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Introduction

Aortic diseases represent a variety of conditions from clinically silent to acutely symptomatic, which affect virtually any part of the aorta (Fig. 2.1). In-depth studies of the mechanisms of aortic disease (via clinical observations, genetic studies, molecular biology research, and bioengineering modeling) conducted increasingly over the past two decades have significantly enhanced our understanding that the aorta is an active living organ and not just a passive hollow conduit that transports blood [1, 2]. Understanding how the aorta functions under normal circumstances as well as under pathologic conditions is critical for predicting its behavior in order to allow effective and timely management of patients with aortic disease.

Aneurysms of the thoracic aorta are among the most challenging conditions to detect and treat, primarily because of their silent yet virulent nature [1]. Patients who harbor an aneurysm in the chest are often unaware until the “silent killer” [3] strikes, producing either death or a serious complication that is likely to lead to death, such as aortic rupture or dissection [4]. Therefore, the main goals of physicians treating thoracic aortic aneurysm (TAA) are first to identify those individuals harboring or at risk of developing an aneu-

rysm, and second to predict accurately the likely behavior of the diseased aorta in these individuals.

TAAAs are often identified incidentally during diagnostic imaging procedures performed for other purposes. However, active identification of affected patients can be achieved by screening relatives of patients with known aortic disease and by detecting certain conditions that have been shown to be associated with thoracic aortic disease (TAD). These conditions include bicuspid aortic valve [5], intracranial aneurysm [6], aortic arch anomalies (such as bovine aortic arch, isolated left vertebral artery, and aberrant right subclavian artery) [7, 8], abdominal aortic aneurysm [9], temporal arteritis [10], simple renal cysts [11], inguinal hernias [12], among others. Accordingly, we recommend a “guilt-by-association” approach for detecting individuals either harboring a TAA or at risk of developing a TAA in the future (Fig. 2.2) [13].

In this chapter we review in detail the second component—the mechanism of development and natural history (or behavior) of TAD as a means for predicting behavior of the diseased aorta.

Most Common Types of Thoracic Aortic Pathology

It is important to define the various types of thoracic aortic pathology whose mechanisms and natural history are discussed throughout this chapter. For the purpose of this chapter we selected the following clinically relevant types of TAD:

1. *Aortic aneurysm*—is an enlargement of the aorta to greater than 1½ times its normal size [14]. Depending on the involvement of the aortic root and the ascending aorta in the disease process, aneurysms in this proximal anatomic region can be classified as being supra-coronary (involvement of the ascending aorta only, with the aortic root normal in size), Marfanoid (predominant involvement of the aortic root only, while much of the ascending

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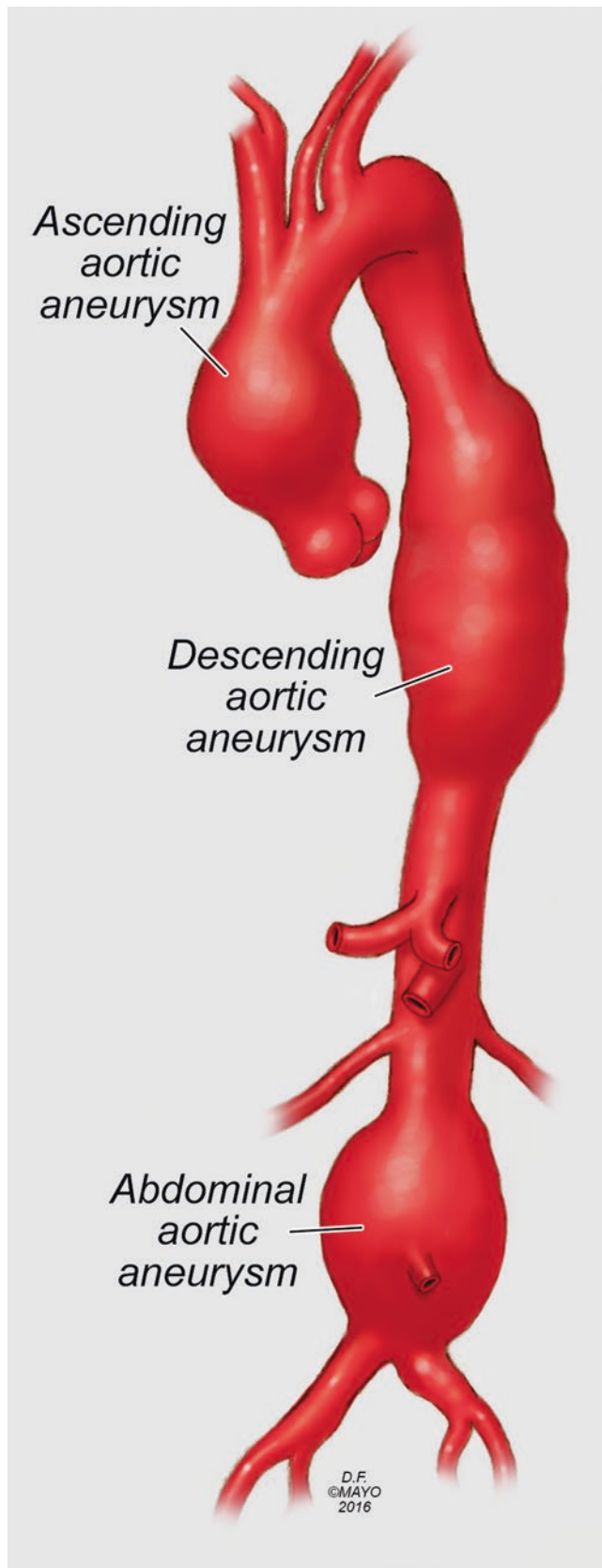


Fig. 2.1 Aortic aneurysm disease can affect virtually any part of the aorta—the ascending and arch portion, the descending thoracic, and the abdominal segments. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

aorta is normal in size), and tubular (involvement of both the aortic root and ascending aorta). See Fig. 2.3 (please note that the aorta may have a “Marfanoid” configuration in the absence of clinical Marfan’s disease in the patient).

Aneurysms located in the descending thoracic and thoracoabdominal segments of the aorta are categorized using the original Crawford classification system [15] (Fig. 2.4):

- (a) *Type I*—involves the majority of the descending thoracic aorta and the suprarenal part of the abdominal aorta.
 - (b) *Type II*—involves the entire descending thoracic aorta and the entire abdominal aorta down to the aortoiliac bifurcation.
 - (c) *Type III*—involves the lower (distal) part of the descending thoracic aorta and the entire abdominal aorta down to the aortoiliac bifurcation.
 - (d) *Type IV*—involves the abdominal aorta below the diaphragm and down to the aortoiliac bifurcation.
 - (e) *Type V (Safi modification [16])*—involves the lower (distal) part of the descending thoracic aorta and the suprarenal part of the abdominal aorta.
2. *Acute aortic syndrome* is a collective term that includes the following heterogeneous group of painful, emergent, and potentially life-threatening conditions (Fig. 2.5):
 - (a) *Aortic dissection*—splitting of the layers of the aortic wall, usually occurring within the medial layer of the aorta with an evident intimal tear, allowing longitudinal propagation of a false lumen filled with blood [4].
 - (b) *Intramural hematoma*—a concentric, circumferentially oriented collection of thrombus in the aortic wall, without the discrete transluminal flap typical of aortic dissection.
 - (c) *Penetrating aortic ulcer*—localized perforation of the medial layer of the aortic wall beneath an atherosclerotic plaque (Figs. 2.5 and 2.6).
 - (d) Any of the three above-mentioned conditions can lead to another acute condition called *aortic rupture* (as can a severely enlarged aneurysm), which is a self-explanatory term.
 3. *Aortic transection* is usually traumatic in etiology. A transection is a disruption of the continuity of the aortic wall, without a propagating dissection (Fig. 2.7). Contrary to aortic dissection, the aortic wall is intrinsically normal and resistant to the dissection process [2].

Pathophysiology Involved in the Development of Aortic Aneurysm

For decades significant efforts have been undertaken to elucidate the pathophysiology of thoracic and abdominal aortic aneurysm formation [4, 17–22]. This process is complex and includes multiple components, such as inflammation, proteolysis, matrix injury, and dysfunction and necrosis of smooth muscle cells in the aortic wall (Fig. 2.8) frequently in the

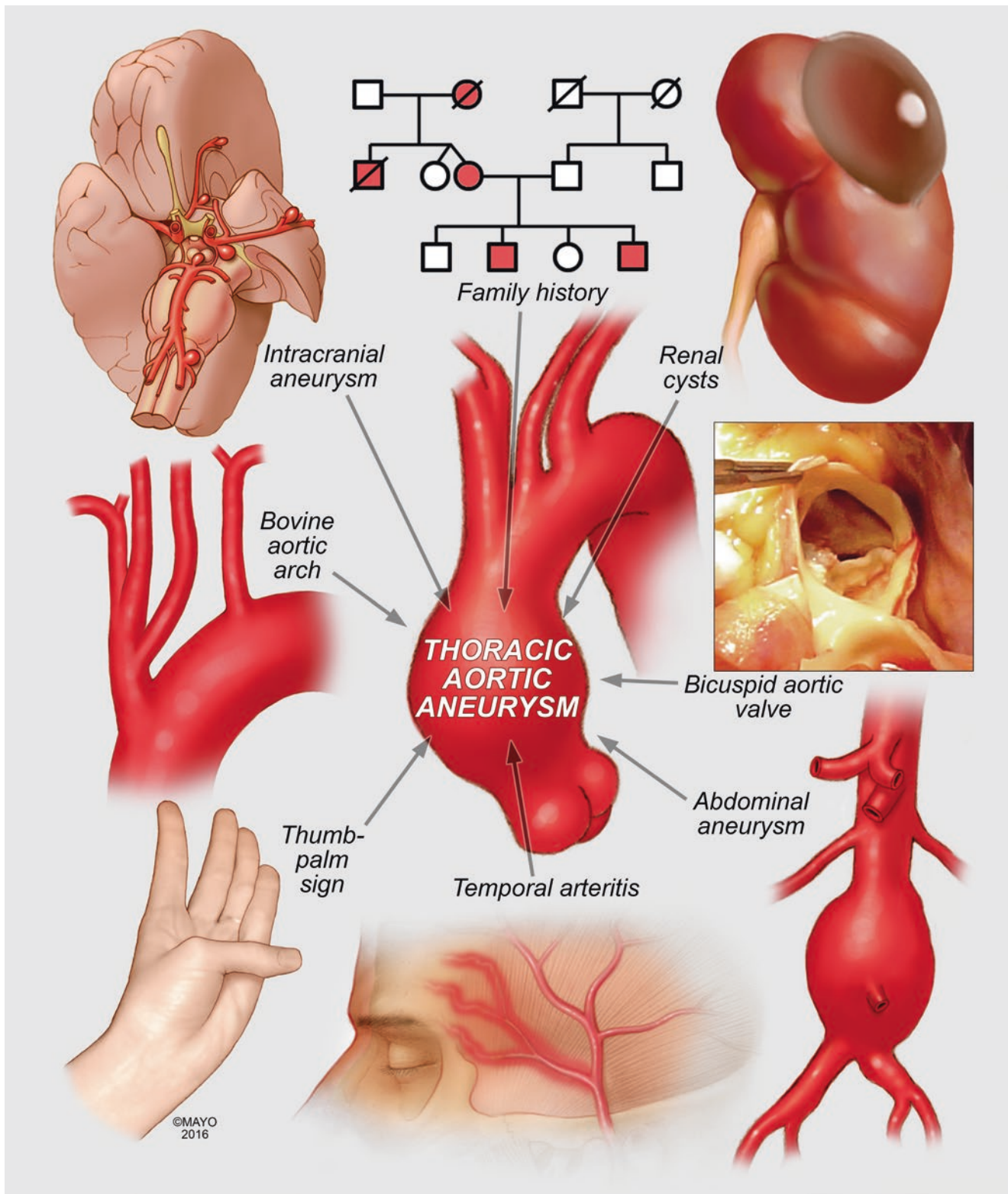


Fig. 2.2 Paradigm of “guilt by association” for detection of silent thoracic aortic aneurysm. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

Fig. 2.3 A schematic illustration comparing the normal ascending aorta to three common patterns of ascending aortic aneurysmal disease: supracoronary, annuloaortic ectasia (also known as Marfanoid-type aneurysm), and tubular. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

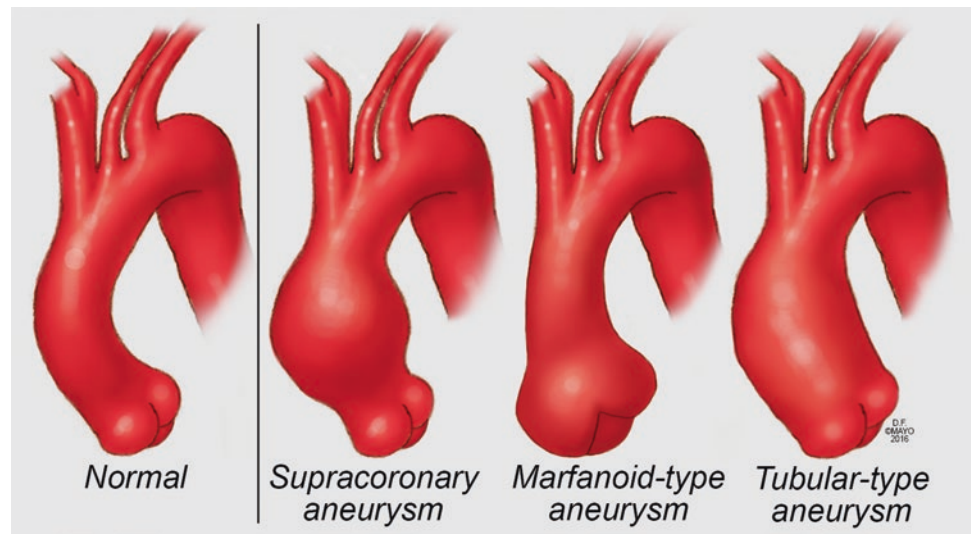
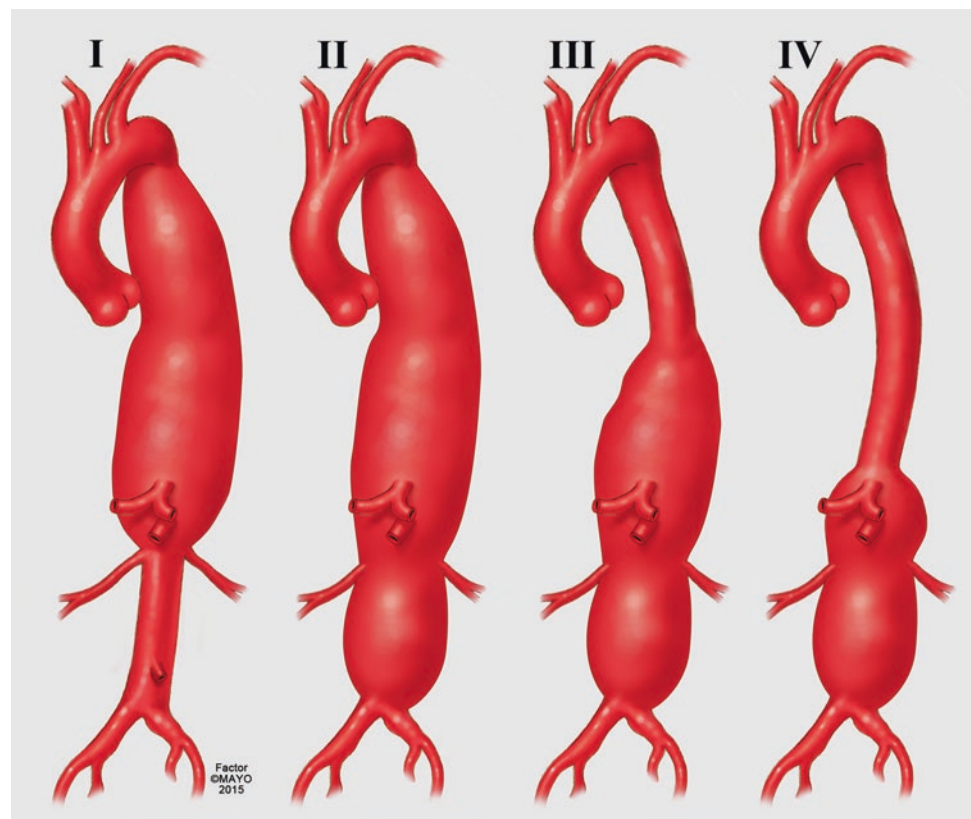


Fig. 2.4 Classification of thoracoabdominal aortic aneurysms. See text for details. By permission of Mayo Foundation for Medical Education and Research. All rights reserved



setting of fundamental genetic abnormalities [23]. It is the interplay of all these varying cellular and molecular mechanisms that leads to the disintegration of the medial layer of the aortic wall, producing an aneurysm (please see Fig. 2.9 for a histologic image of an aneurysmal aorta showing a complete loss of the medial layer).

A family of proteolytic enzymes called matrix metalloproteinases (MMPs) has been implicated as a major player in the deleterious medial degeneration process. MMPs are zinc-dependent enzymes that degrade elastin, fibrillin, and collagen—the main structural proteins of the aortic wall [22]. Such medial degradation is part of a physiological

Fig. 2.5 Acute aortic syndromes [107]: Typical aortic dissection with a flap traversing the lumen; intramural hematoma involves a circumferential collection of blood in the aortic wall, but without a frank flap; penetrating ulcer of the aorta closely resembles duodenal ulcer in its overall appearance. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

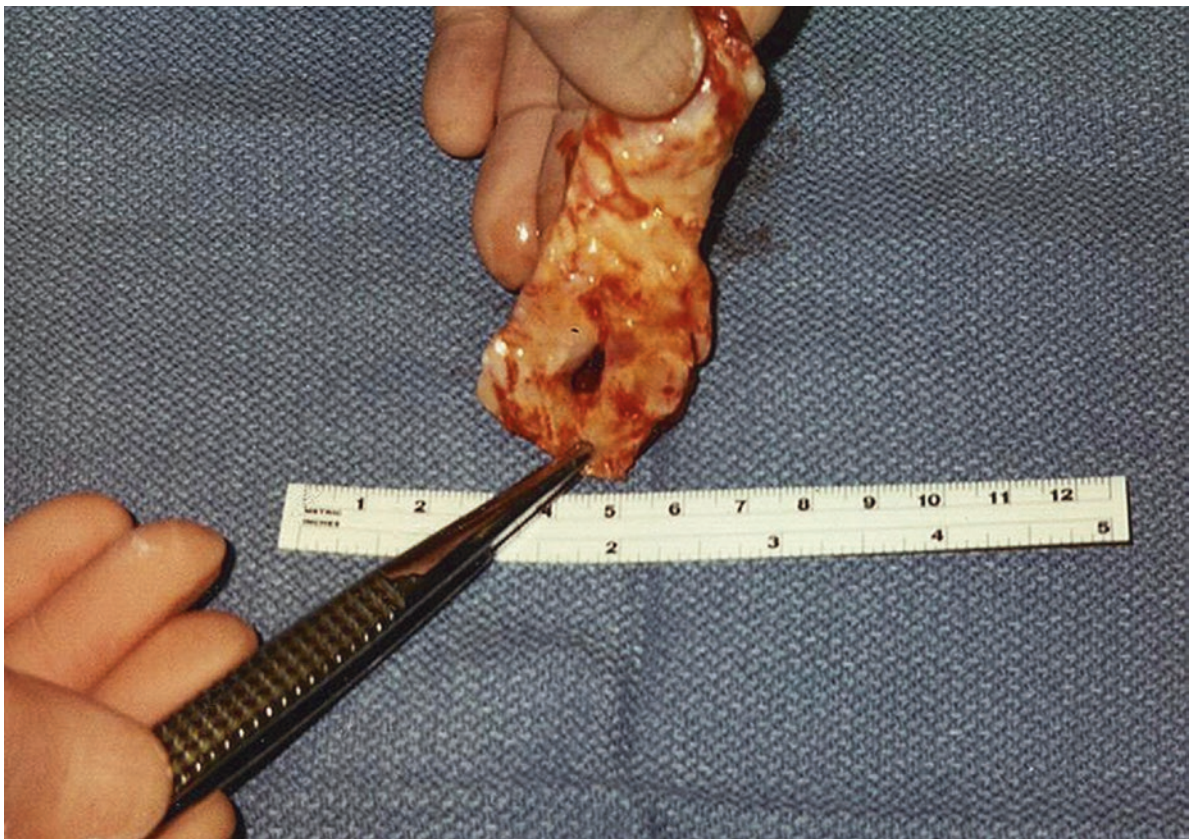
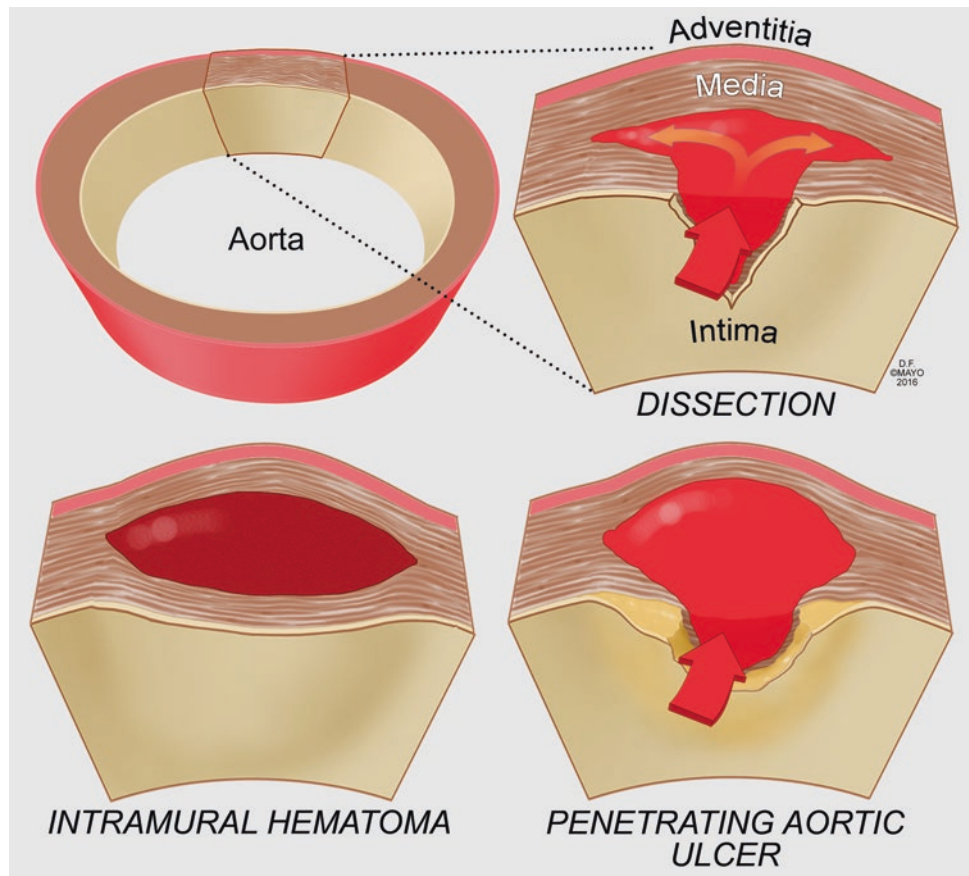


Fig. 2.6 Gross macroscopic image of a resected penetrating ulcer. Reproduced with permission from Coady M, Elefteriades JA. The Natural History of Thoracic Aortic Aneurysms: Etiology, Pathogenesis,

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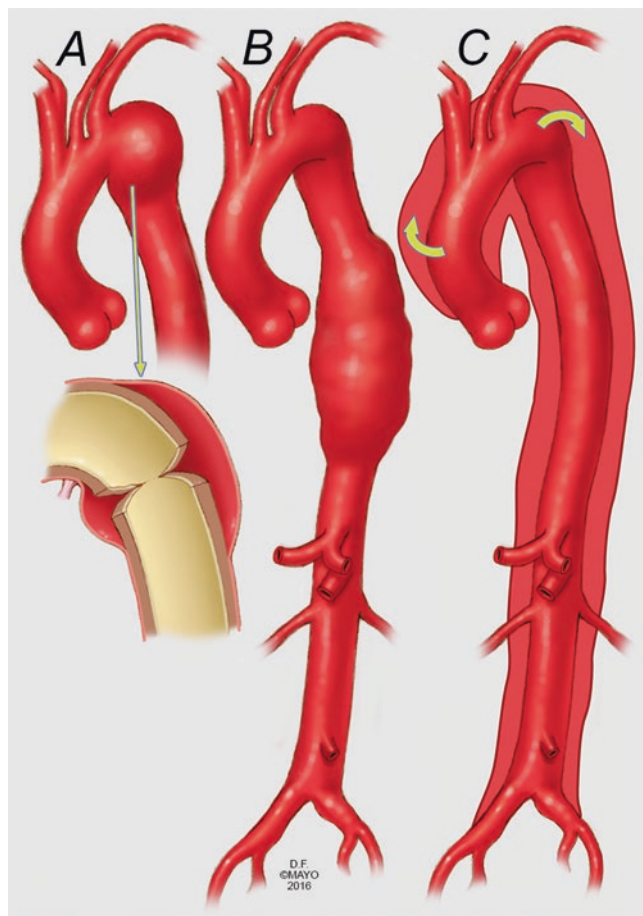


Fig. 2.7 Three commonly confused disorders: (a)—acute aortic transection; (b)—“atherosclerotic” aneurysm of the descending aorta; (c)—acute aortic dissection. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

matrix turnover process, regulated primarily by macrophages [22]. Under normal conditions, MMP tissue activity is regulated by coexisting tissue inhibitors of metalloproteinases (TIMPs), which prevent excess degradation of aortic wall proteins. However, in the diseased aorta, activity of the MMPs is markedly elevated, while the activity of TIMPs may be reduced. This leads to a significant imbalance between synthesis and degradation of the extracellular matrix of the aorta (favoring proteolysis), which subsequently leads to weakening of the aortic wall and aneurysm formation.

Currently, MMPs have been proven to play an important role in the development of both abdominal [24, 25] and thoracic aortic aneurysms [22, 26–30]. The family of MMPs includes more than two dozen enzymes. However, MMP types 1, 2, 3, 9, 12, 13, and 14 have been most prominently associated with aortic disease [4]. In investigations conducted by our group, we looked specifically at the profiles of proteolytic enzymes and their tissue inhibitors in the aortic wall of aneurysm patients and compared these profiles to those of normal individuals. We found a marked elevation of two subtypes of MMPs—2 and 9—and a marked depression of

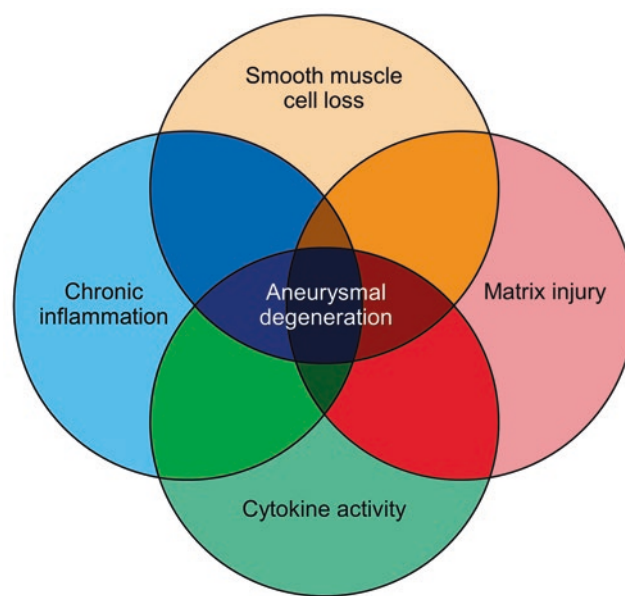


Fig. 2.8 Diagram illustrating multiple pathophysiological components that overlap and contribute to aortic aneurysm formation. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

the inhibitory enzymes (TIMPs) in ascending aortic aneurysms and dissections (Fig. 2.10) [29, 30]. Our current belief is that aneurysm patients are genetically programmed to manifest excessive MMP activity, leading ultimately to degradation and thinning of the aortic wall [31]. This is shown in Fig. 2.11, where the wall of a patient’s aorta became so thin in a 6 cm aneurysm that a ruler placed behind the wall can be seen clearly through the tissue. It is hard to imagine how such a thin structure was maintaining the main blood flow to all organs of the body and not rupturing under arterial pressure. The recognition of pathophysiologic mechanisms of aneurysm development raises the potential for innovative drug therapies, such as administration of matrix protease inhibitors, in order to produce a slowing or halting of the evolution of thoracic aneurysm disease.

Another important contributor to the pathophysiology of aortic aneurysm is inflammation [32]. Specimens of surgically removed aneurysmal aortic tissue often show powerful excess of inflammatory cells within the aortic media and adventitia [23, 33], including macrophages, monocytes, plasma cells, B-lymphocytes, and T-lymphocytes. However, the exact role of each of these cell types in the process of aneurysm formation remains unclear, although some studies have identified T-helper 1 and T-helper 2 lymphocytes as important participants in the immune responses leading to aortic aneurysm formation [33, 34].

Inflammatory cytokines (IL-1 β , IL-6, IL-8, INF- γ , and others) and loss of smooth muscle cells have also been shown to contribute to the process of aneurysm development [4, 23]. Inflammatory cytokines act by attracting and

Fig. 2.9 Microscopic image of a cross section of the aortic wall. A clear transition from a normal to an abnormally thin aorta is seen, which is due to complete loss of the medial layer of the blood vessel. This causes aneurysmal dilation of the aorta and ultimately leads to dissection and/or rupture

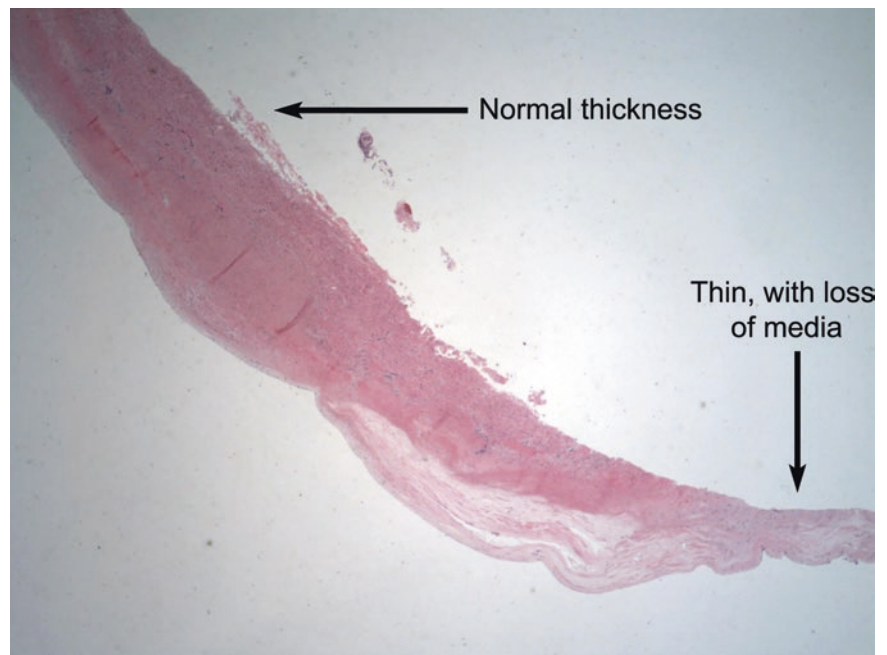
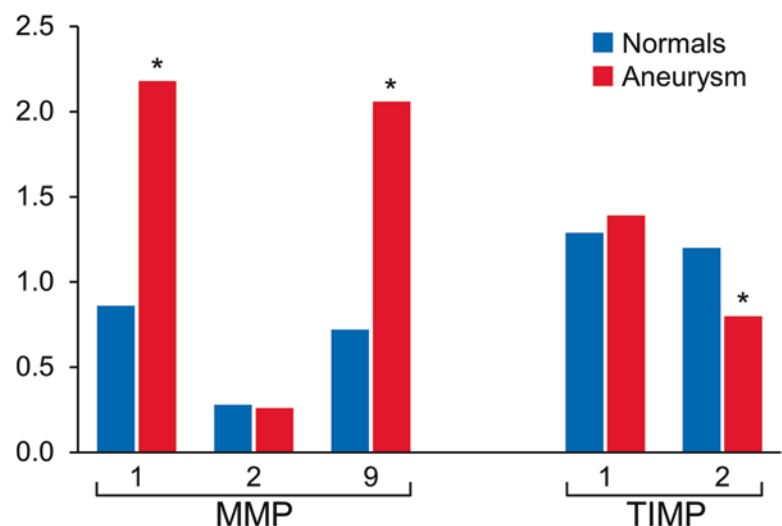


Fig. 2.10 Graph depicting matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression scores in aneurysms and controls (asterisk indicates statistical significance). Adapted with permission from [30]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved



activating macrophages and other immune cells, which in response release MMPs. In situations when such activation of inflammatory cells is excessive, an abundance of MMPs are released, leading to excessive medial degeneration. The loss of smooth muscle cells (as seen also in Fig. 2.9) has been shown in abdominal aortic aneurysms, where a 75 % loss was seen in aneurysmal aortas compared to normal abdominal aortas [35]. Two primary mechanisms that are thought to contribute to smooth muscle cell loss [23] are the following:

1. First, increased apoptosis in aneurysm smooth muscle cells, possibly due to release of inflammatory cytokines

and mediators from inflammatory cells, which initiate programmed cell death. Previous studies have shown a threefold increase in apoptosis in aortic aneurysms [36–38].

2. Second, reduced growth capacity of smooth muscle cells in diseased aortas (based on observations of the abdominal aorta) [39].

In summary, proteolysis via MMPs, inflammation with participation of various cell types and inflammatory cytokines, matrix injury, and loss of normally functioning smooth muscle cells are all important contributing factors in the pathophysiology of aortic aneurysm development.

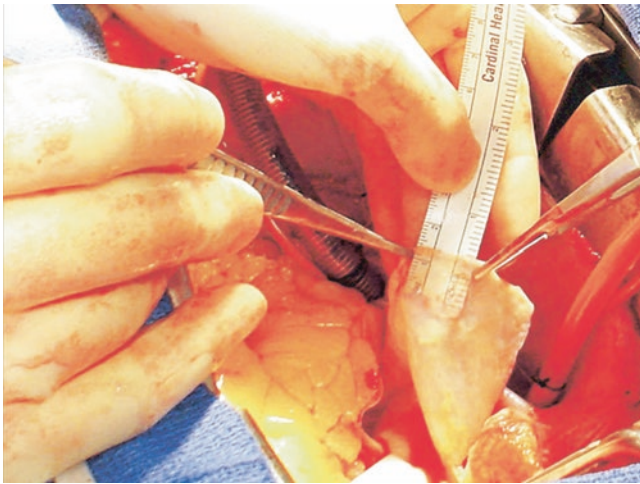


Fig. 2.11 An intraoperative image of a 6.0 cm ascending aorta, which became so thin that the writing on a ruler can be read directly through the aortic wall. It is sobering to think that this was all the tissue restraining the bloodstream and blood pressure in this patient. It is presumed that MMPs participated in the underlying destruction of the aortic wall that resulted in such loss of substance. Reproduced with permission from Elefteriades JA. Thoracic aortic aneurysm: reading the enemy's playbook. *Curr Probl Cardiol* 2008;33:203–277

Ascending and Descending Aortic Aneurysm Are Two Different Diseases

For many years, arteriosclerosis was considered the primary etiologic factor in aortic aneurysm development [40, 41], although several early studies questioned whether dilatative diseases of the aorta shared any etiologic similarities with occlusive aortic disease [42, 43]. Over the past decade more and more evidence has been accumulating suggesting that aortic aneurysm, particularly in the ascending aorta and arch, has little to do with arteriosclerosis [1, 44, 45]. In fact, it appears that ascending and descending aortic aneurysms are fundamentally different in the mechanism of disease development and morphological appearance. Ascending aneurysms are smooth, without significant calcium deposits, debris, or clot, and are not related to traditional arteriosclerotic risk factors. On the contrary, descending aortic aneurysms are irregular, calcified, arteriosclerotic, and full of debris and clot, and patients usually present with the classic risk factors (such as hypertension, smoking, and dyslipidemia). Therefore, it appears that the separation point between these two different diseases is approximately at the *ligamentum arteriosum* (Fig. 2.12) [1]. It is conceivable that such differences between ascending and descending aortic aneurysms are due to different embryologic origins of the corresponding anatomic locations of the aorta: the ascending aorta develops from the tissues of the neural crest, while the descending aorta is a product of the mesoderm (Fig. 2.13) [21, 46–48].

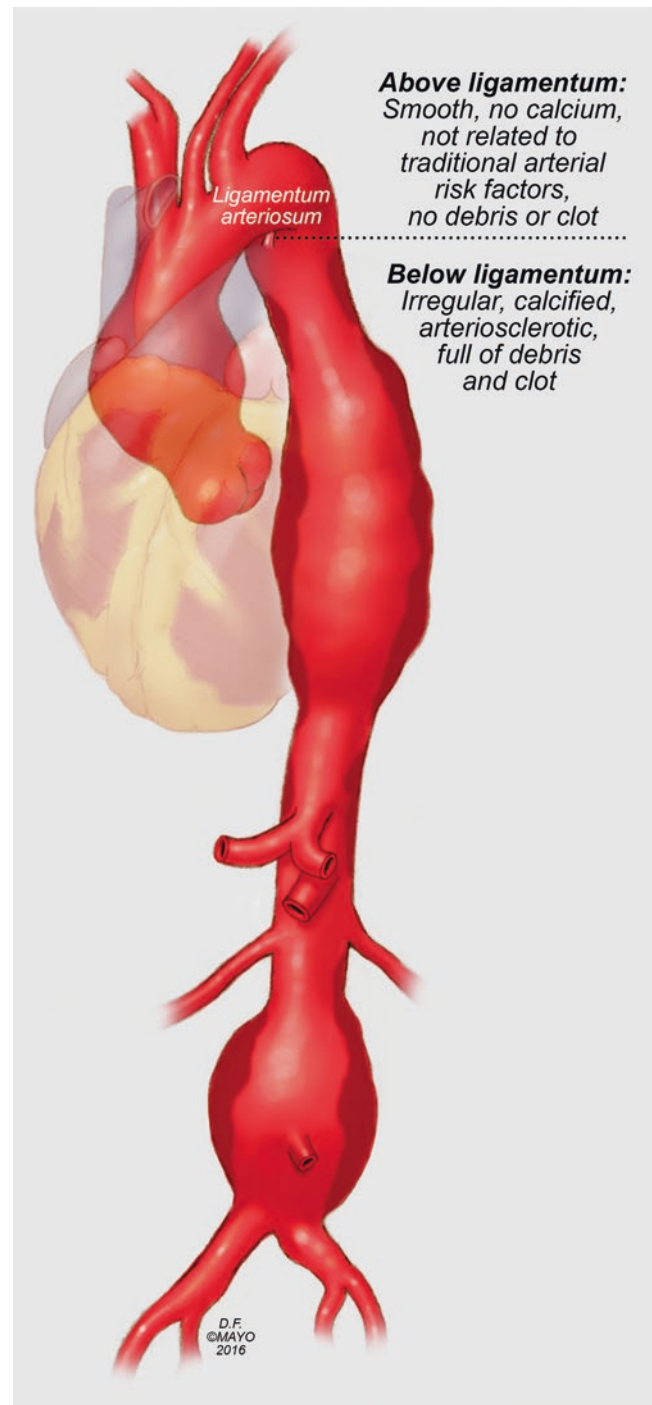
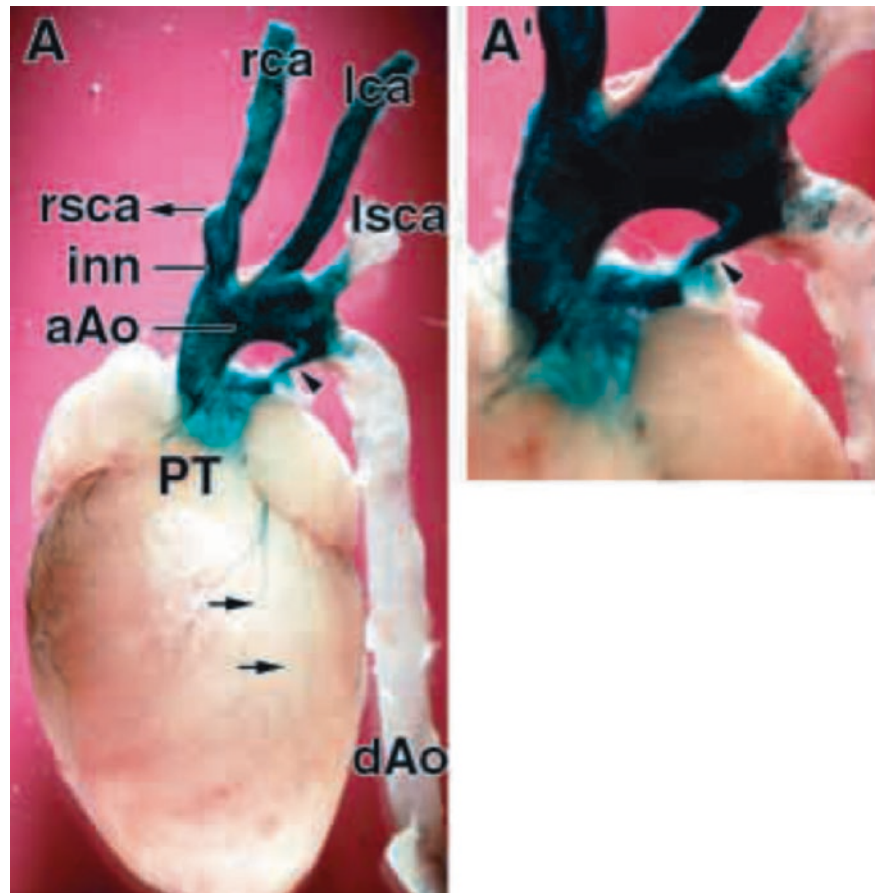


Fig. 2.12 Aortic aneurysm is really two diseases: Ascending/arch disease differs markedly from descending/abdominal disease. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

Clinical observations into this phenomenon have revealed that ascending aortic aneurysms appear to be protective against systemic arteriosclerosis [1, 49]. This has been shown in studies that evaluated the total body calcium score [49], the carotid intimal thickness [50], and even the prevalence of myocardial infarctions [51] in patients with

Fig. 2.13 Staining of neural crest cells in a 7-week adult heart. Note the extensive staining in the ascending aorta and the arch of the aorta, in the innominate and left and right carotid arteries, but not in the dorsal aorta or in the left subclavian artery. Reproduced with permission from Jiang X, Rowitch DH, Soriano P, McMahon AP, Sucov HM. Fate of the mammalian cardiac neural crest. *Development* 2000;127:1607–1616



ascending aortic aneurysm. It is possible that certain specific MMPs play a dual role in ascending aneurysm formation: *pro-aneurysmal* and *antiatherogenic* [52, 53].

Thoracic Aortic Aneurysm Is a Genetic Disease

The role of genetics and family history of aortic disease was first described by Tilson and colleagues for abdominal aortic aneurysm in the mid-1980s [54, 55]. However, for the thoracic aorta the knowledge lagged behind. The genetics of the well-appreciated Marfan syndrome were known: an autosomal dominant disorder, first described in 1896, characterized by dolichostenomelia (long, thin extremities), ligamentous redundancy or laxity, ectopia lentis, ascending aortic dilation, and incompetence of the aortic or mitral valves (or both) [56]. However, Marfan syndrome explained fewer than 5% of all cases of thoracic aortic aneurysm, while many other cases seemed clinically to run in families [57, 58]. It was not until the late 1990s when two independent centers utilizing Mendelian genetic techniques nearly concurrently reported a 21% incidence of familial non-syndromic thoracic aortic disease, with one or more affected relatives in a family in addition to the pro-

band (Fig. 2.14) [59, 60]. These two studies laid the foundation for numerous further intense investigations of the genetics of TAD. Current “genetic” classification separates thoracic aortic aneurysm into two separate categories: syndromic (that is, with manifestations in other organs besides the aorta) and non-syndromic cases (that is, without extra-aortic manifestations) [57, 58]. Syndromic causes of TAD include Marfan syndrome [61, 62], and other rare syndromes such as Ehlers-Danlos [63, 64], Turner [65, 66], and Loeys-Dietz [67, 68]. In these patients the aortic dilation is just one of many features and extra-aortic manifestations of connective tissue abnormalities are abundant. Syndromic conditions are often inherited and run in families. Patients with syndromic thoracic aortic pathology usually have a positive “thumb-palm sign,” the ability to cross the thumb across and beyond the edge of a flat palm as shown in Fig. 2.15. All syndromic cases put together still constitute little more than 5% of all cases of TAD seen in the population. The non-syndromic category is much larger and includes two subcategories—familial and sporadic. Familial cases of TAD are proven to run in families, but, in contrast to syndromic aortic disease, aortic pathology is the only manifestation of the disease. Sporadic forms of thoracic aortic dissection are the most common type and likely represent the first presentation of TAD in a given family.

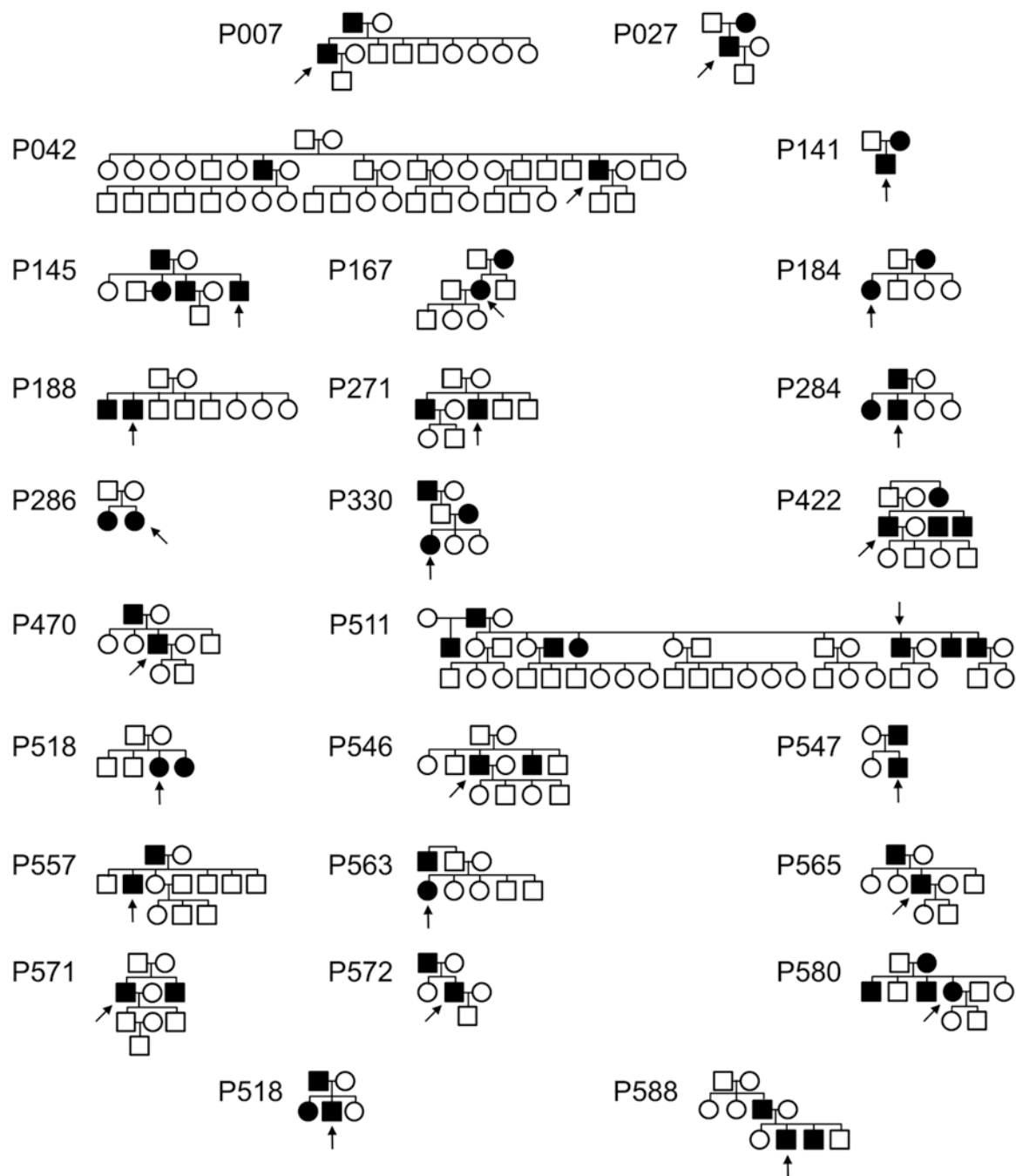


Fig. 2.14 Among the authors' first 100 constructed pedigrees, 21 were positive for a family pattern. These 21 positive pedigrees are displayed here. Reproduced with permission from Coady MA, Davies RR,

Roberts M, et al. Familial patterns of thoracic aortic aneurysms. *Arch Surg* 1999;134:361–367

In-depth investigation of the genetic patterns of TAD has revealed that autosomal dominant inheritance is far and away the most common pattern in patients with this disease [69]. Other modes of inheritance (recessive, X-linked) have also been identified, but less commonly [69]. Furthermore, patients with an ascending aortic aneurysm are more likely to have a relative with an ascending aortic aneurysm, while

patients with a descending thoracic aortic aneurysm are much more likely to have a relative with an abdominal aortic aneurysm (Fig. 2.16) [69]. (This finding substantiates the division of aortic disease into two zones by the ligamentum arteriosum.)

Currently investigations into the genetics of TAD have shifted to the molecular genetic level. At the time that this

chapter is being written, as many as 21 genes have been implicated to be causative of thoracic aortic aneurysm and dissection (this includes genes that cause both syndromic and non-syndromic cases of TAD) (Fig. 2.17). These encode



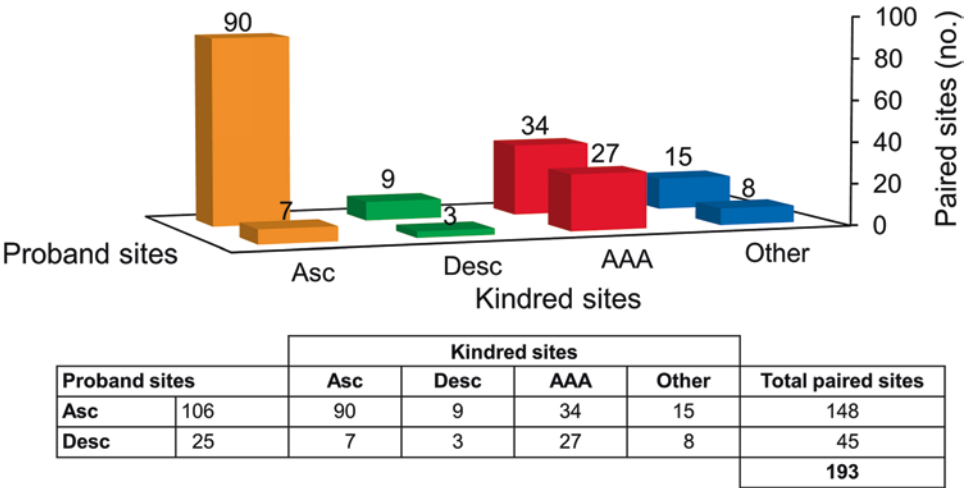
Fig. 2.15 Patient with a positive “thumb-palm” sign for connective tissue disease. Being able to cross the thumb beyond the edge of the palm indicates that the long bones are excessive and the joints are lax. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

molecules that regulate the extracellular matrix (FBN1, FBN2, COL1A1, COL1A2, COL3A1), the cytoskeleton of smooth muscle cells (ACTA2, MYH11, MYLK), and the TGF- β signaling pathway (TGF β 2, TGFBR1, TGFBR2, SMAD3, SLC2A10). New genes responsible for this disease are being discovered regularly and it is likely that many more new genes will be identified in connection to TAD.

There are certain genes that influence substantially the natural history of thoracic aortic disease. For example, some mutations are exclusively involved in aortic dissection without aneurysm formation (MYLK gene [70]), or cause aortic dissection at small aortic sizes (ACTA2 gene [71, 72]). These mutations in part explain the phenomenon of aortic dissection occurring at a smaller aortic size than the current surgical criterion [73]. Patients who harbor these mutations are a challenge in terms of timely surgical intervention, because the dissection can occur before any significant enlargement is noted.

Current US guidelines on the management of patients with thoracic aortic disease recommend screening first- and second-degree relatives of patients with a known aneurysm or dissection via imaging studies (echocardiography, CT, or MRI) [74]. However, in the era of molecular genetics, genetic testing of patients and their relatives may offer some advantages in comparison to screening solely by conventional imaging techniques. For example, if an index patient (proband) is identified as a carrier of a pathogenic genetic defect that causes TAD, all family members can also be tested to determine whether they also carry the pathogenic abnormality or not. Such testing is beneficial for both carriers of the mutation, as it provides the opportunity for advanced and regular screening and subsequent timely prophylactic surgery, and noncarriers since it removes the need for regular imaging and the emotional burden of potential aneurysm disease. Such genetic testing can be accomplished using panels of genes or next-generation sequencing techniques, such as

Fig. 2.16 Distribution of sites of arterial aneurysms and dissections in kindred of familial probands. Adapted with permission from [69]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved



Genes Causative of Thoracic Aortic Disease

Syndromic Thoracic Aortic Aneurysm and Dissection

1. FBN1	→	Marfan Syndrome
2. COL1A1	}	→ Ehlers-Danlos Syndrome
3. COL1A2		
4. COL3A1		
5. COL5A1		
6. COL5A2		
7. TGFBR1	}	→ Loeys-Dietz Syndrome
8. TGFBR2		
9. TGFβ2	→	TGFβ2-related vasculopathy
10. SMAD3	→	Aneurysm-Osteoarthritis Syndrome
11. FBLN4	}	→ Cutis Laxa Syndrome
12. ELN		
13. SLC2A10	→	Arterial Tortuosity Syndrome
14. FLNA	→	Periventricular Heterotopia Syndrome
15. ADAMTS10	→	Weill-Marchesani Syndrome
16. FBN2	→	Contractural arachnodactyly

Non-Syndromic Thoracic Aortic Aneurysm and Dissection

1. TGFBR1	}	→ Familial Thoracic Aortic Aneurysm
2. TGFBR2		
3. ACTA2		
4. MYLK		
5. SMAD2		
6. TGFβ2		
7. PRKG1		
8. MYH11	→	Familial Thoracic Aortic Aneurysm with Patent Ductus Arteriosus
9. NOTCH1	→	Familial Thoracic Aortic Aneurysm with Bicuspid Aortic Valve

Fig. 2.17 Genes that are currently known to cause syndromic and non-syndromic thoracic aortic aneurysm and dissection. Adapted with permission from [76]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

whole-exome sequencing (Fig. 2.18) [75]. A clinical experience with routine whole-exome sequencing in patients with thoracic aortic aneurysm and dissection has recently been reported [76]. Follow-up testing of relatives for an identified particular variant/mutation can be conducted via single-site (Sanger) sequencing. Advanced genetic testing of patients with TAD provides the opportunity for personalized management of patients tailored to the specifics of the genetic mutation.

Natural History of Thoracic Aortic Disease

How Big Is the Normal Aorta?

Much analysis of the natural history of the thoracic aorta is based on aortic size. Before moving on to discuss size criteria and growth rates, it is useful to review aortic size under normal conditions. Recent reports from the Multi-Ethnic Study of Atherosclerosis that analyzed the size of the ascending aorta in 3500 individuals identified the mean diameter of

the ascending aorta to be 3.2 ± 0.4 cm [77, 78]. The diameter of the aortic arch is not much different from the ascending aorta. The proximal portion of the descending aorta is about 2–2.3 cm and the abdominal aorta narrows further to 1.7–1.9 cm.

Where Should We Measure the Aorta?

Since accurate sizing of aortic diameter in patients with TAA is essential to enable preemptive surgical intervention before rupture and other complications occur, our group has proposed a system of uniform measurements of the aortic size at eight levels (Fig. 2.19) [79]: (1) aortic annulus, (2) sinuses of Valsalva, (3) sinotubular junction, (4) widest portion of the vertical ascending aorta (at any specific level), (5) the widest diameter in the aortic arch region between the takeoff of the innominate artery and the distal margin of the left subclavian artery, (6) widest portion of the vertical descending aorta (at any specific level), (7) suprarenal portion of the abdominal aorta, and (8) infrarenal portion of the abdominal aorta.

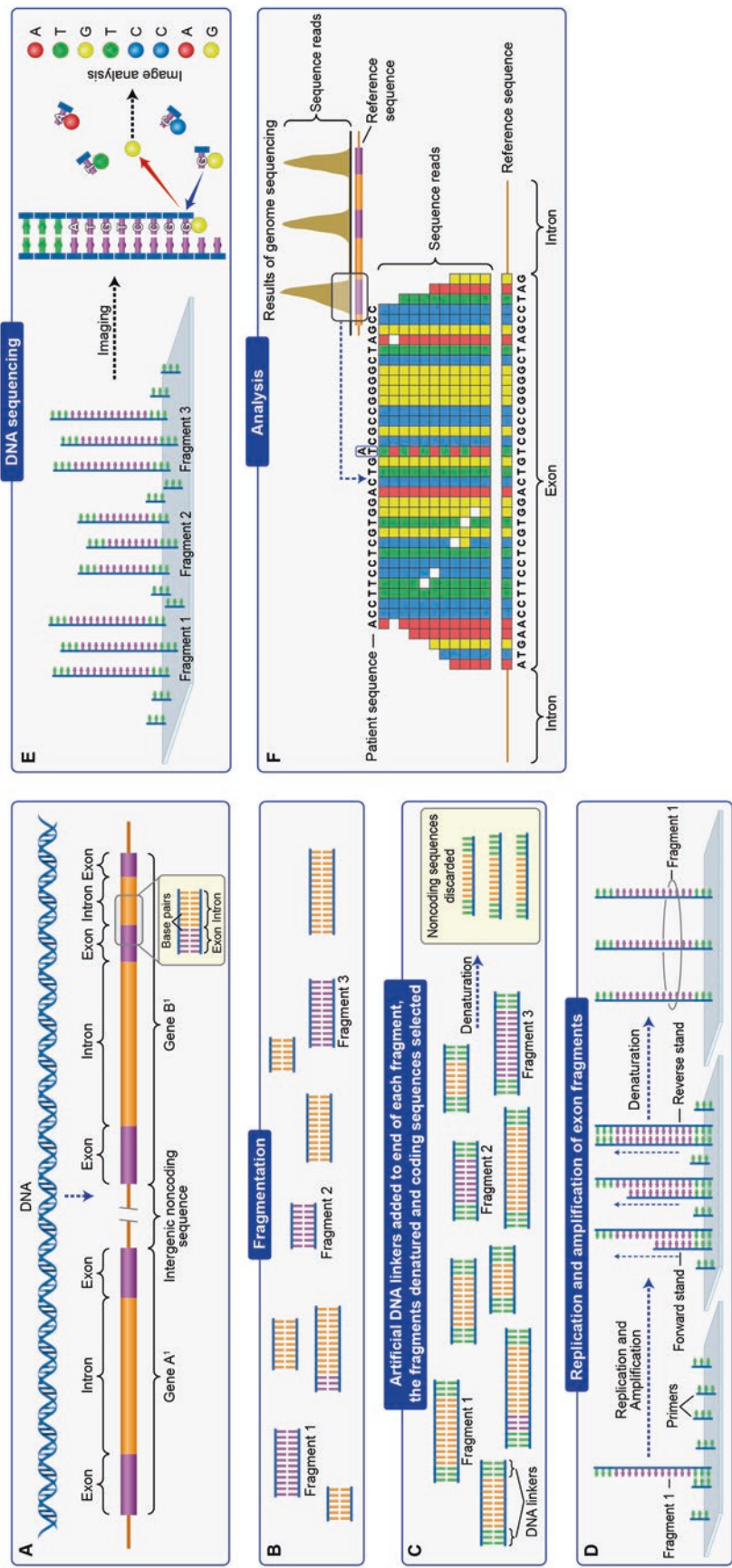


Fig. 2.18 Schematic overview of exome sequencing. Exome sequencing targets the approximately 1% of the genome that is made up of exons, which encode protein sequence. The DNA from the patient (*Panel A*) is isolated and broken into fragments (*Panel B*); the DNA fragments are coupled to artificial DNA linker segments (*Panel C*), and the fragments are selected with the use of artificial DNA or RNA baits that are complementary to targeted DNA (not shown). The sequencing process starts with the binding of the end of each DNA fragment to a solid matrix and in situ amplification (*Panel D*), and the DNA fragments are then sequenced on the slide in a series of reactions in which a complementary nucleotide with one of the four colored fluorescent dyes is added to each cluster of identical molecules (*Panel E*). The identity of the colored fluorescent indicator of each cluster is imaged with a laser and a camera coupled to a microscope, the fluorescent indicator is removed, and the cycle is repeated to generate a nucleotide sequence read that is 75–150 nucleotides in length. The sequence reads are aligned to a reference DNA sequence (*Panel F*), and a genotype call for each position is made. In this example, most of the positions are homozygous reference sequence, but one position is called as heterozygous A/T. Adapted with permission from [75]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

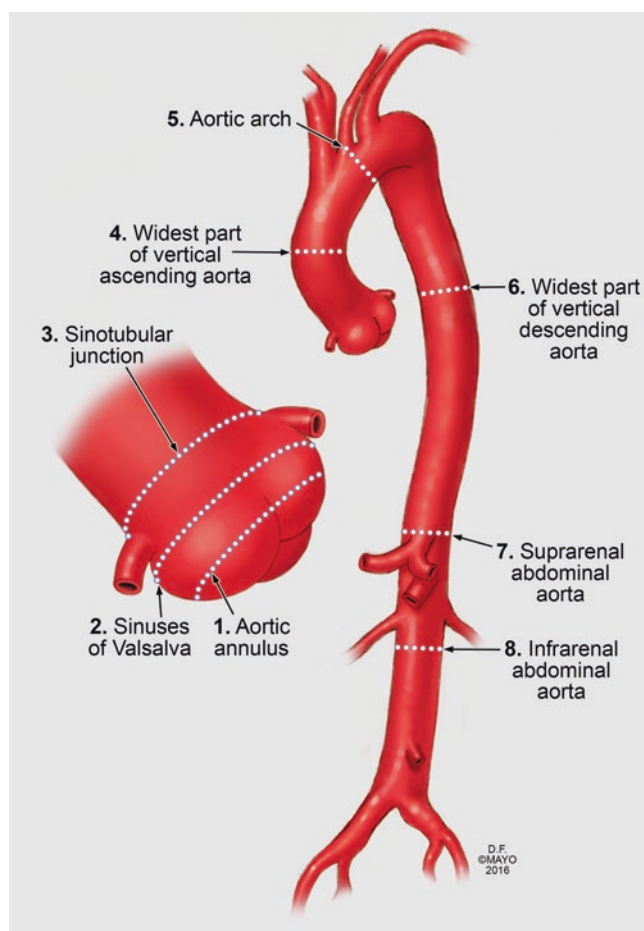


Fig. 2.19 Eight locations for uniform measurement and reporting of aortic diameter. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

Growth Rate of the Thoracic Aorta

One of the most important parameters that defines the natural history of aortic disease is the rate of growth of the aorta. Estimating aortic growth rate is not a simple calculation of the difference in aortic size at the same anatomic location between two time points divided by the time between these points. Many different factors need to be accounted and controlled for, such as imaging modality, interobserver variability, and measurement error, among others. Therefore, sophisticated statistical methods have been developed to accurately assess the rate of aortic growth [80, 81]. Our early studies revealed that the aneurysmal aorta grows slowly—at a mean rate of 0.10 cm/year [82–84]. This figure is an incidence-weighted average of the 0.07 cm/year growth rate of the ascending aorta and a 0.19 cm/year rate for the descending aorta [82–84]. However, our more recent study on a larger number of patients from the same institution showed higher growth rates: 0.20, 0.26, and 0.23 cm/year for

the ascending aorta and arch, descending aorta, and thoracoabdominal aorta, respectively [85]. Another notable finding is that the growth rate of the aorta increases with an increase in the size of the aorta in all three anatomic locations (Fig. 2.20) [85]. In other words, the larger the aneurysm, the faster it grows. This observation vividly emphasizes the dangers of a large aortic size, as the enlargement process intensifies in a vicious cycle. Epidemiologic studies of aortic growth rates may be hindered by two specific types of selection biases. First, patients seen at major referral centers may be different from the general population of TAD patients. This type of bias might lead to overestimating the growth rates since referral centers see more advanced aortic disease than that of the general population [80]. The second type of selection bias stems from the fact that patients with larger aneurysms (which might be fast growers) are selected out for prophylactic surgery quicker than patients with smaller aneurysms (slow growers). Such a bias would lead to underestimation of the true aortic rate of growth [80].

The current US guidelines recommend considering prophylactic surgical intervention if the size of the ascending aorta increases by more than 0.5 cm/year (class 1 recommendation, level of evidence C) [74]. We feel that increases of this magnitude are often spurious, based on oblique imaging planes or comparison of non-concordant segments [1]. Such large-diameter changes may be real in the unusual setting of clinically silent intercurrent aortic dissection—between the times of the two measurements.

Risk of Adverse Events

The other very important characteristic of the natural history of TAD concerns the risk of developing adverse events, such as rupture or dissection (or death from either of these) at different aortic sizes. This can be presented as either the lifetime risk of adverse events or the yearly risk.

Analysis of the lifetime risk of manifesting an aortic catastrophe showed that for the ascending aorta 34% of patients will have suffered a rupture or a dissection by the time the size of the aorta reaches 6.0 cm (Fig. 2.21a) [82, 83, 86]. For the descending aorta the lifetime risk of an adverse event is dramatically increased as the aorta reaches the 7.0 cm point. At this size, 43% of patients will have suffered rupture or a dissection (Fig. 2.21b) [82, 83, 86]. These sizes of the ascending and descending aorta represent “hinge points.” Prophylactic surgical interventions should be carried out prior to the aorta reaching this size in order to prevent potentially lethal complications.

Yearly risk of rupture, dissection, or death is also a very useful indicator. The annual risk of adverse event with an aneurysm of a certain size is an easier concept for discussion with patients. Analysis of the yearly risk of adverse events showed a stepwise increase in risk with increasing aortic size (Fig. 2.22) [86]. The maximal risk is

Fig. 2.20 Rates of annual growth of the thoracic aorta at three anatomic levels: the ascending aorta, the descending aorta, and the thoracoabdominal aorta. Note that growth rate increases as the aorta grows. Adapted with permission from [85]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

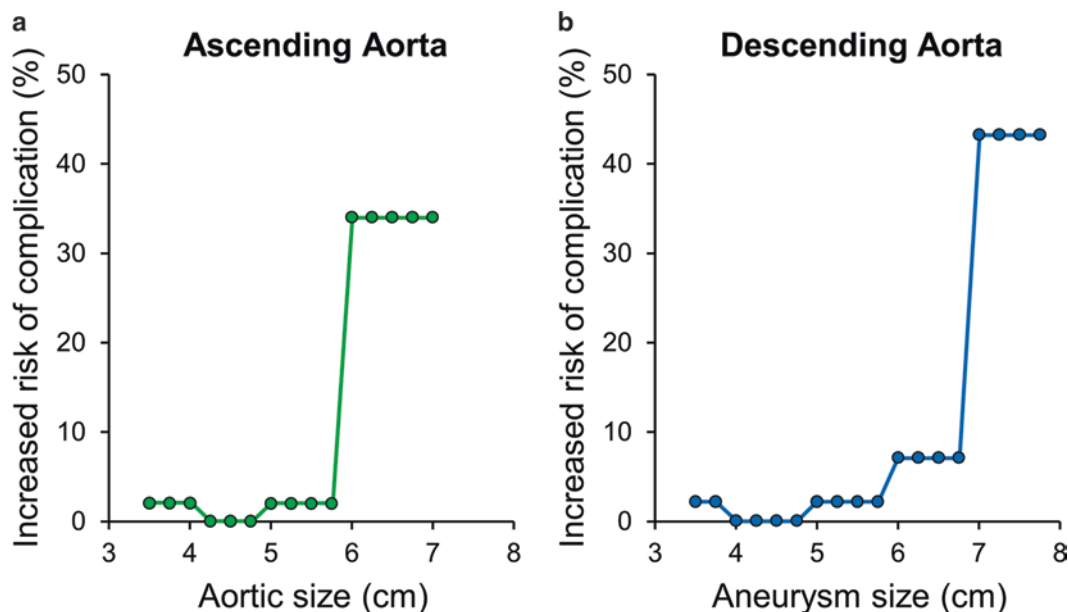
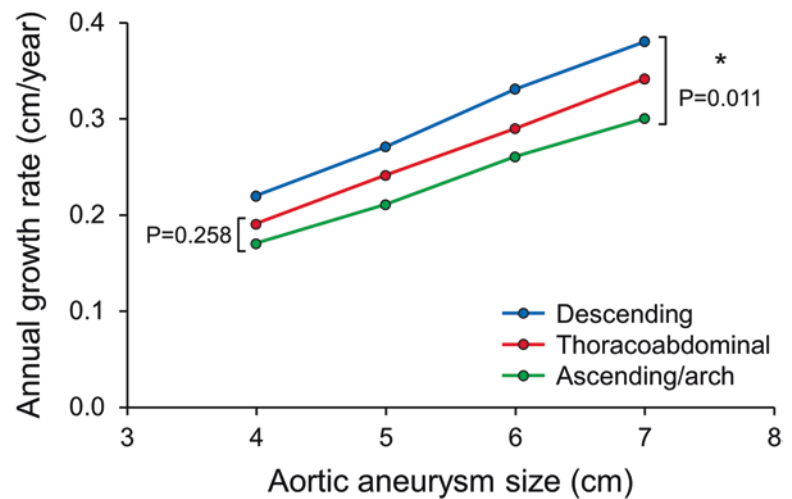


Fig. 2.21 The increase in risk of rupture or dissection as the thoracic aorta enlarges to specific dimensions. Note the abrupt hinge point at 6 cm for the ascending aorta (*Panel A*) and at 7 cm for the descending

aorta (*Panel B*). Adapted with permission from [82]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

found in aortas greater than 6.0 cm. At 6 cm, the yearly risk of rupture, dissection, or death in patients with ascending aortic aneurysms is as high as 14.1 % [86]. (Of course, not all these deaths are aortic related, but for many the aorta is the cause.)

Based on these studies describing the risk of adverse events for patients with TAD, evidence-based intervention criteria have been developed that are still in use today and included in the most recent US guidelines for managing patients with TAD. For the ascending aorta, prophylactic sur-

gery is recommended when the aorta reaches 5.5 cm, and for the descending aorta at 6.5 cm [84, 87]. When surgery can be delivered at low risk, it is appropriate to drop these criteria to 5.0 cm for ascending and 6.0 cm for descending aneurysm. All these criteria likely will be “personalized” based on specific causative mutation within the next decade. For patients with Marfan syndrome and other connective tissue disorders the recommended criteria are slightly lower—5.0 and 6.0 cm for the ascending and descending aorta, respectively (Fig. 2.23) [84, 87].

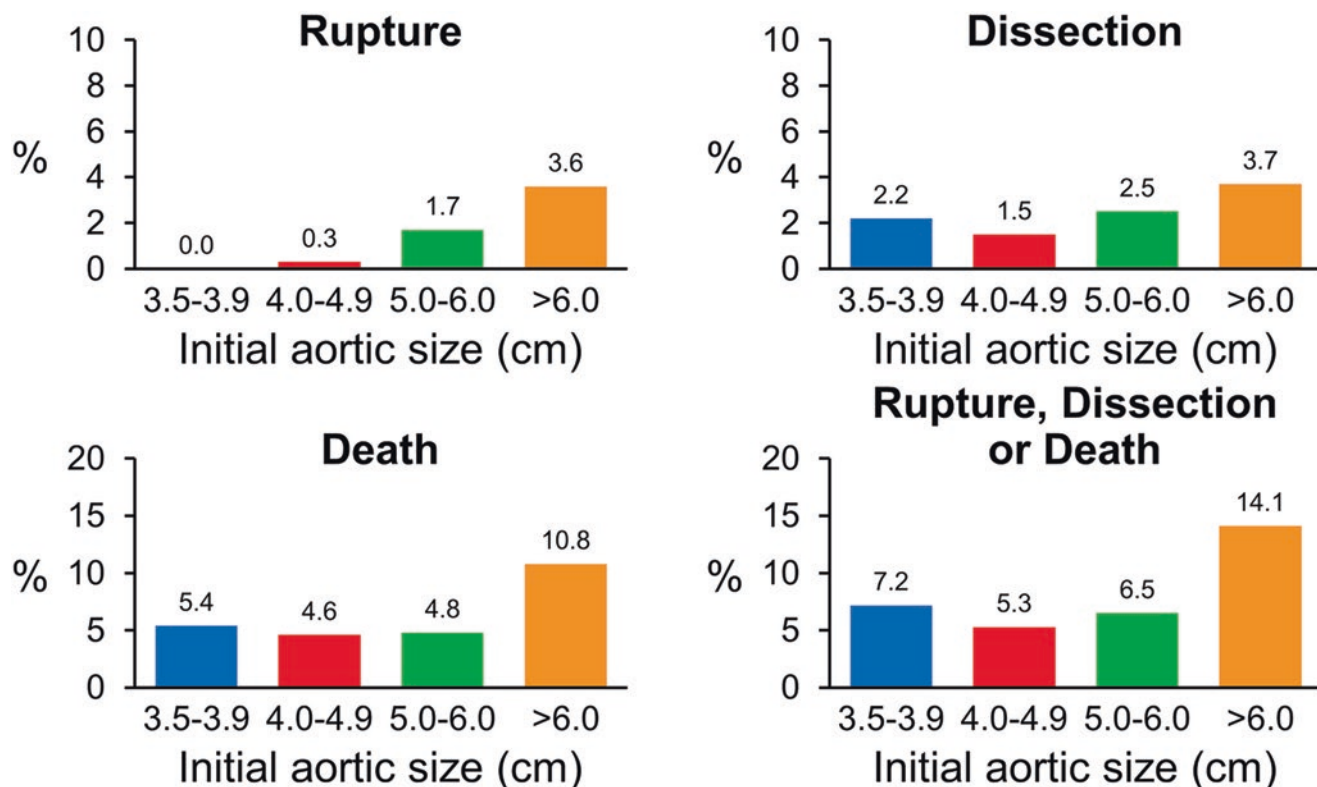


Fig. 2.22 These graphs illustrate the yearly rates of rupture, dissection, and combined end point of death and rupture dissection or death as the aorta enlarges. Adapted with permission from [4]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

The Yale Center for Thoracic Aortic Disease Recommended Surgical Intervention Criteria for Thoracic Aortic Aneurysms

1. Rupture
2. Acute aortic dissection
 - a. Ascending requires urgent operation
 - b. Descending requires a “complication-specific approach”
3. Symptomatic states
 - a. Pain consistent with rupture and unexplained by other causes
 - b. Compression of adjacent organs, especially trachea, esophagus, or left stem bronchus
 - c. Significant aortic insufficiency in conjunction with ascending aortic aneurysm
4. Documented enlargement
 - a. Growth ≥ 1 cm/yr or substantial growth and aneurysm is rapidly approaching absolute size criteria
5. Absolute size (cm)

	Marfan's	Non-Marfan's
Ascending	5.0 cm	5.5 cm
Descending	6.0 cm	6.5 cm

Fig. 2.23 Size algorithm for intervention for asymptomatic thoracic aortic aneurysm. Adapted with permission from [87]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

Role of Body Surface Area

Although the intervention criteria mentioned above are designed to be used generally, we realized that adjustments are necessary for extremes of body size. For example, for a 7-foot-tall basketball player an ascending aorta of 4.4 cm might actually be within the normal size range, given the large body and commensurate circulatory demand. On the other hand, a 4.4 cm aorta for a petite 5-foot-tall lady might be very significant and put her at high risk for adverse aortic events. Therefore, it became apparent that body surface area had to be included into the risk calculations for adverse events. Table 2.1 shows the corresponding risk for patients of varying sizes based on their body surface area [88]. The risk is stratified as either being low (~4% annual risk), medium (~8% annual risk), or high (~20% annual risk) [88]. This data provides important information that will make it possible to “fine-tune” the traditional intervention criteria that are routinely used in practice based on the person’s body size.

Mechanical Properties of Thoracic Aorta Underlie Its Natural History

It is important to note that the natural history data described above, which are based on imaging studies and clinical observations, are largely supported and confirmed by concurrent bioengineering studies that assess the mechanical properties of the thoracic aorta. These studies have shown that the biomechanical properties of the thoracic aorta markedly

deteriorate as the aortic size reaches 6 cm—the exact same size at which the natural history studies show the risk of adverse events to increase significantly. As the aorta enlarges and reaches 6 cm in diameter, it loses its distensibility (Fig. 2.24) and elasticity, thereby resembling a non-distensible rigid tube that has been stretched to its limits [89]. Therefore, in a large, noncompliant aorta the entire force of each cardiac contraction is directly translated into wall stress, since the aneurysmal aortic wall cannot stretch elastically [89]. The larger the aorta gets, the higher is the wall stress (please see the stepwise increase in wall stress in Fig. 2.25),

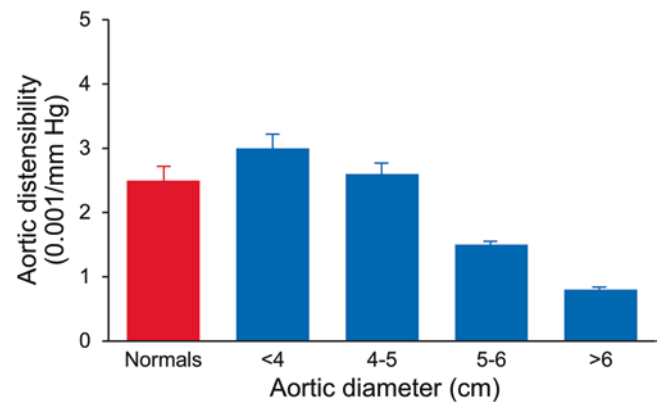


Fig. 2.24 Distensibility values in normal aortas and aortic aneurysms of different diameters. Distensibility of ascending aortic aneurysms decreases rapidly as diameter increases, to very low values at dimensions greater than 6 cm. Adapted with permission from [89]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

Table 2.1 Risk of complication in aortic aneurysm as a function of aortic diameter (horizontal axis) and patient body surface area (vertical axis)^a
^aAdapted from [88]

	Aortic size (cm)									
	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
BSA										
1.30	2.69	3.08	3.46	3.85	4.23	4.62	5.00	5.38	5.77	6.15
1.40	2.50	2.86	3.21	3.57	3.93	4.29	4.64	5.00	5.36	5.71
1.50	2.33	2.67	3.00	3.33	3.67	4.00	4.33	4.67	5.00	5.33
1.60	2.19	2.50	2.80	3.13	3.44	3.75	4.06	4.38	4.69	5.00
1.70	2.05	2.35	2.65	2.94	3.24	3.53	3.82	4.12	4.41	4.71
1.80	1.94	2.22	2.50	2.78	3.06	3.33	3.61	3.89	4.17	4.44
1.90	1.84	2.11	2.37	2.63	2.89	3.16	3.42	3.68	3.95	4.22
2.00	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75	4.00
2.10	1.67	1.90	2.14	2.38	2.62	2.86	3.10	3.33	3.57	3.80
2.20	1.59	1.82	2.05	2.27	2.50	2.72	2.95	3.18	3.41	3.64
2.30	1.52	1.74	1.96	2.17	2.39	2.61	2.83	3.04	3.26	3.48
2.40	1.46	1.67	1.88	2.08	2.29	2.50	2.71	2.92	3.13	3.33
2.50	1.40	1.60	1.80	2.00	2.20	2.40	2.60	2.80	3.00	3.20

 = low risk (~4% per year)
 = moderate risk (~8% per year)
 = severe risk (~20% per year)

and at 6 cm the wall stress of the aorta has the potential to exceed the ultimate tensile limits of the aorta if the blood pressure reaches 200 mmHg, which would result in dissection and/or rupture [1, 89]. Overall, these sophisticated bio-engineering studies are consonant with the natural history findings and provide additional scientific justification for the current size criteria for prophylactic aortic replacement.

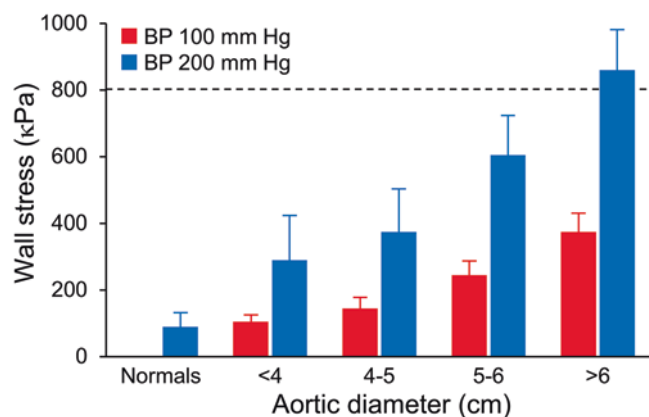


Fig. 2.25 In vivo mechanical properties of human ascending aorta. Exponential relationship between wall stress and aneurysm size in ascending aortic aneurysms. The *red columns* represent a blood pressure of 100 mmHg, and the *blue columns* represent a blood pressure of 200 mmHg. The lines at 800–1000 kPa represent the range of maximum tensile strength of the human aorta. Adapted with permission from [1]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

How Does Aortic Dissection Pick a Particular Time to Occur?

Although the studies on the natural history of aortic disease give an accurate estimate of the size at which a dilated aorta is likely to dissect or rupture, until recently the precipitating events that cause a dissection to occur at a particular time were unknown. In fact, aortic dissection was previously considered to be a completely random event that can occur practically on any day and at any time. However, there is evidence that occurrence of aortic dissection is not random and that certain predisposing and inciting factors and conditions need to be met for a dissection to occur at a particular time. In Fig. 2.26 we provide a schematic (based on many clinical observations and studies) that depicts our current understanding of the mechanism of how an aortic dissection is likely to occur [1, 4, 90]. This includes a sequence of five important components: (1) genetic predisposition to TAD; (2) degeneration of the medial layer of the aorta (via MMP action); (3) weakening of the aortic wall and aneurysm formation; (4) an acute hypertensive episode (sudden spike in blood pressure); and (5) aortic dissection.

Most of the abovementioned components were previously discussed in this chapter. However, the hypertensive episode deserves a more detailed analysis. The importance of blood pressure increase in inciting aortic dissection is currently well accepted, with antihypertensive drugs being the first line of medical management for patients at risk.

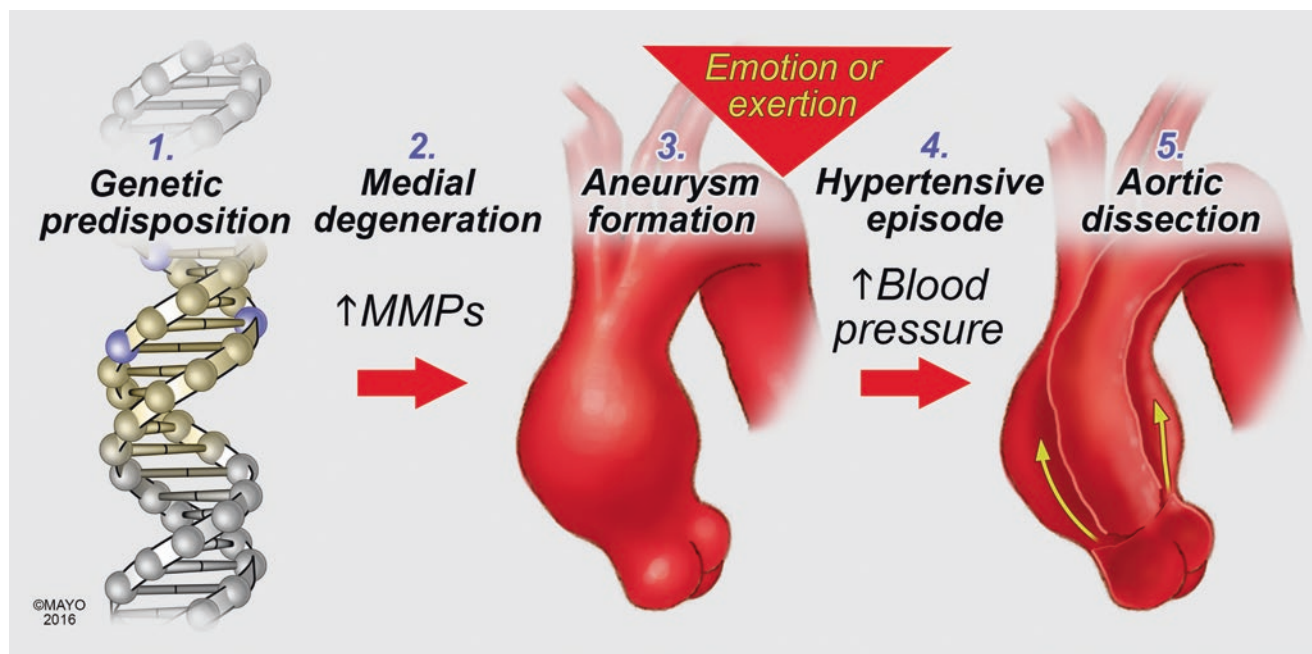


Fig. 2.26 Schematic presentation of possible relationships underlying the instigation of an acute aortic dissection at one particular time. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

However, this relationship was not as obvious a decade ago until the phenomenon of aortic dissection was discovered in weightlifters [91, 92]. Through an experimental study on volunteers, our group was able to show that during severe weightlifting the arterial blood pressure can exceed 300 mmHg (Fig. 2.27) [31]. Such extreme blood pressures are not commonly seen even in such acute environments as the cardiac intensive care unit, where hypertension is a very common condition. Furthermore, the significance of a hypertensive episode in aortic dissection was further supported by a study that showed that extreme physical exertion (moving

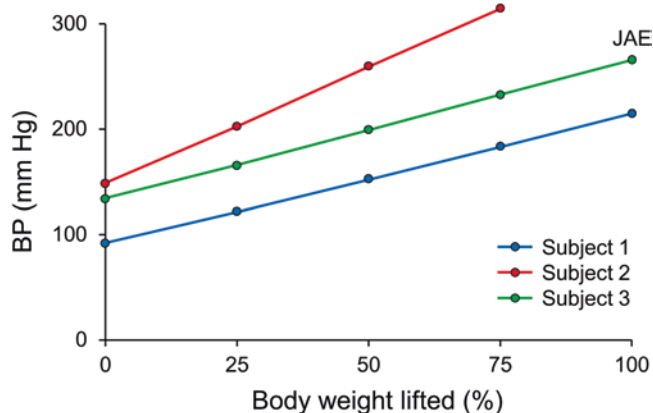


Fig. 2.27 Determination of instantaneous blood pressure during a weight-lifting exercise. Blood pressure during lifting was related to percent of body weight lifted in the bench press exercise. Subject 1 was a healthy 16-year-old athlete; he reached a blood pressure exceeding 200 mmHg at 100 % body weight lifted. Subject 2 was a prior athlete, now sedentary; his lifting was stopped when he attained a blood pressure of 320 mmHg at 75 % of his body weight. Subject 3, the senior author, an experienced weight lifter, reached a blood pressure of 250 mmHg at 100 % of body weight lifted. Adapted with permission from [4]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

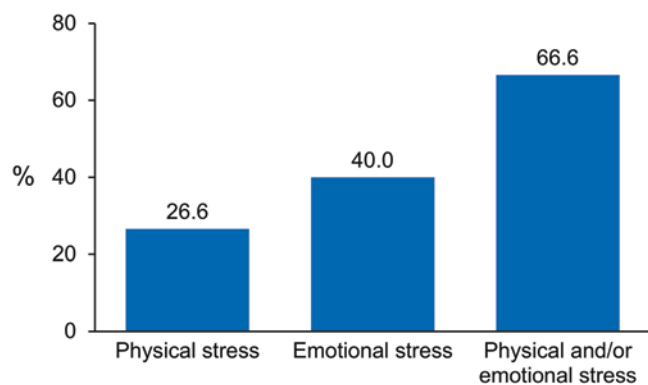


Fig. 2.28 Emotional or exertional events immediately preceding the onset of the pain of acute aortic dissection. Adapted with permission from [90]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

furniture, shoveling snow, etc.) or emotional stress (loss of a loved one, news of an illness, extreme work-related stress, etc.) preceded aortic dissection in 67 % of patients with this condition (Fig. 2.28) [90]. Although not as intuitive as physical exercise, emotional stress too can provoke a serious spike in blood pressure, enough to incite aortic dissection [93]. The role of hypertension in inciting aortic dissection is also evidenced by studies that have found a higher rate of occurrence of these events in the winter months and in the morning periods of the day, when the blood pressure is known to be highest [94–97].

The hypothesis depicted in Fig. 2.26 is based on the widely accepted assumption that the dissection starts with a tear in the intimal layer of the aorta. However, this assumption has recently been challenged by Humphrey and colleagues [98, 99], who have postulated an alternative hypothesis that the dissection actually starts within the medial layer of the aorta via pooling of glycosaminoglycans and proteoglycans (Fig. 2.29). This in turn initiates a delamination process within the medial layer, which biomechanically promotes aortic dissection. In this scenario the intimal tear is the result of an initial degradative process within the media, rather than being the initial event of the dissection [98, 99].

Why Do Some Aortic Dissections Occur at Small Sizes?

In 2007 the International Registry of Acute Aortic Dissection (IRAD) made an important observation that almost half of all cases of aortic dissection occur at a size of the aorta that falls below the currently used intervention criteria [73]. This study might lead the readers to believe that the guidelines are not correct in their assessment of risk and need to be revised with a leftward shift (i.e., recommended prophylactic surgical intervention at smaller aortic size). However, the IRAD authors wisely did not make this recommendation based on the “size paradox” that they found.

How can this paradox be explained? The IRAD data were only able to assess the occurrence of dissection events (numerator), but were not able to estimate the actual risk of dissection at a certain aortic size, because the number of individuals at risk in each size category (denominator) remained unknown. From the MESA database [77, 78] we know that the size of the ascending aorta follows a nearly typical bell-shaped distribution curve (Fig. 2.30). This means that, at the right “tail” of the curve, the number of individuals with smaller aortas is manyfold greater than individuals with larger aortas. This in turn means that the risk of a patient developing an aortic dissection at a small aortic size is significantly lower, because of the large number of susceptible patients with aortas of this size. Using this numerator/denominator data, we were able to calculate the

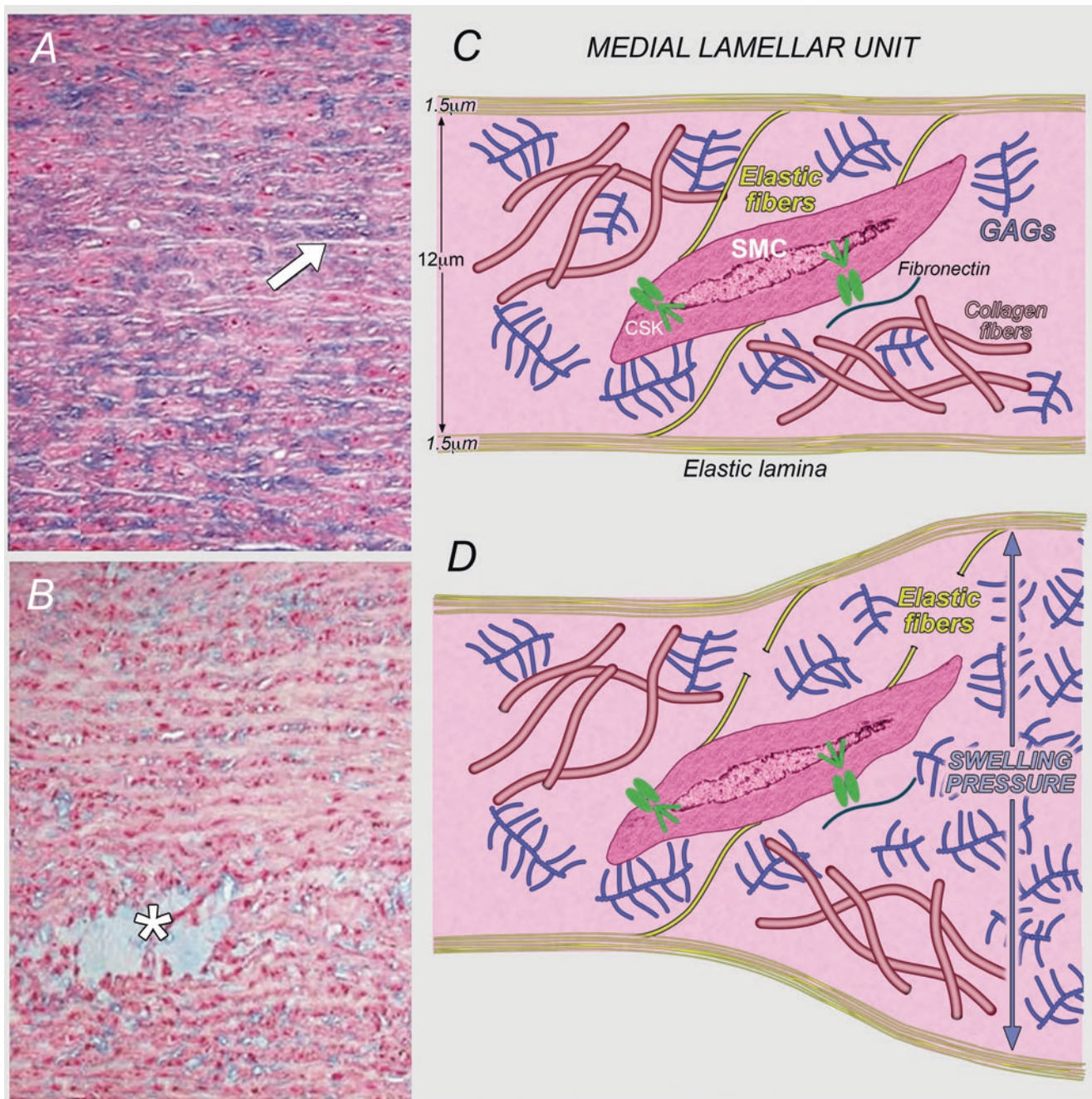


Fig. 2.29 This comparative illustration summarizes the hypothesis that pools of glycosaminoglycans/proteoglycans initiate the dissection from within. (*Panels A and B*) Sections of the medial layer of the human ascending aorta stained with alcian blue (which stains glycosaminoglycans blue) for both a normal (*panel A*) and an aneurysmal (*panel B*) aortic wall. Reproduced with permission from Borges LF, Touat Z, Leclercq A, et al. Tissue diffusion and retention of metalloproteinases in ascending aortic aneurysms and dissections. *Hum Pathol* 2009;40:306–13 [108]. (*Panel C*) Schematic drawing of a normal aortic medial lamellar unit consisting of paired elastic laminae (at the *top and bottom*) with an embedded smooth muscle cell (SMC) as well as collagen fibers, adhesion molecules (e.g., fibronectin), and glycosaminoglycans (GAGs) (not to scale). Shown, too, are thin “radially oriented” elastic fibers (i.e., elastin and associated microfibrils, predominately fibrillin-1) that may provide direct mechanical

connections between the elastic laminae and smooth muscle cell and thus a mechanosensory capability beyond the typical cytoskeletal (CSK)–integrin–extracellular matrix (fibronectin/collagen) axis. It is possible that negatively charged GAGs sequester water and may thereby contribute a normal intralamellar pressure that could help maintain the thin elastic fibers in tension. (*Panel D*) This schematic drawing depicts a localized accumulation of GAGs, on the right side of the medial lamellar unit, which results in an increased swelling pressure, which in turn helps to separate the elastic laminae and possibly disrupt connections between the SMCs and either thin elastic fibers or the collagenous matrix. Such effects could initiate a local delamination and/or altered mechanosensitive cellular response leading to dysregulated wall homeostasis. *Panels C and D* courtesy of Professor Jay Humphrey, Yale School of Engineering and Applied Sciences and Yale University School of Medicine

Fig. 2.30 The aortic size follows a modified bell curve distribution. The population at risk increases dramatically moving leftward from the right “tail” of the bell curve. The corollary of this observation is that, at small aortic sizes, a huge population is at risk; therefore, although dissections do occur, the relative risk is very low compared with the huge “at-risk” population. Adapted with permission from [1]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

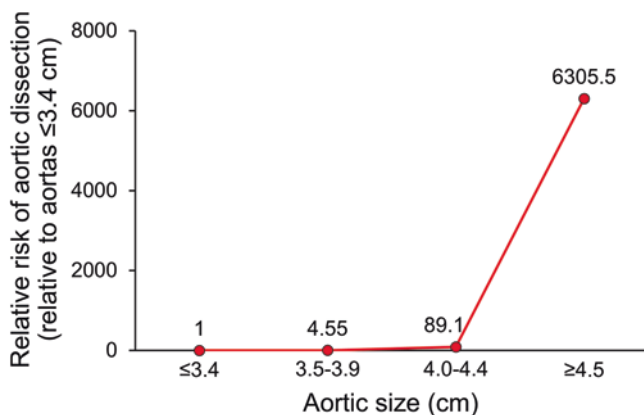
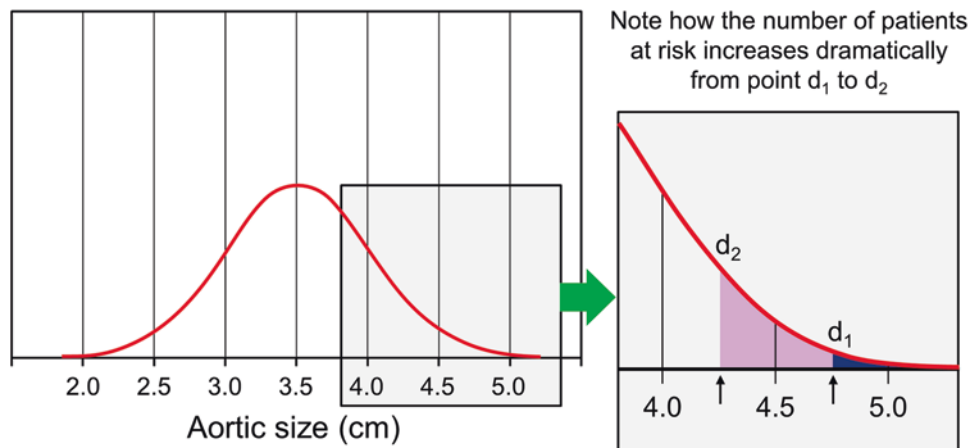


Fig. 2.31 The graph illustrates that the relative risk of aortic dissection is >6000-fold higher for large aortas than for small ones (calculated based on published data from IRAD and MESA databases). Adapted with permission from [78]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

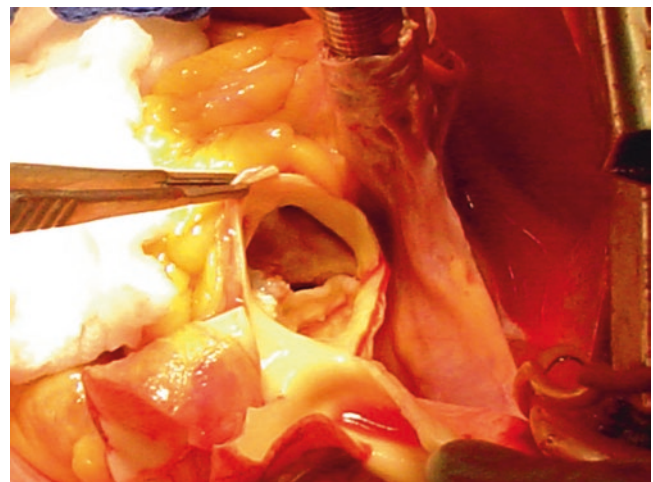


Fig. 2.32 Intraoperative image of a heavily calcified bicuspid aortic valve. Reproduced with permission from Friedman T, Mani A, Elefteriades JA. Bicuspid aortic valve: clinical approach and scientific review of a common clinical entity. *Expert Rev Cardiovasc Ther* 2008;6:235–248

relative risk of an aortic dissection occurring in a large aorta; we found this to be a full 6000 times higher than in small aortas (Fig. 2.31). Thus, comparing the observed number of dissections with the actual number of patients at risk who harbor an aneurysm of the corresponding size confirms the validity of the surgical intervention criteria that are being used today.

Thoracic Aortic Disease in the Setting of a Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly and is estimated to affect 1–2 % of the population (Fig. 2.32) [100–102]. Many patients with BAV

also develop ascending aortic aneurysm (as part of bicuspid aortopathy, Fig. 2.33). Although the exact frequency of aneurysm formation in BAV patients is hard to determine, multiple studies estimate this figure to be in the broad range of 20–84 % [102]. A study from the International Bicuspid Aortic Valve Consortium found that the risk of aneurysm development is 80 times higher than in the general population [103]. There is some equivocal evidence in the literature to suggest that thoracic aortic aneurysms in patients with a BAV behave in a more malignant way than regular aneurysms. They grow faster—0.19 cm/year vs. 0.13 cm/year—for patients with a trileaflet aortic valve (Fig. 2.34) [5] and are known to play a major role in the causation of aortic dissection [104, 105]. Also, a higher proportion of BAV patients require surgery for their aneu-

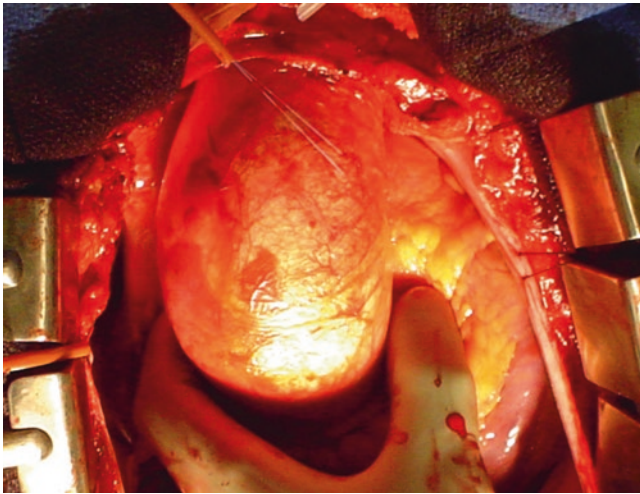


Fig. 2.33 Intraoperative image of an ascending aortic aneurysm in a patient with a bicuspid aortic valve (shown in Fig. 2.32)

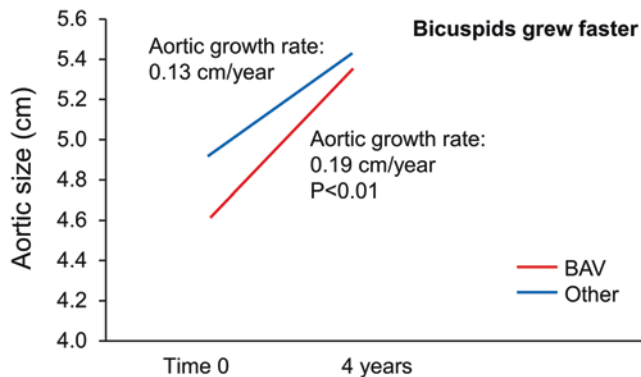


Fig. 2.34 Aortic growth rate chart, illustrating a faster growth of aneurysms for patients with a bicuspid aortic valve than in patients with non-BAV-related aneurysms. Adapted with permission from [101]. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

rysmal aortas (72.8 % vs. 44.8 %) at a significantly younger age (48.9 vs. 63.1 years) [5]. Despite the seemingly more aggressive course of aortic disease in BAV patients, recent studies have demonstrated that with appropriate diagnosis and care the outlook for patients with a BAV is no different from the general population [106–108].

Conclusion

The pieces of the puzzle in the playbook of thoracic aortic aneurysm are coming together (Fig. 2.35):

- A genetic abnormality predisposes to aneurysm development.

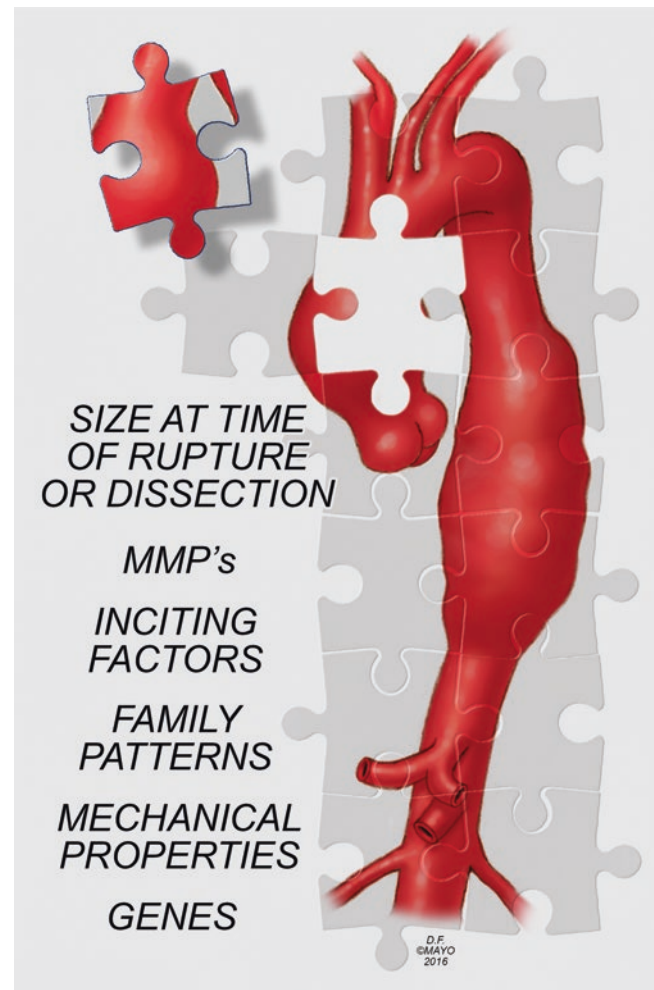


Fig. 2.35 Pieces in the puzzle of the playbook of thoracic aortic aneurysm. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

- The MMPs participate significantly in a complex aneurysm pathophysiology.
- Definite family patterns prevail.
- Mechanical properties of the aorta are dramatically altered.
- Aortic dissection and rupture tend to occur at or above 5 cm aortic diameter.
- Exertion or emotion are acute inciting factors for aortic dissection
- Specific genetic mutations (including single base change) are being identified in individual patients via modern whole-exome sequencing.

These advances in understanding put aortic specialists in a better position than ever before to combat the silent, virulent, and capricious disease of thoracic aortic aneurysm.

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