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Clinical Investigation

Insights From the Histopathologic Analysis of Acquired and Genetic Thoracic Aortic Aneurysms and Dissections

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Abstract

Objective: The purpose of this study was to apply contemporary consensus criteria developed by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology to the evaluation of aortic pathology, with the expectation that the additional pathologic information may enhance the understanding and management of aortic diseases.

Methods: A scoring system was applied to ascending aortic specimens from 42 patients with heritable thoracic aortic disease and known genetic variations and from 86 patients from a single year, including patients with known genetic variations (n = 12) and patients with sporadic disease (n = 74).

Results: The various types of lesions of medial degeneration and the overall severity of medial degeneration overlapped considerably between those patients with heritable disease and those with sporadic disease; however, patients with heritable thoracic aortic disease had significantly more overall medial degeneration (P = .004) and higher levels of elastic fiber fragmentation (P = .03) and mucoid extracellular matrix accumulation (P = .04) than patients with sporadic thoracic aortic disease. Heritable thoracic aortic disease with known genetic variation was more prevalent in women than in men (27.2% vs 9.8%; P = .04), and women had more severe medial degeneration than men (P = .04). Medial degeneration scores were significantly lower for patients with bicuspid aortic valves than for patients with tricuspid aortic valves (P = .03).

Conclusion: The study's findings indicate considerable overlap in the pattern, extent, and severity of medial degeneration between sporadic and hereditary types of thoracic aortic disease. This finding suggests that histopathologic medial degeneration represents the final common outcome of diverse pathogenetic factors and mechanisms.

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Introduction

Diseases of the aorta and its branches constitute a large and heterogeneous group of disorders.[1,2] Patients with aortic disease may present with chronic aortic aneurysms or acute manifestations of disease (designated as acute aortic syndrome) resulting from acute aortic dissection, intramural hematoma, penetrating aortic ulcer, or ruptured thoracic aortic aneurysm.[3-5]

The purpose of analyzing the pathology of aortic specimens obtained during open surgical intervention or autopsy is to gain information regarding the pathogenesis of the various conditions. Medial degeneration is the primary pathologic lesion in heritable or genetically mediated diseases of the aorta; however, it also occurs in various sporadic disorders, such as aortic dissection associated with uncontrolled systemic hypertension.[1,3,5] Historically, the descriptions of aortic disease pathology and terminology have been inconsistent, giving rise to a confusing plethora of descriptive terms, such as *cystic medial necrosis* and *cystic medial degeneration*.

To bring order to the taxonomy of aortic diseases through systematic analysis, the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) convened working groups to develop and publish consensus criteria for diagnosing and classifying inflammatory and noninflammatory degenerative diseases of the aorta.[1,2]

The consensus criteria are based on the systematically documented extent and severity of several distinctive histopathologic changes in aortic specimens. This information is used in the overall assessment and grade of the extent and severity of the medial degeneration to yield a medial degeneration score.[1] A systematic approach to evaluating aortic pathology is critical in surgical pathology practice for patients with aortic diseases.

Here, the application of the contemporary consensus criteria for evaluating aortic pathology was evaluated and documented in a surgical pathology practice at a tertiary referral medical center for patients with aortic diseases.[6] A particular focus of these studies was comparing cases of thoracic aortic aneurysm and aortic dissection between patients with known heritable genetic etiology and patients with sporadic, acquired etiology.[3,5,7-10] Thoracic aortic aneurysm with heritable genetic etiology is designated as *heritable thoracic aortic disease* (HTAD), and it includes syndromic and nonsyndromic subcategories.[7] Thoracic aortic aneurysm and aortic dissection are distinct and interrelated entities; aortic dissection occurs with or without a preexisting aneurysm.[3,5]

Key Points

- Systematic histopathologic analysis showed considerable overlap in patterns and severity of medial degeneration in known genetic and sporadic ascending aortic aneurysm and dissection; however, patients with HTAD had more MEMA than patients with sporadic aortic aneurysms.
- Thoracic aortopathy was more prevalent in men than in women, but women had a higher prevalence of HTAD and more severe medial degeneration than men.
- Medial degeneration scores were significantly lower for patients with BAV than for patients with TAV (P = .03).
- Earlier age of onset, family history, and severe medial degeneration provide presumptive evidence for a genetic basis of aortic aneurysm classified as sporadic.
- This study's findings suggest that histopathologic medial degeneration represents the final common outcome of diverse pathogenetic factors and mechanisms.

Abbreviations and Acronyms

AECVP	Association for European Cardiovascular Pathology
BAV	bicuspid aortic valve
HTAD	heritable thoracic aortic disease
MEMA	mucoid extracellular matrix accumulation
SCVP	Society for Cardiovascular Pathology
TAV	tricuspid aortic valve

Patients and Methods

This study was performed as part of the projects reviewed and approved by the University of Texas Health Houston Committee for the Protection of Human Subjects institutional review boards (HSC-MS-01-251 Genetic Basis of Aortic Aneurysms and Dissections and HSC-MS-06-054 Genetic Basis of Vascular Diseases).

The study's analysis used pathology data from 2 studies in which aortic specimens were obtained during open surgical procedures performed by colleagues at a tertiary hospital, a referral center for aortic diseases in the Texas Medical Center in Houston.[6] The first study included 42 patients with HTAD with documented genetic variations. The data were collected from 2012 to 2020 and were identified by a database query within the Division of Medical Genetics, a member of the GenTAC Alliance.[10] The main inclusion criterion was the availability

of a genetic test result and tissue from open aortic surgery. The second study involved a detailed examination of histologic sections from all operative cases of thoracic aortic disease from 2019. The second study's main inclusion criterion was the availability of tissue from any patient undergoing operative repair in the year selected. Patients who did not meet these criteria were excluded.

Using the SCVP/AECVP consensus criteria, tissue sections were stained with hematoxylin-eosin, Verhoeff–van Gieson elastic tissue stain, trichrome stain, and (in some cases) immunohistochemical stain for □-smooth muscle actin, then analyzed. Numerical scores were assigned according to the extent and severity of specific lesions, including mucoid extracellular matrix accumulation (MEMA) and alterations of elastic fibers and smooth muscle cells. The sum of these scores yielded an overall medial degeneration score of mild (1-5), moderate (6-10), or severe (11 to ≥20) (Table I and Fig. 1).[1]

Statistics

Statistical analysis was performed using IBM SPSS Statistics, version 26, software. For the first study, which included 42 patients with HTAD with documented genetic variations, the Kruskal-Wallis test was used to compare the grade of medial degeneration among genes. The grade of medial degeneration was measured on an ordinal scale, with scores ranging from 1 (mild) to 3 (severe). A χ^2 test was used to compare the frequency of aortic dissection across the genes.

For the second study involving the detailed examination of histologic sections from all operative cases of thoracic aortic disease in a single year (2019), the Pearson χ^2 test was used to compare the frequency distributions of categorical data between groups. The Mann-Whitney test was used to compare variables across the dichotomous groups. The variables were measured on an ordinal scale.

TABLE I. Systematic Assessment of Medial Degeneration

A. Definition	Overall degenerative alterations or damage to the aortic media resulting from the sum of individual histopathologic degenerative lesions (see below) affecting the lamellar unit (both cellular and extracellular).
B. Sampling	Six strips of aorta in 2 cassettes (optimal), with sections stained with hematoxylin-eosin, an elastic tissue stain (Movat pentachrome, Verhoeff–van Gieson, combined Masson elastic), and an optional Masson trichrome stain for collagen and smooth muscle cells
C. Individual components of medial degeneration[a]	• Mucoid extracellular matrix accumulation: intralamellar and extralamellar • Elastic fiber fragmentation or loss • Elastic fiber thinning • Elastic fiber disorganization • Smooth muscle cell nuclei loss • Laminar medial collapse • Smooth muscle cell disorganization • Medial fibrosis
D. Grading of each component lesion	Distribution: none (0), focal (≥1%, ≤10%), multifocal (≥2%, 10%-30%), extensive (≥3%, >30% medial area) Severity: none (0), mild (≥1, ≤3 lamellar units), moderate (≥2, 4-10 lamellar units), severe (≥3, >10 lamellar units) Grading of medial degeneration is based on the average overall severity of specific histopathologies, as described, considering the worst areas sampled from multiple slides and aorta sections
E. Diagnosis	Medial degeneration is used as an overarching ("top-line") term for any aortic surgical specimens that demonstrate any combination of the specific histopathologies The overall top-line assessment for medial degeneration is obtained from a combination of the severity and distribution of the individual degenerative lesions as follows: mild (1-5 points), moderate (6-10 points), and severe (11 to ≥20 points)

[a] Photomicrographs of the different types of lesions are shown in the supplement to Halushka et al.

Adapted from Halushka et al. *Cardiovasc Pathol.* 25(3), 247-257. Used with permission from *Cardiovasc Pathol.*

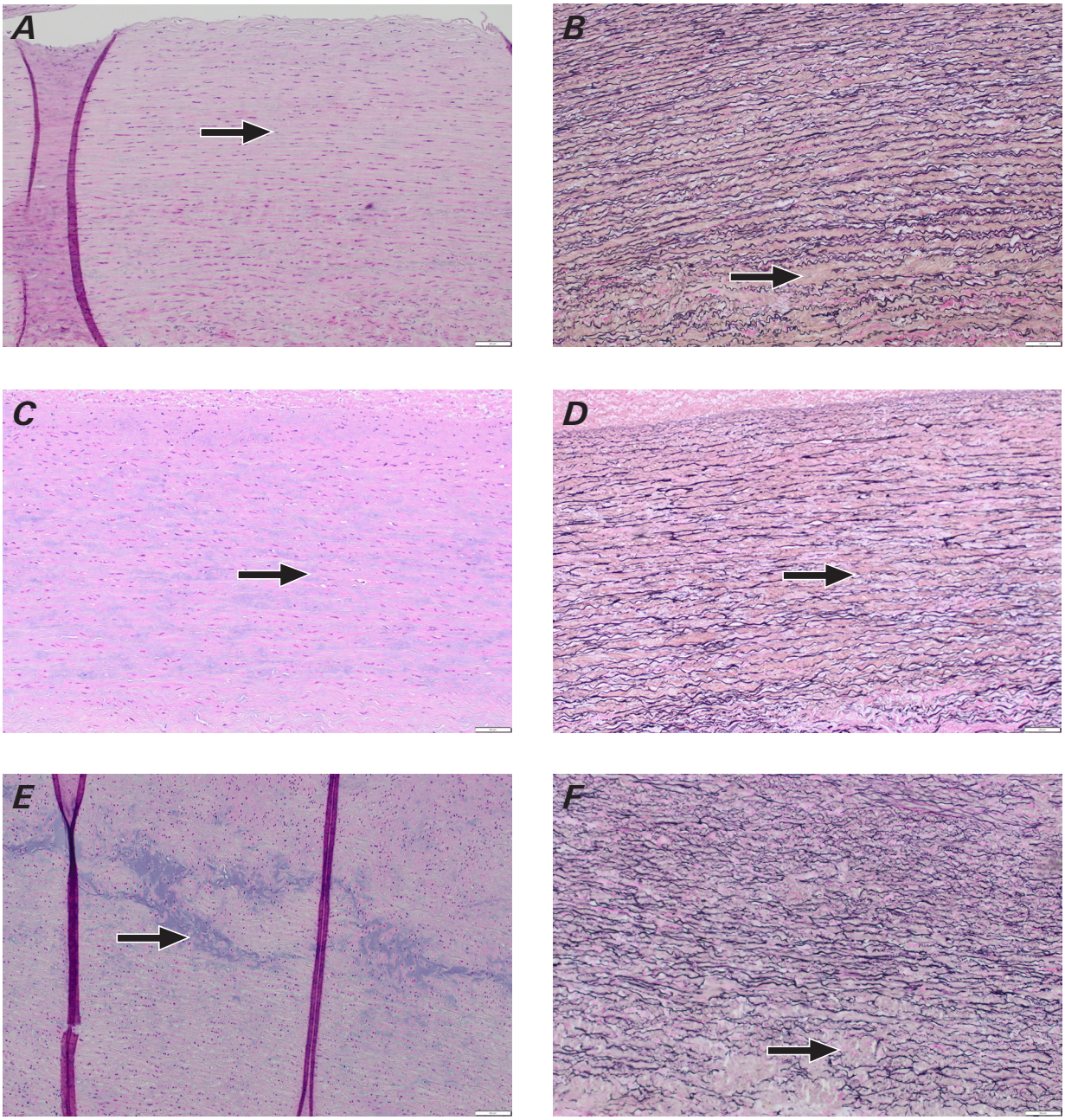


Fig. 1 Representative photomicrographs show mild, moderate, and severe medial degeneration in histologic sections stained with hematoxylin-eosin (**A**, **C**, **E**) and Verhoeff–van Gieson elastic tissue stain (**B**, **D**, **F**). **A**) Mild medial degeneration exhibits a mild increase in basophilic intralamellar MEMA (arrow) in a section stained with hematoxylin-eosin and (**B**) the mild loss of elastic fibers (arrow) in a section stained with elastic tissue stain. **C**) Moderate medial degeneration shows a multifocal increase in intralamellar MEMA (arrow) and (**D**) multifocal attenuation of elastic fibers (arrow). **E**) Severe medial degeneration exhibits multifocal translamellar MEMA (arrow) and (**F**) multifocal translamellar loss of elastic fibers (arrow). Each scale bar represents 100 μm; original magnification for all images is ×50.

MEMA, mucoid extracellular matrix accumulation.

Results

HTAD With Documented Genetic Variations

Patients with HTAD were identified by querying the Division of Medical Genetics database.[6,9,10] Forty-two patients had positive genetic tests and surgical pathology material available that had been obtained during open surgical repair from 2012 to 2020. The 42 individuals had pathogenic variants in 1 of the following 10 established genetic aortopathies: *FBN1,*[11] *ACTA2,*[6] *TGFBR1,*[10] *TGFBR2,*[3] *TGFβ2,*[3] *SMAD3,*[3] *LOX,*[2] *MYLK,*[2] *PRKG1,*[2] and *COL3A1.*[5,7-10]

These aortic specimens were evaluated for intimal lesions, medial dissection, and medial degenerative lesions based on SCVP/AECP consensus criteria.[1] A spectrum of extent and severity of medial degenerative changes was observed: 8 patients (19%) had mild disease, 18 patients (43%) had moderate disease, and 16 patients (38%) had severe disease (Table II). Mucoid extracellular matrix accumulation was particularly prominent in patients with Marfan syndrome (Fig. 2). Of the 42 patients in this study, 17 had aortic dissection and 25 had nondissected aneurysms. When the data were analyzed according to the affected genes, neither the differences in the grade of medial degeneration nor the differences in the frequency of aortic dissection were statistically significant.

Comparative Studies

In an analysis of 86 operative cases of thoracic aortic disease within 1 year, 34 cases were type A aortic dissection, and 52 cases were ascending thoracic aortic aneurysms without aortic dissection (Fig. 2 and Fig. 3). Notable differentiating features of the 86 cases were heritable aortopathy with known genetic variation (12/86) or sporadic disease (74/86), bicuspid aortic valve (BAV) (21/86) or tricuspid aortic valve (TAV) (65/86), and aortic root involvement (23/86) or aortic root spared (63/86). The grading of medial degeneration in the various categories is shown in Figure 3.

Overall medial degeneration was significantly different between inherited and sporadic aortopathy groups, with the inherited group typically having higher severity levels than the sporadic group ($P = .004$). The extent of elastic fiber fragmentation and translamellar MEMA was significantly different between the inherited and sporadic aortopathy groups (elastic fiber fragmentation, $P = .03$; MEMA, $P = .04$), with greater severity observed in the inherited aortopathy group.

TABLE II. Medial Degeneration in Heritable Thoracic Aortic Aneurysm and Dissection (Genetic Aortopathies)

Variant gene	Phenotype	Aortic dissection, No.	Grade of medial degeneration		
			Mild	Moderate	Severe
FBN1 (n = 13)	Marfan syndrome	5	2	6	5
ACTA2 (n = 6)	Aortic aneurysm thoracic familial 6	4	1	1	4
TGFBR1 (n = 7)	Loeys-Dietz syndrome 1	2	3	3	1
TGFBR2 (n = 3)	Loeys-Dietz syndrome 2	1	0	2	1
TGFβ2 (n = 3)	Loeys-Dietz syndrome 4	2	0	1	2
SMAD3 (n = 3)	Loeys-Dietz syndrome 3	1	1	1	1
LOX1 (n = 1)	Aortic aneurysm thoracic familial 10	0	–	1	0
MYLK (n = 1)	Aortic aneurysm thoracic familial 4	1	0	0	1
PRKG1 (n = 1)	Aortic aneurysm thoracic familial 8	0	0	1	0
COL3A1 (n = 4)	Vascular Ehlers-Danlos syndrome	1	1	2	1
Total (N = 42)		17 (40%)	8 (20%)	18 (43%)	16 (37%)

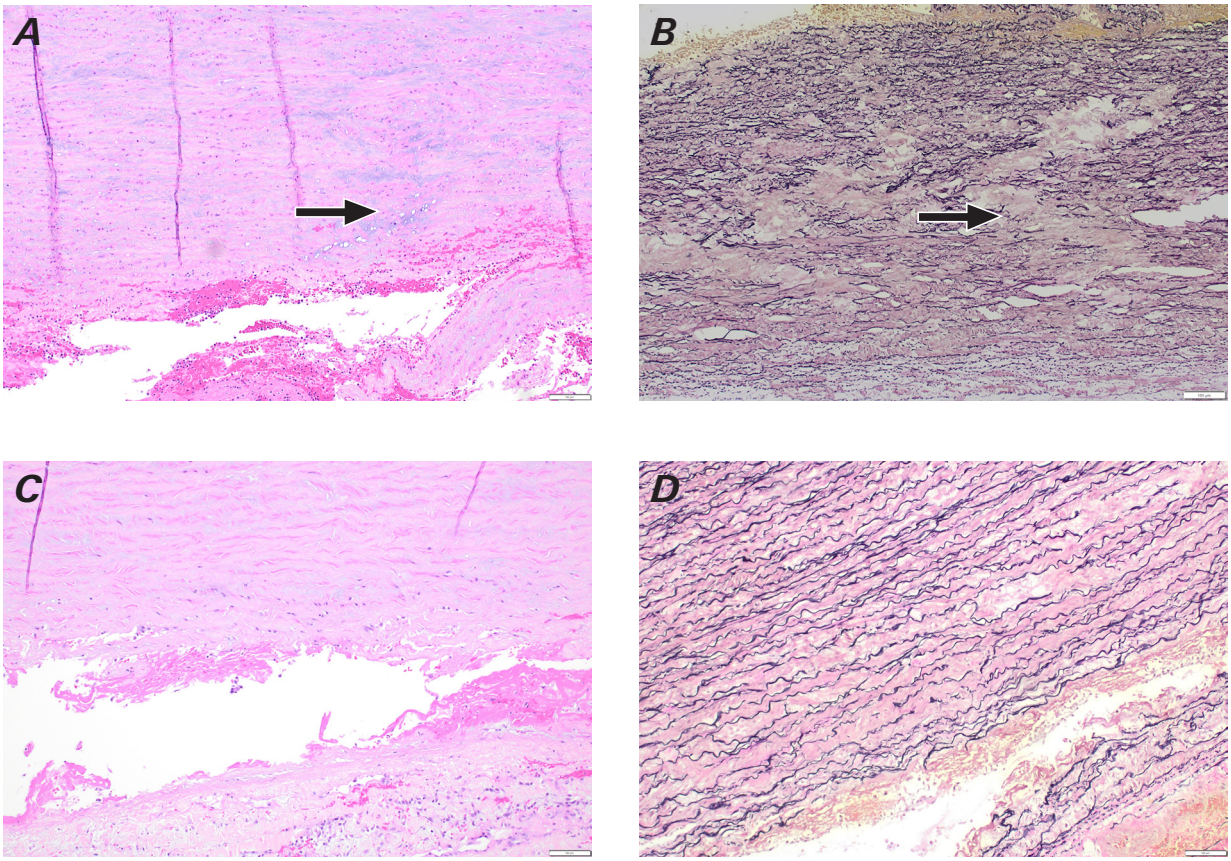
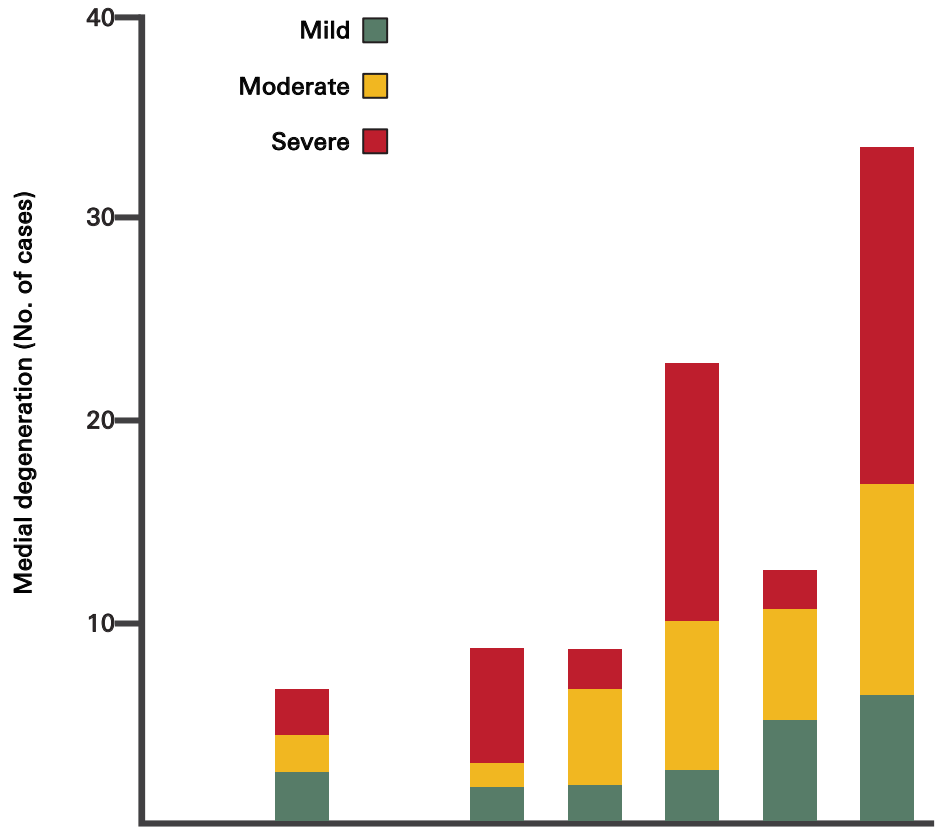


Fig. 2 Representative photomicrographs show the severity of medial degeneration in a patient with documented Marfan syndrome and type A aortic dissection compared with the severity of medial degeneration in a patient with sporadic type A aortic dissection with hematoxylin-eosin stain (**A**, **C**) and with Verhoeff–van Gieson elastic tissue stain (**B**, **D**). **A**) In the patient with Marfan syndrome, the outer and inner media adjacent to the dissection plane show abundant MEMA (arrow; ×50) and (**B**) extensive loss of elastic fibers (arrow; ×50). **C**) In the patient with sporadic aortic dissection, the outer and inner media adjacent to the dissection plane show minimal MEMA accumulation (×150) and (**D**) attenuation of elastic fibers (×150). Each scale bar represents 100 μm.

MEMA, mucoid extracellular matrix accumulation.

Medial degeneration scores were not significantly different between patients with type A aortic dissection and patients with nondissected aneurysms. Extent and severity of elastic fiber fragmentation were significantly lower for patients with BAV than for patients with TAV ($P = .001$ and $P = .002$, respectively). Age was not significantly different between patients with BAV and patients with TAV (mean [SD] age, 57.5 [11.5] years vs 58.2 [16] years; $P = .8$). Most patients with BAVs had a mild (1-5) to moderate (6-10) medial degeneration score. In contrast, most patients with TAVs had a moderate (6-10) to severe (11 to ≥20) medial degeneration score and more frequent type A aortic dissection.

Cases with and without aortic root involvement were also compared. Aortic root involvement was defined as involving the aortic sinuses (Table III). Of the 23 patients with aortic root involvement, 21 had an aneurysm of the sinus of Valsalva, and 2 patients had acute type A aortic dissection. In addition, 7 of the 23 patients had heritable aortopathy with a known genetic variation. The procedures patients underwent included valve-sparing aortic root replacement (David procedure; n = 13), aortic root replacement with a prosthetic aortic valve (n = 6), and reoperation with aortic root or valve replacement (n = 4). The overall medial degeneration severity was significantly different between patients with and without aortic root involvement, with the aortic root involvement group typically having more severe disease than the group with no aortic root involvement ($P = .01$).



Hereditary (H) or sporadic (S)	H	H	H	H	S	S	S	S
Aortic dissection?	YES	YES	NO	NO	YES	YES	NO	NO
BAV or TAV	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

Fig. 3 Histopathologic grading of medial degeneration is shown for 86 patients with thoracic aortic aneurysm and aortic dissection. Overall medial degeneration was significantly different between hereditary and sporadic aortopathy groups, with the hereditary group typically having higher severity levels than the sporadic group ($P = .004$). Significant differences were observed between the hereditary and sporadic aortopathy groups regarding the extent of elastic fiber fragmentation ($P = .03$) and translamellar MEMA ($P = .04$), with both being more severe in the hereditary aortopathy group. 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 ($P = .03$). $P < .05$ was considered statistically significant.

BAV, bicuspid aortic valve; MEMA, mucoid extracellular matrix accumulation; TAV, tricuspid aortic valve.

Another focus of this investigation was sex differences among the cohort of 86 patients with proximal thoracic aortic disease (64 men and 22 women) (Table IV). The overall incidence of thoracic aortopathy was higher in men, accounting for 74.4% of individuals with proximal thoracic aortic disease; however, heritable aortopathy with known genetic variation was more prevalent in women than in men (27.2% vs 9.8%; $P = .03$). Histopathology data showed that women more frequently had translamellar MEMA (45.4% vs 21.8%; $P = .04$), extensive (54.5% vs 22.8%; $P = .02$) and severe (59% vs 32.8%; $P = .04$) elastic fiber fragmentation, extensive smooth muscle nuclei loss (13.6% vs 4.9%; $P = .05$), and focal laminar medial collapse (13.6% vs 1.6%; $P = .01$) than men. Overall histopathologic medial degenerative scores were higher in women than in men ($P = .047$). Among the 86 patients, women had a lower prevalence of thoracic aortic disease treated with open repair than men; however, women who developed thoracic aortic disease harbored a greater burden of aortic wall pathology.

A separate analysis examined the incidence of type A aortic dissection in patients with heritable aortopathy and patients with sporadic etiology, primarily as a complication of hypertension. Of the 34 patients with type A aortic dissections, 10 had genetic aortopathy (group 1), and 24 had sporadic disease (group 2). The percentage of type A aortic dissections was not significantly different between groups 1 and 2 (23.8% vs 27.9%; $P > .5$). Patients in group 1 were significantly younger than patients in group 2 (group 1 mean [SD] age, 49.5 [14.9] years vs group 2 mean [SD] age, 61.9 [16.8] years; $P = .048$). Group 1 had no patients with atheromatous lesions, whereas group 2 had 5 patients with aortic atherosclerosis ($P < .02$). Regarding medial degeneration, no significant differences were observed between groups regarding elastic fiber fragmentation (mean [SD],

TABLE III. Medial Degeneration in Patients With and Without Aortic Root Involvement[a]

Medial degeneration	Mild	Moderate	Severe
Root involvement (n = 23)			
Aortic dissection, No.	0	0	2
Aneurysm, no dissection, No.	1	9	11
Total, No. (%)	1 (4)	9 (39)	13 (57)
No root involvement (n = 63)			
Aortic dissection, No.	5	14	13
Aneurysm, no dissection, No.	11	10	10
Total, No. (%)	16 (25)	24 (38)	23 (37)

[a] The difference in the distribution of medial degeneration scores between patients with and without aortic root involvement did not reach statistical significance ($P = .09$). $P < .05$ was considered statistically significant.

TABLE IV. Assessment of Medial Degeneration in Women and Men With Thoracic Aortic Aneurysm and Dissection[a]

	Score in women				Score in men			
	Mild	Moderate	Severe	Total for women	Mild	Moderate	Severe	Total for men
Hereditary	0	2	4	6	0	1	5	6
Sporadic	2	6	8	16	19	24	15	58
Total	2 (9%)	8 (36%)	12 (55%)	22	19 (30%)	25 (39%)	20 (31%)	64

[a] The difference in the distribution of medial degeneration scores was significant, with significantly greater severe medial degeneration in women than in men ($P = .04$). $P < .05$ was considered statistically significant.

4.4 [1.7] points vs 4.0 [1.5] points; $P = .5$), smooth muscle cell nuclei loss (2.2 [2.3] points vs 1.9 [2.2] points; $P = .70$), or laminar medial collapse (1.1 [1.4] vs 0.5 [1.2] points; $P = .20$). Group 1, however, had a significantly higher level of MEMA than did group 2 (mean [SD], 4.7 [2.1] points vs 2.6 [3.4] points; $P = .04$) (Fig. 2). In both groups, medial degeneration lesions were concentrated on the outer one-third of the aortic media.

Discussion

The study's findings confirm the utility and feasibility of applying the SCVP/AECVP consensus criteria to assess in detail the pathologic substrate of thoracic aortic disease. Its results align with those of other studies that have applied a systematic approach to analyzing aortic specimens.[11-17] Notably, however, managing a patient's situation on the basis of aortic wall pathology is always a postoperative consideration.

Comparative Analysis of Medial Degeneration Among Aortopathies

A particular focus of this study was comparatively assessing patients with sporadic aortopathies and documented heritable aortopathies. Among patients with heritable aortopathy and documented pathogenic genetic variants, considerable overlap in the various types of medial degeneration lesions and the overall severity of medial degeneration was observed (Table IV). Specific trends, however, were noted. Patients with Marfan syndrome frequently had prominent translamellar MEMA (Fig. 2). Some patients with Ehlers-Danlos syndrome had minimal histologic change, despite severe clinical manifestations. This finding can be explained by a basic genetic variation that leads to defective collagen and intact elastic fibers. As was previously reported, *ACTA2* variations[18] showed evidence of dysplasia of the vasa vasorum and disorganization and loss of smooth muscle cells in the aortic media.[18]

In this study's analysis of cases within a single recent year (Fig. 3), overall medial degeneration was significantly different between patients with heritable aortopathy and patients with sporadic aortopathy, with significantly more elastic fiber fragmentation and translamellar MEMA in patients with heritable aortopathy. In both groups, the markers of medial degeneration were concentrated on the outer one-third of the aortic media.

The overall medial degeneration score was high in patients with aortic root aneurysm and HTAD. Most patients with BAVs had low medial degeneration scores, whereas patients with TAVs had moderate medial degeneration scores and a high incidence of type A aortic dissection. In this patient population, women had a lower prevalence of thoracic aortic disease treated with open repair; however, those women who developed thoracic aortic disease harbored a greater burden of aortic wall pathology and had a higher probability of worse outcomes. The adverse outcomes of women with thoracic aortic disease have been noted in other clinical studies.[3]

From this study's findings, the authors posit that the extent and severity of individual pathologic lesions and overall medial degeneration reflect a final common pathway for aortic diseases of genetic and sporadic etiologies; however, the comprehensive analysis was useful in identifying certain features that may differentiate a sporadic from a genetic etiology of proximal thoracic aortic disease, such as more MEMA in patients with HTAD than in patients with sporadic disease (Fig. 3).

Consideration of Findings in the Broader Context of the Literature

Clinicians can gain a broad perspective by comparing these findings with those of other groups that have performed systematic histopathologic analysis of proximal thoracic aortic disease specimens.[11-17] Leone et al[15,16] performed a detailed histopathologic analysis of aortic specimens from patients with ascending thoracic aortic aneurysms and acute aortic syndromes. In a series that examined 158 patients, 2 histologic patterns were identified: medial degenerative alterations alone in 122 patients (77%) and mixed degenerative-atherosclerotic lesions in 36 patients (23%). Patients with mixed degenerative-atherosclerotic disease had a distinct clinical profile characterized by a clinical presentation that often mimics acute coronary syndrome.[16] In another series of 255 patients with surgically treated ascending thoracic aortic aneurysms, the histopathologic lesion was most often a medial degenerative change (67.5%) but with a considerable prevalence of atherosclerotic lesions (18.8%) and aortitis (13.7%).[15] The authors concluded that although degenerative histopathology is the most frequent type of lesion in ascending thoracic aortic aneurysm, atherosclerosis and inflammation also contribute to chronic thoracic aortic aneurysm disease development. This conclusion is in contrast with the current study's findings of a low frequency of aortitis

and minimal atherosclerosis in most patients with ascending thoracic aortic aneurysm or dissection.

In a study by Waters et al,[11] the SCVP/AECVP consensus criteria grading system was used to evaluate 148 surgically resected specimens. The authors found that overall patterns of histopathologic change could be used to distinguish patients with BAVs and nonsyndromic disease from patients with Marfan syndrome and Loeys-Dietz syndrome. Patients with Marfan syndrome had significantly more overall medial degeneration and MEMA than patients with other syndromes. This finding is in agreement with the current study's findings regarding patients with Marfan syndrome.

In a retrospective study, Amemiya et al[13] analyzed aortic specimens from a large cohort (N = 496) surgically treated for aortic diseases at a major European aortic center. Their findings revealed the following: (1) patients without BAVs have higher medial degeneration scores than patients with BAVs; (2) higher medial degeneration scores are correlated with increased aortic diameter; (3) thoracic aortic disease can occur frequently in small aortas associated with high medial degeneration scores; and (4) the clinical risk stratification of aortic dissection based on aortic dimensions is imperfect.

In another large retrospective study of 719 patients, Amemiya et al[12] examined the role of aging and other degenerative processes compared with inflammation in damaging the aortic wall. Using the SCVP/AECVP consensus criteria, they observed higher medial degeneration scores for all aortic sizes in a group of patients with aortitis than in a group of patients without aortitis, especially with respect to elastic fiber damage and smooth muscle cell loss. The authors concluded that aortitis is strongly associated with severe damage to the aortic wall, resulting in advanced medial degeneration scores, and that the inflammatory process induces greater medial degeneration in the aortic wall than aging or other degenerative processes.

In another study, Stejskal et al[17] evaluated aortic dissection specimens using the SCVP/AECVP consensus criteria. They presented their results from 62 ascending aortic dissection biopsies during a 5-year period at a single institution. The most common finding was medial degeneration in 61 patients (98.4%). Atherosclerosis was identified in 19 patients (30.6%), and a chronic giant cell aortitis pattern was seen in 1 patient (1.6%). The results were compared between subgroups of patients with BAVs (n = 7 [11.3%]) and patients with TAVs (n = 55 [88.7%]). No significant differences were observed, except for more severe ($P = .04$) translamellar fibrosis in the BAV group than in the TAV group ($P = .04$). These findings contrast with the current study's finding that patients with TAVs had more severe medial degeneration changes than patients with BAVs.

In summary, studies from several centers, including the current study, have reported histopathologic data generated by applying the SCVP/AECVP consensus criteria for systematically assessing thoracic aortic disease pathogenesis. A particular contribution of the study by Amemiya et al[13] was the reporting of aortic size in relationship to the histopathologic findings.

A consistent finding from most of the studies that applied the consensus criteria was that aortic medial degenerative changes are less severe in patients with BAVs than in patients with TAVs. This finding has been reported by others, as well.[14] Grewal and colleagues[19] further characterized the aortic wall in patients with BAVs and found a vascular smooth muscle differentiation defect in ascending aorta with BAVs before the development of medial degenerative changes and aneurysm formation.[19] They described a significantly thinner intimal layer without features of atherosclerosis ($P < .001$) and a significantly thicker medial layer ($P < .001$) with more MEMA ($P < .001$) in nondilated ascending aortic walls with BAVs than in aortic walls with TAVs. The aortic media had significantly fewer differentiated vascular smooth muscle cells in the BAV group than in the TAV group ($P < .0001$), with reduced expression of α-smooth muscle actin, SM22-α, and smoothelin ($P < .001$) between the neatly regulated elastic lamellae in the BAV group. The findings of Grewal et al[19] are consistent with a vascular smooth muscle differentiation defect in the ascending aorta of patients with BAVs before the development of medial degenerative changes and aneurysm formation.[19]

The Role of Genetic Variants in Thoracic Aortic Disease

Underlying genetic variants strongly influence the risk of thoracic aortic disease.[7-10] To date, pathogenic variants in at least 11 genes have been found to predispose individuals to either syndromic or nonsyndromic heritable thoracic aortic aneurysm and dissection.[7-10] An estimated 30% of patients with HTAD, which is typically inherited in an autosomal dominant manner, also have a pathogenic variant in 1 of these genes. Saxon and colleagues[20] identified pathogenic variants in these 11 genes by analyzing the postmortem tissue or blood in 23.5% of the study's population, individuals who died

suddenly of thoracic aortic disease. These gene variants predispose individuals to aneurysms and dissections of the thoracic aorta and, in some cases, to vascular complications throughout the arterial tree.[7-10] These genes are involved in vascular smooth muscle cell contraction and metabolism, extracellular matrix integrity, and transforming growth factor-β signaling.[7-10] The gene mutation creates an altered milieu, which leads to activation of local inflammation, cytokine activation, increased proteolysis of extracellular matrix components, and deficient smooth muscle cell function.[7-10] Further study is ongoing to correlate the extent and type of medial degenerative lesions with specific gene variations. Research is also in progress to identify other genes that predispose individuals to thoracic aortic disease. In 60% of cases, the gene variation is currently unknown.

Genetic factors are also believed to be important in the pathogenesis of sporadic or late-onset thoracic aortic diseases—specifically, genes that predispose the individual to the disease in combination with other risk factors, such as hypertension. Single-cell transcriptome analysis has revealed dynamic cell populations and differential gene expression patterns that control aneurysmal aortic tissue.[21] Proteomic analysis has shown some overlapping differentially expressed proteins between aneurysmal and nonaneurysmal descending thoracic aortas at risk of dissection compared with normal aortas as well as uniquely altered molecular pathways that may represent mechanisms for dissection.[22] These findings imply that selective gene activation is integral to developing different types of aortic pathology.

A unifying hypothesis to explain the spectrum of thoracic aortic disease is that variant genes and the selective activation of genes in sporadic disease cause vasculopathy by producing alterations in the functional integrity of the lamellar units.[23-25] Ultrastructural analyses have identified impaired connections between vascular smooth muscle cells and elastic fiber extensions and the loss of interconnecting elastic fibers that bind the longitudinal elastic fibers across lamellar units, particularly in the outer media.[23,25] These alterations have been postulated to lead to altered mechanotransduction and the progressive impairment of aortic smooth muscle function and structure, followed by the accumulation of MEMA and degeneration of the longitudinal elastic fibers of the lamellae.[9,24] This process, in turn, leads to the various lesions of medial degeneration identified by using the SCVP/AECVP consensus criteria.[1]

Although the literature has shown the importance of genetic factors in the pathogenesis of thoracic aortic aneurysm and dissection, this study has shown that formal genetic analytical data are often unavailable in everyday practice. This finding has led to the development of a proposed scheme for assigning a genetic component to cases of thoracic aortic disease (Table V).

Limitations

This study had limitations. Most notably, the number of patients in both substudies was relatively small. Also, the obtained pathologic information was available only after the surgeries were complete and was unavailable for making intraoperative decisions.

TABLE V. Proposed Paradigm for Assessing the Genetic Contribution to Thoracic Aortic Disease

Major genetic contribution (labeled HTAD)	Individuals with identifiable pathogenic variants in a gene causing thoracic aortic disease or individuals with relatives with thoracic aortic disease or with early-onset disease (age, <55 y) who do not have an identifiable variation in a known HTAD gene.
Intermediate genetic contribution	Individuals without an identifiable gene variation or family history who present at a relatively young age (<55 y) and have other environmental or lifestyle risk factors. In these patients, thoracic aortic disease is likely the result of a combination of lower-penetrance genetic variants and risk factors such as hypertension.
Minor genetic contribution	Individuals with relatively late-onset disease (age, >60 y) and no identifiable variation or family history. In these patients, thoracic aortic disease is primarily driven by risk factors such as hypertension or smoking.

HTAD, heritable thoracic aortic disease.

Conclusion

The SCVP/AECVP consensus criteria have made important contributions to the establishment of a uniform system for reporting pathologic findings and have provided a histopathologic basis for ongoing research in aortic diseases. The current study's findings indicate considerable overlap in the pattern, extent, and severity of medial degeneration between sporadic and hereditary types of aortic disease, suggesting that histopathologic medial degeneration represents a final common outcome resulting from diverse pathogenetic factors and mechanisms. This study's findings are consistent with those of others, supporting the concept that less aortic pathologic change occurs in patients with BAVs than in patients with TAVs. The study's findings also highlight important differences in disease features between men and women. It is therefore recommended that future studies perform sex-based analyses of all research on thoracic aortic diseases.

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