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EPIDEMIOLOGY OF THORACIC AORTIC ANEURYSMS, AORTIC DISSECTION, INTRAMURAL HEMATOMA, AND PENETRATING ATHEROSCLEROTIC ULCERS

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THORACIC AORTIC ANEURYSMS

Anatomically the thoracic aorta is divided into a several distinct segments (Figure 1.1). The ascending aorta extends from the left ventricle (at the aortic annulus) and rises in the anterior mediastinum to the innominate artery. The base of the ascending aorta is referred to as the aortic root. The root is the widest aortic segment and is comprised of three coronary sinuses, which bulge outward, and serves as the support structure for the aortic valve cusps. The portion of the ascending aorta above the root is narrower and tubular in shape. Distal to the ascending aorta is the aortic arch, which moves posteriorly and to the left in the superior mediastinum, extending from the innominate artery to the ostium of the left subclavian artery. Thereafter, the descending aorta courses posteriorly, adjacent to the vertebral column, and continues to the level of the diaphragm, after which it becomes the abdominal aorta.

The true incidence of thoracic aortic aneurysms is difficult to determine, as many go undiagnosed. However, in a Mayo Clinic sampling from 1980–1994, the incidence in Olmstead County, Minnesota, was 10.4 per 100,000 person years\(^1\). This was significantly higher than the incidence in the same
Thoracic aortic aneurysms most often result from cystic medial degeneration, which appears histologically as smooth muscle cell drop-out and elastic fiber degeneration, resulting in the presence in the media of cystic spaces filled with mucoid materia. The histologic changes occur most frequently in the ascending aorta but in some cases may involve the entire aorta. The medial degeneration results in a weakening of the aortic wall, which in turn leads to progressive aortic dilatation and eventually an aneurysm.
CYSTIC MEDIAL DEGENERATION

Hypertension

Cystic medial degeneration is known to occur to some extent with aging, but this process is accelerated by hypertension\(^3\). Hypertension leads to intimal thickening, degradation of the extracellular matrix, loss of elastic fibers, and smooth muscle cell necrosis. As a consequence, the aortic wall becomes stiff and progressively dilates. Thus, advanced age and hypertension are, collectively, important risk factors for the development of thoracic aortic aneurysms.

Marfan Syndrome

On the other hand, when cystic medial degeneration occurs at younger ages, it is classically associated with recognized connective tissue disorders, such as Marfan syndrome (see Chapter 2) or, less commonly, Ehlers–Danlos syndrome (see Chapter 2) or Turner syndrome. Among those with Marfan syndrome, thoracic aortic aneurysms predominantly involve the aortic root in a pattern known as annuloaortic ectasia. Penetrance is variable, and in some with Marfan syndrome the aortic root is significantly aneurysmal by the teenage years, whereas others have much slower progression of disease, and still others have minimal or no aortic dilatation.

Bicuspid Aortic Valve

Other congenital conditions can predispose to thoracic aortic aneurysms. It is now well recognized that those with a congenital bicuspid aortic valve have a significantly increased risk of aortic dilatation, aneurysm, and dissection. Echocardiographic studies of young people with normally functioning (neither stenotic nor regurgitant) bicuspid aortic valves have shown that about 50% have dilatation of the ascending aorta\(^4\). In the majority of cases the dilatation involves the tubular portion of the ascending aorta, whereas in a minority it involves primarily the aortic root (annuloaortic ectasia). A number of studies have identified cystic medial degeneration as the culprit. In one series, of those with bicuspid aortic valve undergoing aortic valve replacement surgery, 75% had biopsy proven cystic medial degeneration, compared with a rate of 14% among those with tricuspid aortic valves undergoing similar surgery\(^5\). One possible mechanism for the association of cystic medial degeneration and bicuspid aortic valve is that inadequate production of fibrillin-1 during embryogenesis results in both the bicuspid aortic valve and a weakened aortic wall\(^6\). No single gene responsible for bicuspid aortic valve has yet been identified, and it may well be genetically heterogeneous.
Familial Thoracic Aortic Aneurysm Syndrome

Cystic medial degeneration has also been found as the cause of thoracic aortic aneurysms among many of those with neither an overt connective tissue disorder nor a bicuspid aortic valve. Moreover, while such cases of thoracic aortic aneurysms may be sporadic, they are often familial in nature and have now been termed the familial thoracic aortic aneurysm syndrome.

In an analysis using a large database of patients with thoracic aortic aneurysms, the Yale group found that at least 19% of patients without Marfan syndrome had a family history of a thoracic aortic aneurysm. Moreover, they found that those with familial syndromes presented at a mean age of 57 years, which was significantly younger than the sporadic cases, who presented at a mean age of 64 years. Most pedigrees have suggested an autosomal dominant mode of inheritance, but some have suggested a recessive mode and possibly X-linked inheritance as well. In a study of 158 patients referred for surgical repair or thoracic aortic aneurysms or dissections, Biddinger et al. found that first-degree relatives of probands had a higher risk (RR 1.8 for fathers and sisters, RR 10.9 for brothers) of thoracic aortic aneurysms or sudden death compared with controls.

The genetics of the familial thoracic aortic aneurysm syndrome are being actively investigated. Milewicz et al. have identified a mutation on 3p24.2-25 that can cause both isolated and familial thoracic aortic aneurysms. Aortic histopathology of these families reveals cystic medial degeneration. There appears to be dominant inheritance, yet there is marked variability in the expression and penetrance of the disorder, such that some inherit and pass on the gene but show no manifestation. More recently, two studies of familial thoracic aortic aneurysm syndromes have mapped mutations to at least two different chromosomal loci, whereas other families mapped to neither of these—suggesting at least a third locus. The genetics may be rather complex; indeed, the fact that there is such variable expression and penetrance suggests that this may be a polygenic condition.

Atherosclerosis

Atherosclerosis is infrequently the cause of ascending thoracic aortic aneurysms and, when it is, tends to be associated with diffuse aortic atherosclerosis. Aneurysms of the aortic arch are most often contiguous with aneurysms of the ascending or descending thoracic aorta. Arch aneurysms may be due to atherosclerotic disease but are often due to cystic medial degeneration and syphilis or other infections. Conversely, atherosclerosis is the predominant etiology of aneurysms of the descending thoracic aorta. These aneurysms tend to originate just distal to the origin of the left subclavian artery and may be either fusiform or saccular. The pathogenesis of such atherosclerotic aneurysms in
the descending thoracic aorta may resemble that of abdominal aneurysms but has not been extensively examined.

**Syphilis**

Whereas syphilis was once the most common cause of ascending thoracic aortic aneurysms, accounting for up to 80% of cases, in the current era of aggressive antibiotic treatment of the disease it is now rarely the cause. The latent period from initial spirochetal infection to aortic complications is most commonly 10–25 years (range 5 to 40 years). During the secondary phase of the disease, spirochetes directly infect the aortic media, with the ascending aorta most often affected. The infection and attendant inflammatory response destroys the muscular and elastic medial elements, leading to weakening of the aortic wall and progressive aneurysmal dilatation.

**Vasculitis**

Takayasu’s arteritis typically causes obliterative lesions of the aorta, producing signs and symptoms of vascular insufficiency, but less often can produce aortic aneurysms. Takayasu’s arteritis primarily affects young the young, typically those 10–30 years old, with females affected in 90% of the cases. It occurs most often in Asian populations. On the other hand, giant cell arteritis tends to affect an older population, especially those over the age of 55, but again with females affected far more often than males. In most cases, giant cell arteritis presents with signs and symptoms of temporal arteritis. When the aorta is affected, it may result in thoracic aortic aneurysms, most often involving the arch or descending aorta.

**Other Causes**

Infectious aneurysms may result from a primary infection of the aortic wall causing aortic dilatation with the formation of fusiform or saccular aneurysms. Thoracic aortic aneurysms can also result from aortic trauma (see Chapter 2) or aortic dissection (see below).

**Natural History**

The natural history of thoracic aortic aneurysms is affected by the size and location of the aneurysm. The best data presently available on the natural history of thoracic aortic aneurysms come from a longitudinal report by Davies et al. from the Yale group in which 304 patients with thoracic aortic aneurysms at least 3.5 cm in size were followed for a mean of more than 31 months. The mean rate of growth for all thoracic aortic aneurysms was 0.1 cm per year. However, the rate of growth was significantly greater for aneurysms of
the descending aorta (0.19 cm per year) than for those of the ascending aorta (0.07 cm per year). In addition, dissected thoracic aneurysms grew significantly more rapidly (0.14 cm per year) than did nondissected ones (0.09 cm per year). Not surprisingly, those with Marfan syndrome also had more rapid aneurysm growth.

In this same study population, the mean rate of aortic rupture or dissection was 2% per year for thoracic aortic aneurysms less than 5 cm in diameter, 3% per year for aneurysms 5.0–5.9 cm, and 7% per year for aneurysms 6.0 cm or larger. In a multivariate logistic regression analysis of the predictors of dissection or rupture, the relative risk of an aneurysm diameter of 5.0–5.9 cm was 2.5, an aneurysm diameter of 6.0 cm or larger was 5.2, Marfan syndrome was 3.7, and female gender was 2.9. Other natural history studies that focused on thoracic and thoracoabdominal aneurysms have found that the odds of rupture are increased by chronic obstructive pulmonary disease (RR 3.6), advanced age (RR 2.6 per decade), and aneurysm-related pain (RR 2.3)\textsuperscript{13}.

Thoracic aortic aneurysm size is an important predictor of rate of growth. Dapunt et al. monitored 67 patients with thoracic aortic aneurysms and found that aneurysms that were 5.0 cm or smaller grew more slowly than did those larger than 5.0 cm, and the only independent predictor of rapid expansion (>0.5 cm per year) was an initial aortic diameter greater than 5.0 cm\textsuperscript{14}. Nevertheless, even when controlling for initial aneurysm size, substantial variation was still seen in individual aneurysm growth rates, thus making such mean growth rates of little value in predicting aneurysm growth for a given patient.

**AORTIC DISSECTION**

The true incidence of acute aortic dissection is difficult to determine, as many cases may go undiagnosed, but its documented incidence is approximately 2.9 per 100,000 per year, with at least 7,000 cases per year in the United States\textsuperscript{15}. A healthy aorta with an intact medial layer rarely dissects. Alternatively, those in whom the integrity of the media is compromised are at risk for aortic dissection. Therefore, any disease process or condition that damages the elastic or muscular components of the media predisposes the aorta to dissection. Indeed, cystic medial degeneration, as discussed above, is a major predisposing factor in aortic dissection.

The peak incidence of aortic dissection is in the sixth and seventh decades of life, with a mean age of 62 years among more than a thousand subjects in the International Registry of Acute Aortic Dissection (IRAD)\textsuperscript{16}. Overall, men are affected twice as often as women (68% vs. 32%) and are affected at younger ages as well, with male patients having a mean age of 60 years and female patients a mean age of 67. However, as shown in Figure 1.2 the male predominance is most striking at young ages, with males outnumbering females 4:1
at ages less than 50. With increasing age, however, the difference lessens, and among those older than 75, males and females are equally represented.

Table 1.1 summarizes the contribution of recognized risk factors on the incidence of aortic dissection among the IRAD population. About three-quarters of patients had a history of hypertension. Only 14% had a known thoracic aortic aneurysm. Many more patients likely had a preexisting aneurysm that had simply gone undetected prior to the aorta’s dissection. Bicuspid aortic accounted for 3.4% of aortic dissection cases, which was not much less than the 5% attributable to Marfan syndrome. As is the case with ascending thoracic aortic aneurysms, the risk of aortic dissection appears to be independent of the severity of the bicuspid valve stenosis. Much less commonly, aorta dissection results from other congenital cardiovascular abnormalities, including coarctation of the aorta and Turner syndrome.

The risk factors for and presentation of aortic dissection differ between younger and older patient populations. In IRAD, 7% of patients were younger than 40 years old. The differences between the two age groups are summarized in Table 1.2. Not surprisingly, Marfan syndrome was the major risk factor among younger patients, accounting for 50% of cases\(^\text{17}\). Conversely, this can be reframed to highlight the fact that 50% of young patients did not have underlying Marfan syndrome as a predisposing risk factor for aortic dissection.
Table 1.1. Known risk factors for aortic dissection from IRAD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age (mean)</td>
<td>62 years</td>
</tr>
<tr>
<td>Male gender</td>
<td>68%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>72%</td>
</tr>
<tr>
<td>Prior aortic dissection</td>
<td>5%</td>
</tr>
<tr>
<td>Known aortic aneurysm</td>
<td>14%</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>5%</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>3%</td>
</tr>
<tr>
<td>Peripartum period of pregnancy</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cardiac catheterization/surgery</td>
<td>5%</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>22%</td>
</tr>
</tbody>
</table>

Table 1.2. Comparison of younger vs. older patients with aortic dissection

<table>
<thead>
<tr>
<th>Feature</th>
<th>Age &lt; 40 (%)</th>
<th>Age ≥ 40 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan syndrome</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>34</td>
<td>72</td>
</tr>
<tr>
<td>Hypertension on presentation</td>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>

Source: Adapted with permission from reference 17.

Moreover, hypertension was much less common as a risk factor among young patients, and only 25% of young patients were hypertensive on presentation.

A number of reports have identified cocaine abuse as a risk factor for aortic dissection, typically among young, black, hypertensive men. However, cocaine likely accounts for less than 1% of cases of aortic dissection, and the mechanisms by which it causes dissection remain speculative.

For decades, there has been recognition that there exists an unexplained relationship between pregnancy and aortic dissection, typically occurring in the third trimester or in the early postpartum period. In IRAD, only 0.2% of all aortic dissection cases were associated with pregnancy, which might suggest at first that it is a relatively minor contributor. However, given that 93% of patients in IRAD were ≥40 years old and the majority of patients were men, only a small minority could even have had pregnancy as a risk factor. Alternatively, if one considered only a cohort of those IRAD patients who were female and under the age of 40, one would find that 12% were associated with pregnancy, implying that there is some causal association. However, it is quite likely that pregnancy is a precipitant of aortic dissection among women.
otherwise at risk (due to some underlying cystic medial degeneration), rather than the primary cause of aortic pathology.

Trauma can also cause aortic dissection. Blunt trauma and deceleration injuries tend to cause localized tears, hematomas, or frank aortic transection but only rarely cause classic aortic dissection. More commonly, iatrogenic trauma is associated with true aortic dissection and accounts for 5% of cases in IRAD\textsuperscript{19}. Both the manipulation of catheters and wires within the aorta and the insertion of intraaortic balloon pumps may puncture the aortic intima and induce aortic dissection. In addition, cardiac surgery also entails a very small risk (0.12–0.16%) of acute aortic dissection, which is usually discovered and repaired intraoperatively. Aortic dissection appears to occur more often as a late complication of cardiac surgery, typically occurring months to years after the procedure; in fact, 22% of those with acute aortic dissection have a history of prior cardiac surgery, 9% had preexisting aortic disease (prior thoracoabdominal aortic aneurysm or dissection repair), and 5% had prior aortic valve replacement. The association of dissection with aortic valve replacement may reflect the fact that many of those having undergone aortic valve surgery did so because of an underlying dysfunctional bicuspid aortic valve and thus would likely have had underlying cystic medial degeneration as well. It could then be the congenital cystic medial degeneration rather than the cardiac surgery itself that predisposed this group to late aortic dissection. Nevertheless, 6% of those with aortic dissection had only a CABG as their surgical procedure.

Data from IRAD indicate that there are chronobiological patterns of acute aortic dissection\textsuperscript{20}. There is diurnal variation in the onset of aortic dissection (see Figure 1.3), with dissection occurring most often in the early daytime.
hours of 6 a.m. until noon and least often during the nighttime hours of midnight to 6 a.m. This circadian pattern was similar for all subgroups examined, suggesting that there are likely common triggers. Of interest is the fact that this pattern is similar to that seen with the onset of acute coronary syndromes. There is also a seasonal variation in the incidence of aortic dissection, with significantly higher rates of aortic dissection in the winter months, whereas event rates were lowest in the summer months (Figure 1.4).

**INTRAMURAL HEMATOMA**

Intramural hematoma is a variant of classic aortic dissection. It results from hemorrhage that occurs in and is contained within the medial layer of the aortic wall, rather from a primary tear in the intima. Consequently, there is no communication between the hematoma and the aortic lumen. Nevertheless, the clinical signs and symptoms associated with intramural hematoma resemble those seen in classic aortic dissection. The distinction is therefore made on the basis of the findings of imaging studies, in which anywhere from 5% to 17% of apparent aortic dissection cases are diagnosed as intramural hematoma.

In the IRAD experience, of 1,010 patients presenting with apparent acute aortic dissection, 58 (5.7%) met the strict criterion of acute intramural hematoma\(^{21}\). Table 1.3 summarizes some of the demographics of the two groups in this study. As shown, those diagnosed with intramural hematoma were significantly older on average than those with classic aortic dissection (61.7 ± 14.3 vs. 68.7 ± 10.4; \(p < 0.001\)). There was no significant difference in the history of hypertension between the groups. Although it did not reach
Table 1.3. Demographics, history, and location of aortic involvement among patients with aortic dissection vs. intramural hematoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Classic aortic dissection, % (n = 952)</th>
<th>Intramural hematoma, % (n = 58)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>61.7 ± 14.3</td>
<td>68.7 ± 10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30.9</td>
<td>39.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Male</td>
<td>69.1</td>
<td>60.3</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85.9</td>
<td>98.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71.1</td>
<td>77.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>5.4</td>
<td>0.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>64.7</td>
<td>39.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B</td>
<td>35.3</td>
<td>60.3</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted with permission from reference 21.

Table 1.4. Demographics of population with penetrating atherosclerotic ulcer

<table>
<thead>
<tr>
<th>Age (mean)</th>
<th>71–77 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>85%</td>
</tr>
<tr>
<td>Smoking</td>
<td>72%</td>
</tr>
<tr>
<td>Known coronary artery disease</td>
<td>61%</td>
</tr>
<tr>
<td>Thoracic or abdominal aortic aneurysm</td>
<td>38–53%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>17%</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>12%</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>31%</td>
</tr>
</tbody>
</table>

Source: Adapted from references 22–24.

Statistical significance, there was a trend toward a lesser proportion of Marfan syndrome patients among those with intramural hematoma compared with classic aortic dissection (5.4% vs. 0%; p = 0.11). The anatomic location of aortic involvement was significantly different between the groups, with aortic dissection presenting twice as often as type A than type B, whereas intramural hematoma presented more often as type B.

**PENETRATING ATHEROSCLEROTIC ULCER**

Penetrating atherosclerotic ulcers are atherosclerotic lesions of the aorta that penetrate the internal elastic lamina and allow hematoma formation within
the media of the aortic wall. The large majority of such ulcerations occur in
the descending thoracic aorta, but less often they may occur in the arch or,
more rarely, in the ascending aorta. The ulcers may progress to form aortic pseudoa-
neurysms or, less often, lead to transmural aortic rupture. Table 1.4 summa-
rizes the collective demographics from three series of patients with intramu-
rural hematoma. Those in whom penetrating atherosclerotic ulcers develop
tend to be elderly and are on average about a decade older than those who
present with typical aortic dissection. Most have a history of hypertension and
smoking. They tend to have severe and extensive atherosclerosis; the majority
have evidence of other atherosclerotic cardiovascular disease and as many as
half also have a history of a preexisting abdominal or thoracic aortic aneurysm.

References
   Improved prognosis of thoracic aortic aneurysms: a population-based study. JAMA 280,
   1926–1929.
   WB Saunders, Philadelphia.
   normally functioning bicuspid aortic valves. Heart 82, 19–22.
5. DeSa M, Moshkovitz Y, Butany J, David TE (1999). Histologic abnormalities of the as-
   cending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical
6. Huntington K, Hunter AG, Chan KL (1997). A prospective study to assess the frequency of
   sivity of familial thoracic aneurysms/dissections. Am. J. Cardiol. 82, 474–479.
    locus for familial aortic aneurysm disease, a genetically heterogeneous disorder. Circulation
    103, 2469–2475.
    rates for thoracic aortic aneurysms: simple prediction based on size. Ann. Thorac. Surg. 73,
    17–28.
13. Griep RB, Ergin A, Gall JD, et al. (1999). Natural history of descending thoracic and
Aortic Dissection and Related Syndromes
Baliga, R.; Nienaber, C.; Isselbacher, E.M.; Eagle, K.A.
(Eds.)
2007, XII, 364 p. 168 illus., Hardcover