11 mutations exhibit prominent proliferative and dysplastic vasa vasorum in addition to medial degenerative changes.[49,50] |
| Loeys Dietz syndrome has the distinctive feature of the recurrence of disease in distal aortic segments and in the branch vessels.[51] |

HTAD = heritable thoracic aortic disease; MEMA = mucoid extracellular matrix accumulation.

**FIGURE 6 Histopathology of Type A Aortic Dissections in Marfan Syndrome and Spontaneous Aortic Dissection**



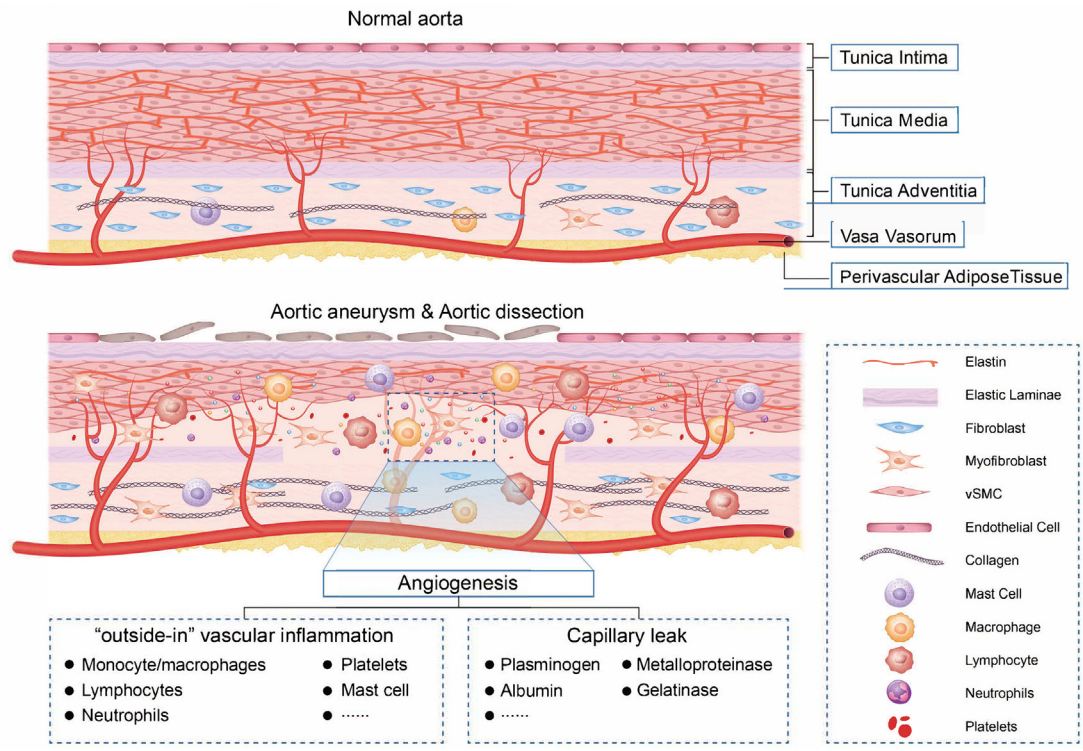

Patient with Marfan syndrome: (A) The outer and inner media adjacent to the dissection plane show abundant MEMA (hematoxylin & eosin [H&E] ×150) and (B) Extensive loss of elastic fibers (elastic Verhoeff-van Gieson [EVG] ×150). Patient with sporadic aortic dissection: (C) The outer and inner media adjacent to the dissection plane show minimal MEMA accumulation (H&E ×150) and (D) Focal attenuation of elastic fibers (EVG ×150). From Buja LM et al.[46] Used under the terms of the Creative Commons Attribution-Non-Commercial License (CC BY-NC, https://creativecommons.org/licenses/by-nc/4.0/). Abbreviations as in Figure 5.

of basement membranes.[57-59] There is an associated increased expression of matrix metalloproteinases.[56] The injury can proceed to the formation of discrete foci of disrupted VSMC-EFE-CU with loss of the large EFL and VSMC in the outer media identifiable by light microscopic examination (Figure 8). These linear, noncystic changes are seen in the settings of AD and chronic hypertension which is a major risk factor for the development of AD (Figure 9).[28]

It has also been postulated that the aorta prone to dissection may have a subtle increase in intralamellar glycosaminoglycans (GAG). Based on computational modeling, GAG swelling could contribute to AD initiation by increasing the intralamellar pressure and the intramural mechanical stress field.[60] Other computational data from models involving selective depletion of GAG, elastin, and collagen have shown that interlamellar collagen fibers have a dominant role in maintaining the integrity of the arterial wall. Avalanche-like failure of the aorta during dissection results from the local buildup of strain energy followed by a cascade failure of inhomogeneously distributed interlamellar collagen fibers.[61]

A synthesis of the observations supports the hypothesis that the development of AD involves 2 concurrent pathological conditions: 1) damage to the outer media occurring as a consequence of hypertension and/or a facilitative genetic profile producing dysfunctional vasa vasorum; and 2) impaired balancing of the radial shear stress across the

**FIGURE 7** Pathological Roles of Vascular Inflammation, Angiogenesis, and Adventitial Remodeling in Aortic Aneurysms and Dissections




The stressed aorta develops low-grade chronic inflammation in the adventitia which leads to remodeling of the adventitial collagen bundles, vasa vasorum sclerotic changes, hypoperfusion of the outer media and secondary angiogenesis with proliferation of thin walled microvessels in the outer media. These changes constitute a pathological substrate for subsequent development of aortic dissection and aneurysm. From Jia et al.[55] Used under the terms of the Creative Commons Attribution-Non-Commercial License (CC BY-NC, https://creativecommons.org/licenses/by-nc/4.0/).

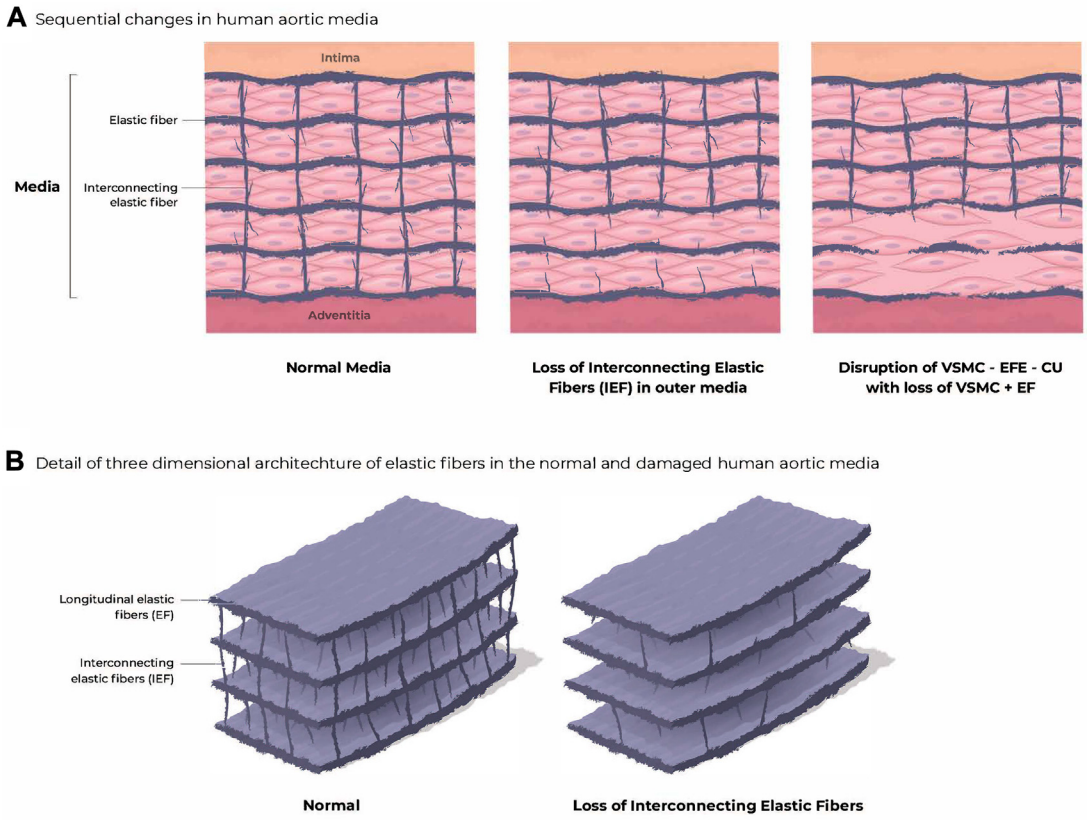
damaged aortic wall between the intima and adventitia. This radial mechanical sheer stress on the damaged aortic wall is likely produced by a longitudinal strain from the vertical swinging motion of the aorta at the aortic root due to the downward movement of the heart with contraction plus tethering of the aorta at the isthmus.[28] In vitro modeling has shown that the translamellar resistance in the outer third of the media is weaker than the interlamellar resistance, predisposing this region to dissection.[62] Although a proximal intimal tear is virtually ubiquitous in cases of AD, the absence of a proximal intimal tear has been reported in about 5% of AD cases.[28] Debate continues as to whether the proximal intimal tear is the primary initiating event ("inside-out hypothesis") vs a secondary event following bleeding into the outer media from dysfunctional vasa vasorum as the primary event ("outside-in hypothesis").[28] The radial mechanical sheer stress is exacerbated by an increased force of cardiac contraction (dp/dt) due to hypertension.[63]

AD progression is mediated by systemic pressure in the false channel coupled with tissue responses, including the release of cytokines from VSMC, inflammatory cell recruitment, the release of proteases, and matrix degradation.[5,6,28] AD is characterized clinically as hyperacute (<24 hours), acute (2-7 days), subacute (8-30 days), and chronic (>30 days).[3] When a distal intimal tear develops, the AD can become chronic by forming a double-barreled aorta. Histologically, acute AD shows thrombus and inflammation in the tissue adjacent to the false lumen and subacute and chronic AD show the formation of a fibrocellular neointima in the false lumen.[64]

## MOLECULAR PROFILE OF DISEASED THORACIC AORTA

Genes with mutations associated with heritable thoracic aortic disease have been localized to different components of the MLU, and they regulate the normal and abnormal functioning of the VSMC-

**FIGURE 8 Pathological Substrate for Aortic Dissection**

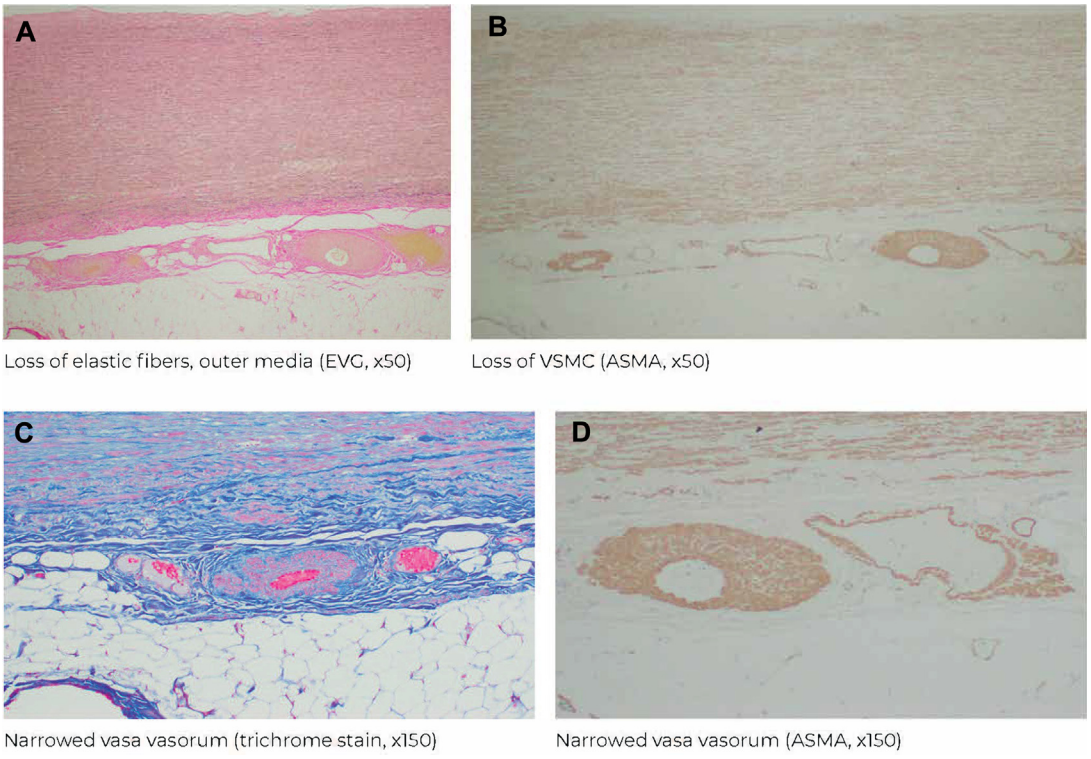



(A) Sequential changes in human aortic media. The normal aortic media has lamellae formed by longitudinal elastic fibers stabilized by interconnecting elastic fibers (IEF). In response to pathological stimuli, the IEF in the outer media are damaged and lost. This leads to disruption of the VSMC-EFE-contractile units due to the loss of longitudinal elastic fibers and VSMC. These lesions serve as the substrate for instability of function of the media, impaired coping with radial stress on the intima and media, intimal tear and dissection. Adapted with permission from Akutsu.[28] Published in General Thoracic and Cardiovascular Surgery, Volume 67, Akutsu K, Etiology of aortic dissection, pp 271 to 276, Copyright Springer Japan KK, 2019. (B) Detail of 3-dimensional architecture of elastic fibers in the medial lamellar units (MLU) in the human aortic media. The loss of interlamellar IEF is present in the external media in cases of chronic hypertension and aortic dissection (AD) (right) vs control (left). Schematic rendition of findings in aortas treated with formic acid to remove components other than elastic fibers and then examined by scanning electron microscopy. Adapted with permission from Nakashima et al.[11] Published in Laboratory Investigation, Volume 62, Nakashima Y, Shiokawa Y, Sueishi K, Alterations of elastic architecture in human aortic aneurysm, pp. 751 to 760, Copyright Elsevier, 1990. Abbreviations as in **Figure 2**.

EFE-CU.[17-19,25,26] These genes code for proteins involved in the regulation of VSMC contractility, ECM, and TGFβ signaling (**Figure 3**). Single-cell transcriptome and proteomic analyses have revealed dynamic cell populations, differential gene expression, and differentially expressed proteins in aneurysmal aortic tissue.[5,6,65-67] Li et al[66] also identified immune cell clusters in aneurysmal aortas. This correlates with our findings, based on quantitative immunocytochemistry, of increased numbers of T lymphocytes, macrophages, and apoptotic cells in aortic tissue from cases of TAA and AD.[68,69] These findings imply that selective gene activation is integral to developing different types of aortic pathology. Mutated genes create an altered metabolic milieu. Selective gene activation is accompanied by activation of a vascular inflammatory response creating an inflammatory milieu in the vessel wall.[70-73] This leads to a proteolytic state with increased expression of matrix metalloproteinases and tissue inactivators of metalloproteinases.[56,68,69] These proteases are produced by endothelial cells, VSMC, fibroblasts, and inflammatory cells in the vessel wall, as well as plasma-born activators of proteolysis.[5,6,70-73]

Signaling pathways, especially the TGFβ and angiotensin II pathways, are important in regulation

**FIGURE 9** Alterations of the Thoracic Aortic Wall Associated With Chronic Hypertension




(A) Outer media stained for elastic fibers. (B) Outer media stained for VSMC. (C) Outer media stained with trichrome stain. (D) Outer media stained for VSMC. Note the loss of elastic fibers and VSMC (stars), particularly in the outer media, and the fibrocellular thickening and luminal narrowing of the vasa vasorum (ASMA = alpha smooth muscle actin stain). Specimen from a 70-year-old man with hypertension, bicuspid aortic valve, severe aortic valve stenosis, and ascending aortic aneurysm. Abbreviation as in Figure 2.

of VSMC, collagen, and elastin homeostasis.[5,21,69] A stage-specific role of TGFβ signaling in TAA pathogenesis has been elucidated (Figure 10).[5,6,17-19,73] Altered signaling leads to epigenetic induction of VSMC phenotype alterations in lesion formation.[74,75] Teleocytes, a distinctive interstitial cell type, appear to be involved in the modulation of the VSMC in lesion formation.[76] Accelerated VSMC senescence, mediated by depletion of nicotinamide dinucleotide deletion and other mechanisms, also can contribute to VSMC loss.[77,78] Vascular stem cell turnover and loss is a dynamic process and involves the participation of vascular stem and progenitor cells.[79]

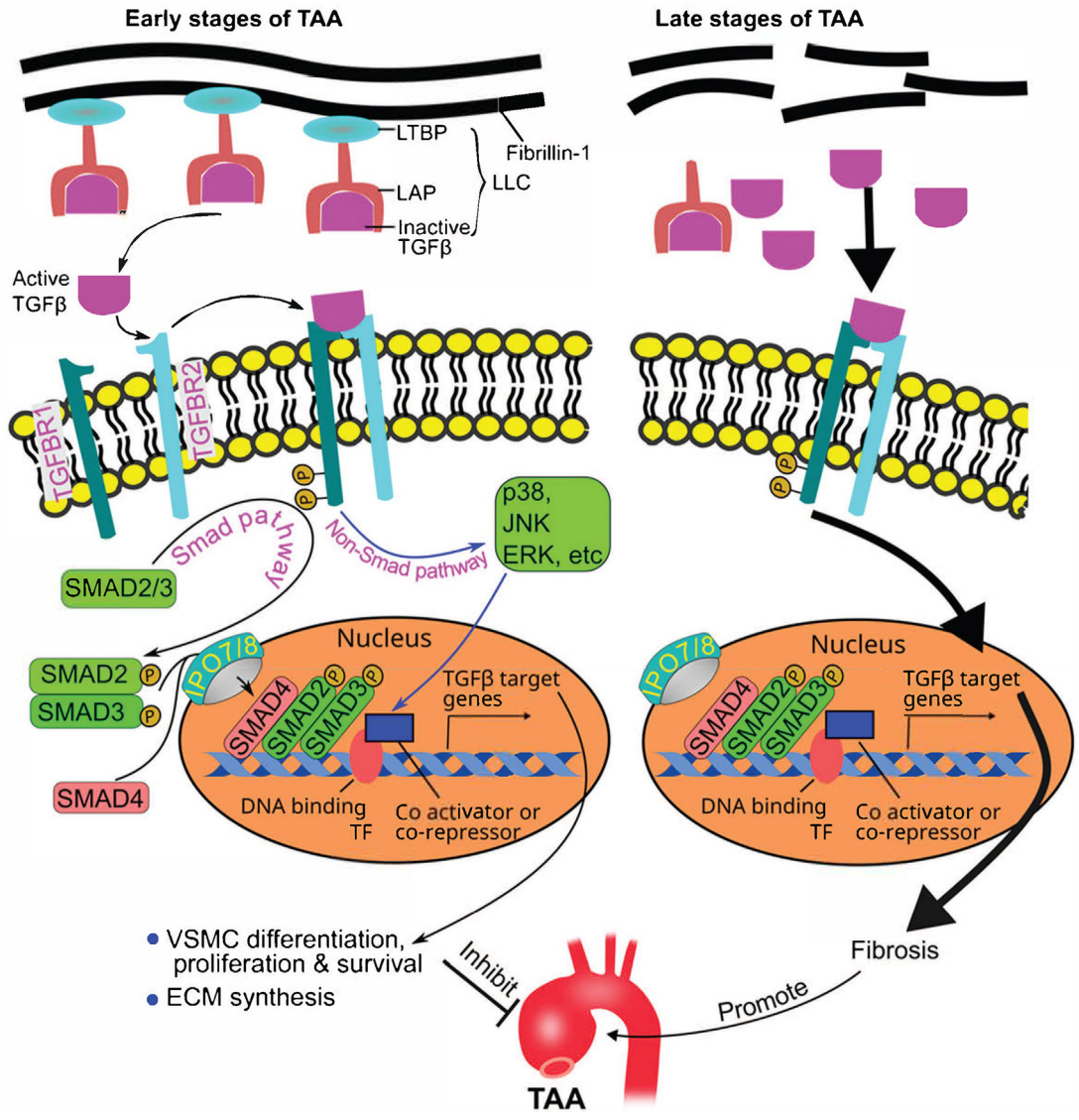
## PATHOBIOLOGY OF THORACIC AORTIC ANEURYSM

In contrast to de novo AD, aneurysms of the ascending thoracic aorta typically exhibit cyst-like foci of MD with elastic fiber fragmentation and accumulation of pools of GAG-rich MEMA throughout the media. They also exhibit remodeling in the adventitia initiated by genetic mutations or hypertension and mediated by an inflammatory milieu characterized by activated inflammatory cells and increased proteolytic activity.[1,2,46,80-84] A quantitative study showed increased turnover of VSMC and ECM associated with aortic dilatation.[37] The process leads to a breakdown in the integrity of the VSMC-EFE-CU, followed by the formation of overt lesions of MD due to apoptosis of VSMC, loss of elastic fibers, and accumulation of MEMA.[5,6,46] Vascular inflammation in the adventitia leads to structural and functional abnormalities in the vasa vasorum, restructuring of the collagen and elastin network and weakening of its barrier function. Loss of structural integrity of the collagen-rich adventitia facilitates aortic dilatation and aneurysm formation.[5,6,80-84]

## CLINICAL CORRELATES

Pathological studies have documented that AD frequently occurs in nondilated ascending aortas with predisposing medial degenerative change in

**FIGURE 10 Stage-Specific Role of TGFβ in TAA Pathogenesis**




In the early stages of TAA formation, TGFβ binds to its receptors and regulates gene expression through SMAD and non-SMAD pathways, leading to SMC differentiation, proliferation, and survival, as well as ECM synthesis. These TGFβ-induced changes inhibit TAA formation. In the late stages of TAA, degradation of the ECM leads to excessive release of active TGFβ and consequent overactivation of TGFβ pathways and thus fibrosis. Excessive fibrosis promotes TAA progression. From Wang et al.[6] Used Under the Terms of the Creative Commons Attribution-Non-Commercial License (CC BY-NC, https://creativecommons.org/licenses/by-nc/4.0/). ECM = extracellular matrix; ERK = extracellular signal-regulated kinase; IPO = importin; Jnk = Jun N-terminal kinase; LAP = latency-associated peptide; LLC = large latent TGFβ complex; LTBP = large latent TGFβ binding protein; SMAD = suppressor of mothers against decapentaplegic; TF = transcription factor; TGFBR1 = TGFβ type 1 receptor; TGFBR2 = TGFβ type 2 receptor; other abbreviations as in **Figures 2 and 3**.

association with chronic hypertension as well as in early stages of genetic aortopathies (Supplemental Figure 1). This is a strong indication for utilizing aortic indices rather than diameter measurements alone for risk stratification.[3,28,34,46] Although genetic factors are of major importance in the pathogenesis of TAAD, formal genetic analytical data are often unavailable in everyday practice. Earlier age of onset, family history, and severe MD provide presumptive evidence for a genetic basis of TAAD.[17-19,25,26] Based on our data, we developed a proposed scheme for assigning a genetic component to cases of thoracic aortic disease (**Figure 3**, **Table 3**).[46] Our recommendations for instituting diagnostic imaging and genetic

**TABLE 3 Proposed Paradigm for Assessing the Genetic Contribution to Thoracic Aortic Disease**

| | |
|---|---|
| Major genetic contribution | Identifiable pathogenic variants in a gene causing thoracic aortic disease, or<br>Relatives with thoracic aortic disease, or<br>Early-onset disease (<55 y) and no identifiable variation in a known HTAD gene |
| Intermediate genetic contribution | No identifiable gene variant or family history<br>Relatively young age (<55 y) + other environmental or lifestyle risk factors<br>TAAD is likely the result of a combination of lower-penetrance genetic variants and risk factors such as hypertension |
| Minor genetic contribution | Relatively late-onset disease (>60 y)<br>No identifiable variation or family history<br>TAAD is primarily driven by risk factors such as hypertension or smoking |

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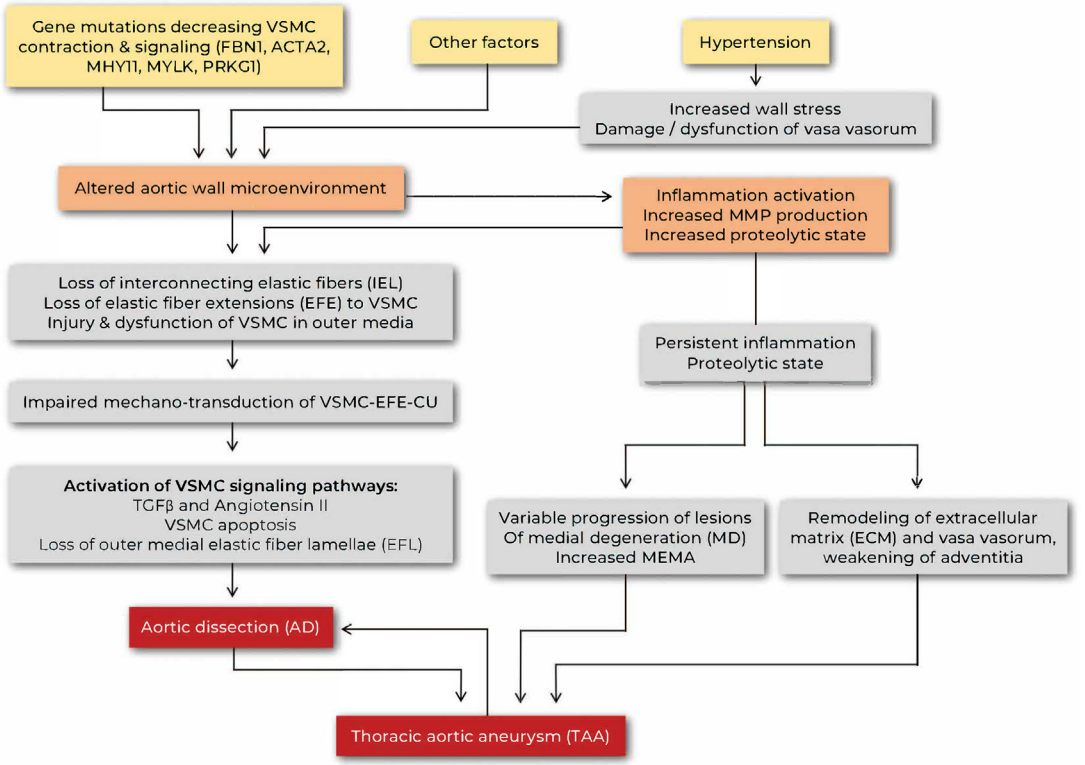
testing are consistent with the guideline recommendations for patients presenting with aortic disease at the age of 60 years or less.[3]

## CONCLUSIONS

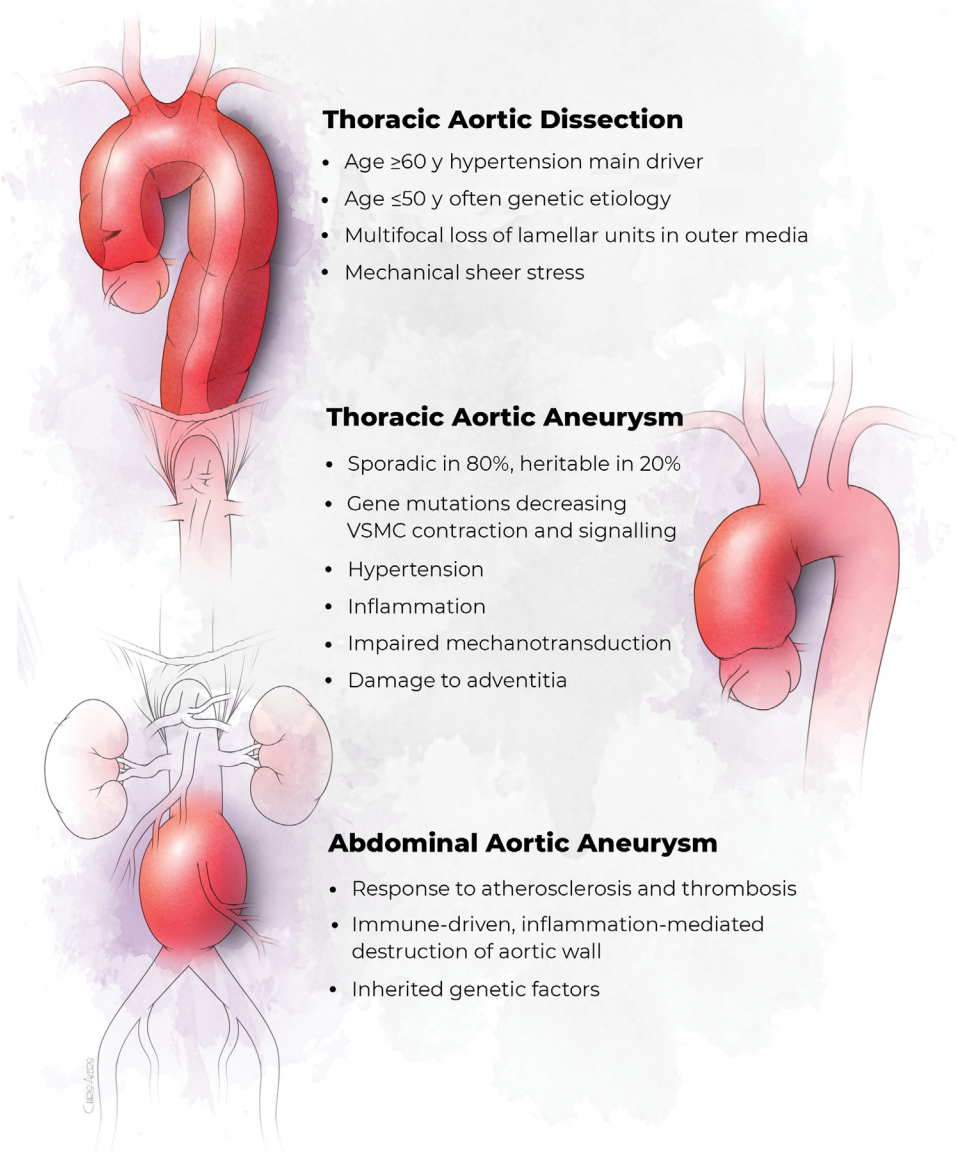
Sporadic AD driven by hypertension is initiated by multifocal discrete alterations in the outer media without severe lesions of MD (ie, classical CMN/D). In contrast, TAAs formed by progressive aortic dilatation typically exhibit prominent lesions of MD, particularly in cases of genetic aortopathy (Figure 11). Histopathologic MD represents the final common outcome of diverse pathogenetic factors and mechanisms. Aneurysm formation involves remodeling of the ECM in the adventitia and media and weakening of the adventitia. The detailed analysis of aortic wall pathology strongly supports the altered mechanotransduction hypothesis for the pathogenesis of the MD in TAAD (Figure 11).[19-21] This paradigm provides an evidence-based pathobiological construct for understanding the mechanisms responsible for TAAD and for designing and implementing therapies to improve the morbidity and mortality from TAAD.[19,70] (Central Illustration).

**FIGURE 11 Pathogenesis of Thoracic Aortic Aneurysm and Dissection**




Proposed pathogenesis of TAAD involving genetic or hypertensive triggers leading to early ultrastructural changes and loss of mechanotransduction function of VSMC followed by activation of inflammation and secondary variable progression of overt medial degeneration and remodeling of the adventitia. These changes constitute the substrate for the development of aortic dissection or thoracic aneurysm with or without complicating aortic dissection. TAAD = thoracic aortic aneurysms and dissections.

**CENTRAL ILLUSTRATION** **Overview of Pathogenesis of Aortic Aneurysms and Dissections**

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Key features are shown for abdominal aortic aneurysm, thoracic aortic dissection, and thoracic aortic aneurysm. Abbreviation as in Figure 2.

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**KEY WORDS** aortic gene mutations, aortic pathology, elastic fibers, medial degeneration, medial lamellar unit, vascular smooth muscle cells

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.