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BIOLOGY OF AORTIC ANEURYSMS AND DISSECTIONS

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Abstract

The biology of aortic aneurysm and dissection has evolved to where we now understand the genetic implications of changes in extracellular matrix proteins, smooth muscle cells, and growth factors and how they affect aortic wall homeostasis. These predeterminants are influenced by smoking, hypertension, and atherosclerosis, and the result is an inflammatory response coupled to an accelerated proteolytic cascade that disrupts both elastin and collagen in the aortic wall.

Biology of Aneurysms

Aortic aneurysms continue to be a significant medical problem with a high associated mortality. In 2000, data from the National Vital Statistics Report on Deaths showed that abdominal aortic aneurysms (AAA) and aortic dissections are the 10th-leading cause of death in men 65–74 years of age (4:1 male to female ratio) and cause more than 12,000 deaths annually.[1] Therefore, understanding the pathogenesis and biology of aneurysms and dissections becomes paramount in the management of these diseases and their associated risk factors.

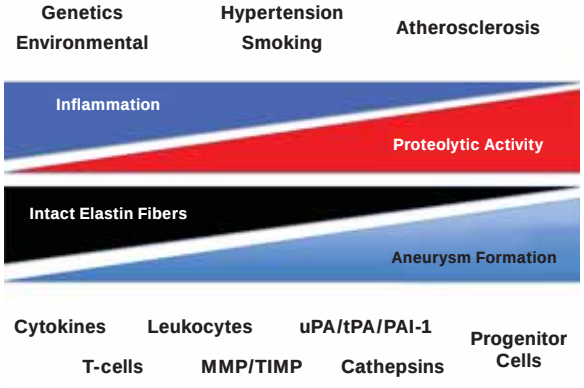

Figure 1. Aortic aneurysm pathobiology. The development of aortic aneurysms is dependent on a combination of predisposing genetic factors and environmental influences that allow for an augmented inflammatory, proteolytic, and cellular response. This milieu of agents induces loss of elasticity and dilatation of the vessel wall.

The pathogenesis of aortic aneurysms is complex and multifactorial (Figure 1). The Committee for Reporting Standards of Arterial Aneurysms defines an aneurysm as a 50% increase in the diameter of a vessel in comparison with its expected normal diameter.[2] Occurrence of extracranial aneurysms has been reported throughout the entire arterial tree, but the predominant location for aneurysms is the infrarenal aorta. In the normal aorta, there is a gradual reduction of the medial elastin fibers, decreasing from 80 layers in the thoracic aorta to 30 in the infrarenal portion. There is also a thinning of collagen within the media and thickening of the intima in the distal aorta. This anatomic difference is the rationale for suturing open aortic grafts as close to the renal arteries as possible to remove all low-collagen-layer infrarenal aorta.

Extent	Origin and Location
I	Distal to L SCA to above the renal arteries
II	Distal to L SCA to below the renal arteries
III	6th IC space to below renal arteries
IV	12th IC space to iliac bifurcation
V	Below 6th IC space to above the renal arteries

Table 1. TAAA classification. L SCA: left subclavian artery; IC: intercostal

Based on their general location (thoracic, thoracoabdominal, and abdominal), each aneurysm is then further classified based on its specific location. Thoracic aneurysms are most commonly located in the descending aorta, arising at the level of the subclavian artery.[3] Aneurysms of the ascending aorta are rare and associated most commonly with Marfan syndrome. The thoracoabdominal aneurysm (TAAA) has a more detailed classification based on origin and extent of dilation caudad. The classification of extent will dictate the tailoring of therapy. Table 1 outlines this TAAA classification.

Abdominal aortic aneurysms are classified primarily based upon how far they extend cephalad. Ninety-five percent of all AAAs are classified as infrarenal AAAs and may or may not extend to the iliac arteries.[4] The management of AAAs associated with common iliac artery aneurysms is the same as the management of the AAA alone; they should be considered a single entity. Juxtarenal aneurysms extend to the level of the renal arteries, and suprarenal aneurysms extend proximally to the level of the superior mesenteric artery and/or the celiac arterial trunk. Despite being found in anatomically distinct locations, the pathogenesis and risk factors associated with the development of aortic aneurysm — whether thoracic, thoracoabdominal, or strictly abdominal — are similar.[5-8]

Risk Factors for and Mechanisms of Aneurysm Formation

Aortic aneurysm formation is associated with advanced age, male gender, cigarette smoking, atherosclerosis, hypertension, and genetic predisposition.[5] The Aneurysm Detection and Management Veterans Affairs Cooperative Study Group (ADAM) identified smoking as the strongest modifiable risk factor for the development of aneurysm. Additionally, elderly age and male

gender were among the three principal risk factors for aneurysmal development and progression.[7, 9] Aortic aneurysm is a disease rarely found in those under the age of 50, and the incidence of death from AAA is 11-fold higher in men aged 60-64 years than in women of the same age.[10] In a recent series, the mean age of patients undergoing repair was 72 ± 7 years.[10] It should be noted that the risk factors for aortic aneurysm development are similar to those of atherosclerosis.[9, 11] Historically, aneurysms were referred to as atherosclerotic aneurysms. This misnomer has been corrected in the medical nomenclature, although atherosclerotic changes are almost universally noted in the aorta at the time of aneurysm repair.[11]

Autoimmune and Genetic Factors

Aortic aneurysm formation has been linked with various autoimmune diseases, including giant cell arteritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, and antiphospholipid syndrome. Similar to these autoimmune diseases, the risk of AAA is perhaps increased by certain genotypes related to human leukocyte antigen class II molecules.[12] Other genetic associations include Marfan and Ehlers Danlos syndromes. The molecular defects in the fibrillin-1 gene, the hallmark of Marfan syndrome, are responsible for impaired structural integrity of the cardiovascular system and specifically that of the aortic root.[13] The defective gene therefore predisposes these individuals to aortic dilation and dissection. These aneurysms are considered to be degenerative. Histologically, fragmentation and degeneration of elastic fibers in the arterial media is commonly observed.

Mycotic Aneurysms

Mycotic aneurysms are rare and can be caused by viral, bacterial, fungal, or spirochetal agents. This is in contrast to the historical prevalence of aneurysms secondary to syphilis in the pre-antibiotic age. Viral and Chlamydia pneumoniae infections may contribute to aneurysm development through the inflammatory cascade. One study on characteristics of the aortic aneurysm wall found Chlamydial antigens in a majority of the AAA tissue when compared to the healthy tissue.[14, 15]

Mycotic aneurysms will typically develop at the focal site of an infected atherosclerotic plaque or an infected long-standing aneurysm. Hemodynamics also play a role in aneurysm formation due to the spatial and temporal variations in hemodynamic forces, the formation of regions of stasis, and the transition to turbulence that facilitate intraluminal thrombus formation, lipid deposition, and various inflammatory mechanisms.[16, 17]

Connective Tissue Degradation and Protease Involvement

Degradation of aortic wall connective tissue has been shown to be a hallmark of AAA formation. Collagen and elastin are the two major connective tissues found in the aorta. Histologically, elastin fragmentation and degeneration are observed in the aneurysm wall.[18] Increased turnover and loss of types I and III fibrillar collagens, as well as excessive elastolysis caused by increased collagenase, elastase, and especially matrix metalloproteinase (MMP) expression, probably underlie aortic dilation and rupture. The major forms of collagen found in the aorta are type I and III.[19] The expression of types I and III is found to be increased in aneurysmal tissue.[20] The increased expression of collagen is localized to adventitial fibroblasts, medial smooth muscle cells, and transformed myofibroblasts found within areas of local inflammation and atherosclerosis.[21] As mentioned previously, there is a gradual reduction of the medial elastin fibers, decreasing from 80 layers in the thoracic aorta to 30 in the infrarenal portion. This reduction plays a critical role in the development of the infrarenal abdominal aortic aneurysm. Elastin, the scaffold of the medial lamellae, is found in a reduced concentration as well as in a fragmented organization within tissues of diseased aorta.[22]

Cytokines regulate matrix metalloproteinase, serine protease, and cathepsin expression. MMPs (MMP-1, -2, -3, -9, -12, and -13), serine proteases (tissue-type plasminogen activator [t-PA]; u-PA; plasmin; and neutrophil elastase), as well as cysteine proteases (cathepsin D, K, L, and S) all localize in aneurysm walls at concentrations higher than those that occur in normal or stenotic atherosclerotic arteries.[23, 24] Endothelial cells, smooth muscle cells, fibroblasts, or macrophages can all produce these proteinases. CD40 ligation on inflammatory and vessel wall cells induces MMPs as well as neutrophil elastase expression and release from human vascular endothelial cells and monocyte/macrophages.

Growth and rupture of aortic aneurysm have been shown to result from increased collagen turnover as evidenced by increased type I collagen degradation products within the wall of aortic aneurysms.[25] Collagen turnover critically depends on specific collagenases that cleave the triple helical region of fibrillar collagen. The study of the pathogenesis of aortic aneurysm has focused on its collagenolytic properties and degradation of the extracellular matrix. The extracellular matrix contains embedded vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), both of which are responsible for maintaining the extracellular matrix. These factors are downregulated by MMPs. Both MMP-2 and MMP-9 expose a cryptic epitope that inhibits angiogenesis and can control the inflammatory response through the modification of pro-inflammatory cytokines, chemokines, and shedding of membrane receptors.[23, 26]

The activity and expression of these and other proteases is altered in the diseased segments of aortic aneurysmal tissue.[27, 28] These degradative enzymes are secreted from macrophages and aortic smooth muscle cells. MMP activation, specifically, plays a role in the degradation of collagen and elastin. Elastases MMP-2, MMP-9, and MMP-12 are shown to have increased expression and activity in aortic aneurysmal tissue.[23, 24, 26] MMP-2, gelatinase A, is constitutively produced by native mesenchymal cells and has the capacity to degrade not only elastin but also intact fibrillar collagen.[23] High concentrations of MMP-2 are found in small aneurysmal aortas, suggesting a role for the proteinase in early aneurysmal formation. MMP-9, gelatinase B, has the ability to degrade elastin as well as partially hydrolyzed collagen. This inducible enzyme localizes to areas of inflammation in the aortic wall, where infiltrating macrophages can be found. The role for MMP-9 has been supported by the observation that MMP-9 knockout mice do not form aneurysms.[29] Confirmation of this finding was achieved by transplanting wild-type bone marrow into the knockout mice and observing aneurysm formation. Also, when compared to aortic tissue in aorto-occlusive disease, MMP-9 is elevated in the tissue of AAA patients.[30] In addition to the well-investigated MMP-2 and MMP-9, other proteases and their inhibitors have been implicated in the pathogenesis of aneurysms. MMP-12 has been localized to areas of elastin destruction and shown to be elevated in diseased tissues when compared to controls.[24] Unlike other proteases, though, its presence is not absolutely required for the genesis of aneurysm.[29] The endogenous inhibitor of cysteine proteases, Cystatin C, has been shown to be reduced in aneurysmal tissues.[31] Treatment with an MMP-inhibiting tetracycline inhibits the development of experimental AAA in vivo.[32] Prolonged administration of doxycycline is safe and well tolerated by patients with small asymptomatic AAAs and is associated with a gradual reduction in plasma MMP-9 levels.[33, 34]

Inflammation

Inflammation is known to play a large role in the development of aortic aneurysms; as aneurysm size increases, the intensity of the inflammatory cell infiltrate also increases. Chronic transmural inflammation, destructive remodeling of the elastic media, and depletion of medial smooth muscle cells are hallmarks of the degradative process.[28] Immune-mediated processes involving acute phase reactants, IFN-γ-producing T cells, and pro-inflammatory cytokines play an important role, especially in the initiation of aneurysms. They have been associated with aneurysm size and are conceivably produced by the aneurysmal tissue itself. In vitro studies reveal that IL-10, IL-6, and C-reactive protein are present at higher circulating levels in AAAs compared to controls. There is decreased expression of multiple cytokines and chemokines as well as diminished leukocyte trafficking in female aortas compared with male aortas.[35]

Studies have shown how this intense inflammatory infiltrate precedes the development of an enlarged aorta. The elastase infusion model has been used to evaluate the aneurysmal process.[27, 28] In this in vivo model, the infrarenal aorta is infused with porcine pancreatic elastase. Mice infused with elastase with cyclosporine or methylprednisolone did not develop AAAs. The transmural infiltration of inflammatory cells has been hypothesized to be the catalyst for the release of cytokines that in turn trigger many of the previously mentioned proteases. It is also thought that this infiltrate may begin or amplify the digestion process by releasing elastin degradation products that have been shown in vitro to attract mononuclear phagocytes. What has not been shown is the inciting event that leads to the elastin degradation cascade. One thought is that the process of aneurysm formation also has an autoimmune component. This is supported by the extensive lymphocytic and monocytic infiltrate in the adventitia and the immunoglobulin G deposition in the aortic wall.[28] This infiltrate leads to the accumulation of cytokines in the aortic wall; these cytokines then activate the MMPs linked to the collagen and elastin breakdown.

Reactive Oxygen Species

Another area of interest has been the role of reactive oxygen species. Superoxide levels in aneurysmal tissue are 2.5-fold higher than in adjacent non-aneurysmal tissue and 10-fold higher than in control aorta.[36] In the elastase infusion model, more than a 50-fold increase in nitric oxide synthase was observed 2 days after infusion with porcine pancreatic elastase.[37] The reactive oxygen species environment has been shown to increase MMP activity in vitro and, more importantly, increase apoptosis. The histology of aneurysmal tissue shows a decreased density of vascular smooth muscle cells (VSMC). Reactive oxygen species have been shown to induce apoptosis in in-vitro models of vascular smooth muscle cell degradation. The oxidative stress may be another catalyst or propagator of the degenerative cascade of aneurysm formation.[38]

Biomarkers for AAA

A large number of studies have associated different circulating biomarkers with AAA presence or progression. Plasma concentrations of D-dimer reflect the extent of fibrin turnover in the circulation.[38] Recent studies have shown a consistent diagnostic value to the use of D-dimer testing for AAA in addition to clinical exam and other biomarkers. D-dimer has also been shown to be elevated in the aorto-occlusive disease group.[39] Plasma concentrations of D-dimer, though, have been shown to be much greater in patients with AAA than in those with atherothrombosis alone.[39] Recent studies show the diagnostic and prognostic value of D-dimer in disparate population samples, including patients with differing risks and associated arterial diseases.[40]

System	Type	Criteria
DeBakey	Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
	Type II	Originates in and is confined to the ascending aorta
	Type III	Originates in the descending aorta and extends distally down the aorta or rarely retrograde into the aortic arch and ascending aorta
Stanford	Type A	All dissections involving the ascending aorta, regardless of the site of origin
	Type B	All dissections not involving the ascending aorta

Table 2. Aortic dissection classification.

Biology of Dissection

Thoracic aortic dissection (TAD) is estimated to occur at a rate of 3–4 cases per 100,000 persons per year.[41] Aortic dissections may be classified according to the DeBakey or Stanford classifications (Table 2). Two-thirds of patients with aortic dissection are male, and 62% have a documented type A dissection. Furthermore, patients with a type B dissection are generally older than their type A dissection counterparts (mean of 66 vs. 61 years, respectively).[42, 43] In contrast, patients with penetrating aortic ulcers and intramural hematomas are even older, with a mean age of 77 years (reflecting the increased frequency of atherosclerosis associated with aortic ulcers) and 69 years, respectively.

Nienaber et al. evaluated differences in aortic dissection by sex.[44] Nearly twice as many women as men older than 70 years experienced an aortic dissection, but surprisingly, fewer women were accurately diagnosed as having an aortic dissection within the first 24 hours of hospital presentation compared with men, despite women having a greater frequency of hypertension in the study. With the exception of age (women older than 70 years were more likely to present with aortic dissection), few significant differences existed in the presenting signs and symptoms between men and women.

Chronic acquired conditions, such as systemic arterial hypertension, sometimes in combination with atherosclerosis, cause thickening and fibrosis of the intimal layer and degradation and apoptosis of smooth muscle cells in the media. These processes lead to necrosis and fibrosis of the elastic components of the arterial wall, which in turn produce wall stiffness and weakness from which dissection and rupture may arise. Seventy-five percent of patients with aortic dissection have a history of hypertension.[42] Other acquired conditions that have been associated with acute aortic dissection include direct blunt trauma, tobacco use, hyperlipidemia, cocaine use (including crack cocaine), and pregnancy.[45]

Risk Factors for and Mechanisms of Aortic Dissection Formation

The biology of dissection is different from that of aortic aneurysms (Figure 2). The aortic wall consists of three layers (tunica intima,

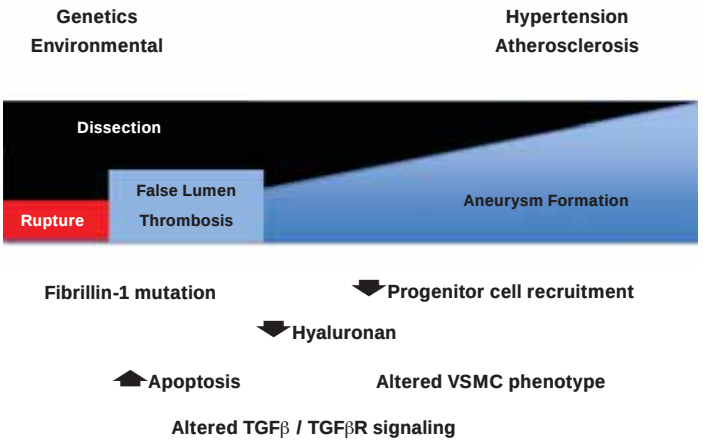

Figure 2. Aortic dissection pathobiology. The development of aortic dissections is dependent on a specific genetic abnormality in extracellular matrix proteins and cytokines, coupled to the presence of chronic hypertension and atherosclerosis. The changes in the vessel wall are associated with loss of vascular smooth muscle cell (VSMC) and a change in VSMC phenotype. Acute dissection can lead to rupture or false lumen thrombosis, and chronic dissections result in aneurysm formation, likely through some of the mechanisms noted in Figure 1.

tunica media, and adventitia). Acute aortic dissection is presumed to occur when an intimal tear develops, permitting entry of blood into a diseased underlying media characterized by elastic degeneration and smooth muscle cell loss. In the normal thoracic aorta, there are peaks in wall stress above the sinotubular junction and distal to the left subclavian artery ostium. This stress distribution may contribute to the pathogenesis of aortic dissections.[46] The dissected aorta is dominated by local, highly disturbed, and possibly turbulent flow with strong recirculation. A significant proportion (about 80%) of the aortic flow enters the false lumen, which may further increase the dilatation of the aorta. High values of wall shear stress have been found around the tear on the true lumen wall, perhaps increasing the likelihood of expanding the tear. Turbulence intensity in the tear region reaches a maximum of 70% at mid-systolic deceleration phase. Incorporating the non-Newtonian behavior of blood into the same transitional flow model has yielded a slightly lower peak wall shear stress and higher maximum turbulence intensity without causing discernible changes to the distribution patterns. In contrast to chronic stable aortic dissection, all acute or acute progressive aortic dissections showed accentuated (18)F- fluorodeoxyglucose uptake at the injured aortic wall or dissection membrane. The maximum standardized uptake values of the dissection membrane or aortic wall were significantly higher in acute aortic dissection than in chronic stable aortic dissection.[47]

The influence of tear location can be examined using three computational fluid dynamics (CFD) configurations. Pressure in the true lumen for all three configurations was similar and varied about 3.4% (largest variation between configuration 1 and 3). Pressure in the false lumen increased by 7.4% for configuration 2 compared to configuration 1 and dropped by 97% for configuration 3 compared to configuration 1.[48] Increased systolic pressure in the false lumen and true lumen was found once the re-entrance tear was occluded (increases by 13%), with the largest intraluminal pressure differences in the distal aorta (2,500 Pa). Occluding the entrance tear, which simulates placement of an EVAR (endovascular aortic repair) device, lowered the false lumen pressure essentially to zero. Removing the intravascular septum to simulate aortic fenestration lowers systolic pressure in the combined lumen by a factor of 3.

Diseases affecting the ascending aorta, such as thoracic aortic aneurysms and type I and II dissections, are primarily associated with medial necrosis on pathologic examination. Medial necrosis is characterized by fragmentation and loss of elastic fibers, loss of smooth muscle cells, and interstitial collections of collagenous tissue and basophilic ground substance. Medial necrosis occurs as part of the normal aging of the aorta but is accelerated by other conditions, including hypertension and genetic alterations that predispose persons to these aortic diseases. In dissecting aneurysms of the thoracic aorta, there is localized expansion of the aortic matrix due to deposition of collagen and other proteins, which decreases the concentration of matrix constituents, including collagen. Comparisons of areas of dissection with corresponding areas of no dissection in aortic specimens showed significant increases in the content of elastin, the content and concentration of proteins other than elastin and collagen, and a decrease in elastin concentration. There were no differences in elastin cross linking. Elastin from dissected aortas had a higher content of aspartate, threonine, serine, glutamate, and lysine and a lower content of glycine, alanine, and valine than elastin from controls. Similar distributions of hyaluronan, versican, decorin, and biglycan were seen in normal and dissected aortas; versican and hyaluronan were more prominent in the external half of the medial layer where the dissection usually occurs.[49]

Type I collagen is the major component of the aortic adventitia, whereas type III collagen comprises the majority of the collagen in the medial layer and is also the major collagen synthesized by smooth muscle cells. In accord with these findings, a number of genetic collagen defects in humans and mice are associated with rupture of the aorta and other large vessels. Patients with type IV Ehlers-Danlos syndrome, caused by mutations in type III collagen, are at risk for rupture of the aorta and other large arteries.[50] Similarly, mice that are null for type III collagen develop dissecting arterial aneurysms that rupture prenatally or in early adulthood. Experimental data has shown that the integrity of the aortic wall depends on an adequate content of type I collagen, and that continued synthesis of collagen in the aorta as a function of age is critically dependent on sequences in the first intron of the COL1a1 gene.[51]

Marfan syndrome (MFS), a relatively common autosomal dominant hereditary disorder of connective tissue with prominent manifestations in the skeletal, ocular, and cardiovascular systems, is caused by mutations in the gene for fibrillin-1 (FBN1). The leading cause of premature death in untreated individuals with MFS is acute aortic dissection, which often follows a period of progressive dilatation of the ascending aorta.[52] There is overexpression of TGF-β in MFS associated with altered hyaluronan synthesis, increased apoptosis, impaired progenitor cell recruitment, and abnormal directional migration. These factors limit tissue repair and are likely to contribute to aneurysm development.[53] Mutations in vascular smooth muscle cell (VSMC)-specific beta-myosin (MYH11) and alpha-actin (ACTA2), two major components of the VSMC contractile unit, cause familial thoracic aortic aneurysms leading to acute aortic dissections.[54] Twenty-two missense mutations in ACTA2, which encodes α-smooth muscle actin, have been identified to cause thoracic aortic aneurysms and dissections.[55]

Studies of the genes that predispose persons without known syndromes to these aortic diseases are focusing on the TAAD1 locus, a major locus for familial thoracic aortic aneurysm and dissection.[56] Familial TAAD demonstrates genetic heterogeneity, and linkage studies have identified three TAAD loci at 5q13-14 (TAAD1), 11q23 (FAA1), and 3p24-25 (TAAD2). The first genes identified to cause TAAD were FBN1, TGFBR2, and TGFBR1. The

underlying genetic heterogeneity of TAAD is reflected in the phenotypic variation associated with familial TAAD with respect to age of onset, progression, penetrance, and association with additional cardiac and vascular features. Recently, mutations in the TGFBR2 gene have been identified as the cause of disease linked to the TAAD2 locus, supporting the hypothesis that dysregulation of TGF-β signaling is a mechanism leading to aneurysms and dissections.[57]

Conclusion

Aortic aneurysm and dissection continues to be a multifactorial disease process with high mortality and morbidity. Both are associated with advanced age, male gender, cigarette smoking, atherosclerosis, hypertension, and genetic predisposition. It is known that inflammatory cell infiltrate and matrix degradation are involved in at least the progression of the aneurysm. Infectious models have been proposed but only substantiated with respect to their involvement in the inflammatory cascade, not the initiating event. Degradation by proteases and under-regulation of proteases by inhibitors have been shown to play a major role in the elastin fragmentation and degradation.

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