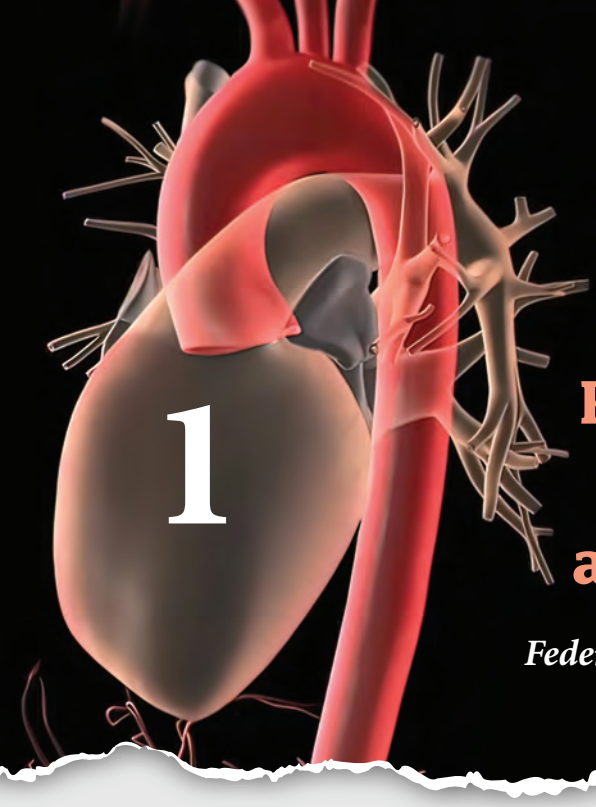

1 Pathophysiology, epidemiology, and classification

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On October 1760 in Kensington Palace, London, King George II got up at about six o'clock, called for his chocolate, and retired into the bathroom. At seven o'clock, one of his servants was alerted by a loud noise and found him lying on the ground, speechless and lifeless. The King was dead. The day after, Dr. Frank Nicholls, physician to his late Majesty, carried out a necropsy. No abnormalities were found in the abdomen and in the head. However, opening the chest, he found: "*in the trunk of the aorta, a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed, under its external coat, and formed an elevated ecchymosis.*"[1]

King George II was the first reported patient affected by acute aortic dissection. Described more than 200 years ago by J.B. Morgagni as "aortic dissection,"[2] and then in 1819 by Laennec as "*aneurysme dissequant*,"[3] the first diagnosis in living patients was made by Swaine and Latham in 1856.[4]

In 1934, Shennan *et al.*[5] defined dissecting aneurysms in 300 subjects. They pointed out the medial degeneration of the aorta as the pathological alteration underlying the disease. The year after, the first surgical attempts to repair dissecting aneurysms were performed with miserable outcomes.[6, 7]

The first report of successful treatment of dissecting aneurysms of the aorta was that by DeBakey, Cooley *et al.* in 1955.[8] They performed: 1) a fenestration procedure in two patients; 2) excision of the aneurysm and graft interposition or direct anastomosis in three patients; and 3) an excision of a saccular aneurysm with a patch implantation

on the aortic defect in one patient. Since then, acute aortic syndromes (AAS) have been better recognized and characterized. However, they still remain a challenging clinical emergency. Over the years, growing improvement in imaging and therapeutic strategies have strengthened the awareness that an early diagnosis is essential to survival.

1.1 Pathophysiology

AAS include a cluster of aortic diseases: aortic dissection (AD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU) (Figure 1.1).

1.1.1 Aortic dissection

AD arises from a tear in the intimal layer that allows the pulsatile blood flow to progressively separate the aortic wall layers along the intimomedial plane of the aorta. Typically, the entry site is transverse and does not involve the entire circumference of the aorta.[9, 10] The dissection flap occurs where the aortic wall is subject to the greatest fluctuations in pressure over time. Computational fluid dynamic analyses have shown that a high shear stress area with a vortex flow is closely associated with future primary entry dissection tear.[11] The intimal flap may partially, intermittently, or completely obstruct distal perfusion to the aorta or any branch vessel.[10]

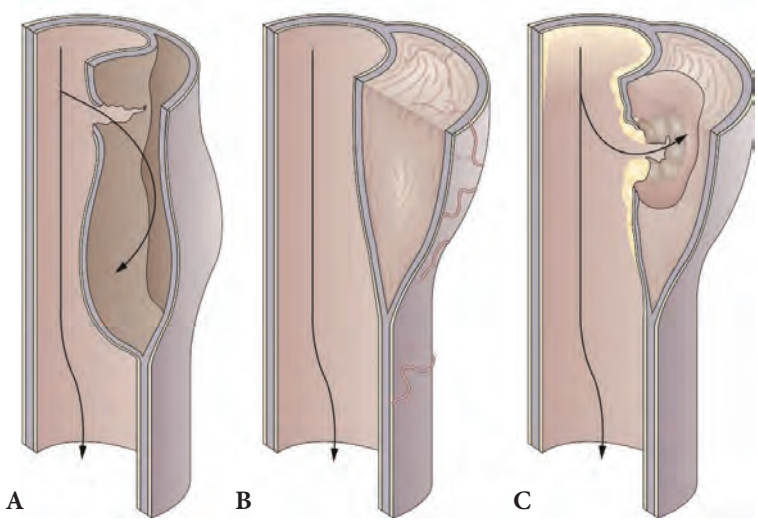

Figure 1.1. Acute aortic syndrome: A) aortic dissection; B) intramural hematoma; and C) penetrating aortic ulcer. The arrows indicate blood flow.
Modified from LeMaire *et al.*[9]

The usual pattern of the dissection plane through the aorta is posterolateral, in a spiral fashion. The outer portion of the aortic media and adventitia are the external wall of the false lumen. The false lumen represents the blood-filled space between the dissected layers of the aortic wall. Dilation of the false lumen may reduce the true lumen volume. Downstream fenestrations within the intimal flap lead to sites of reentry for flow into the true lumen, thus maintaining false lumen patency. However, in a series of sudden deaths fenestrations were absent in 67% of cases.[12] Blood circulation in the false lumen can cause either inadequate perfusion to vital organs (the so-called "malperfusion syndrome") or sudden death because of aortic rupture.[12]

1.1.2 Intramural hematoma

First described as "dissection without intimal tear," an IMH is a bleed into the outer layers of the aortic media without an entry tear. An IMH is a noncommunicating type of dissection strongly associated with an atherosclerotic lesion.[13] There may be small atherosclerotic plaque ruptures in the wall of the vessel that are related to IMH inception.[14] Another hypothesis suggests focal rupture of the vasa vasorum could produce a secondary IMH.[15] A combination of the two mechanisms seems to be the most valuable etiopathogenesis of IMH. However, several studies sustain that common mechanisms could trigger both AD and IMH.[16] It has been also thought of as an AD with acutely thrombosed false lumen. However, recently the existence of intimal tears in some patients with IMH has been documented frequently. This finding is strictly related to the continuous progress in diagnostic imaging. Therefore, it should be referred to as an acute AD with a thrombosed false lumen.[16, 17]

The hematoma propagates along the medial layer of the aorta. Due to the aortic weakening, IMH may evolve either to outward rupture of the aortic wall or to inward disruption of the intima, resulting in AD. The site of an IMH is also prognostic for its evolution. Its localization in the ascending aorta has a high risk of progression to AD and usually requires surgery. IMH is classified into two types as shown in the Table 1.I.[12]

The IMH location is also prognostic of progression to frank dissection and usually mandates repair. An IMH in the ascending aorta is more prone to develop AD or aortic rupture than an IMH in the descending aorta.

1.1.3 Penetrating aortic ulcer

A PAU is an aortic atherosclerotic plaque lesion with ulceration invading the aortic media after disrupting the internal elastic lamina. PAU can progressively develop into aortic hematoma, pseudoaneurysm, dissection, and eventually rupture following the transmural inflammation of the aortic plaque.[18] These lesions typically occur in elderly patients with systemic atherosclerosis. It was first described in 1934 by

Table 1.I. Types of intramural hematoma.

	Type 1	Type 2
Wall thickness	≤0.5 cm	0.6-4.0 cm (median >1.3 cm)
Vessel diameter	<3.5 cm	>3.5 cm
Mean length	<11 cm	Common
Presence of flow on echocardiography	Less common	>11 cm
Association with calcified plaque	Not associated	Associated
Intimal appearance	Smooth	Rough/atherosclerotic
Echocardiographic findings	Echo-free zones present in <30% of cases	Echo-free zones present in >70% of cases

Shennan.[5] However, in 1986, Stanson *et al.*[19] better specified the pathological lesion. Initially, the lesion is asymptomatic and confined to the intimal layer. Then, the lesion advances to a deep atheromatous ulcer that penetrates through the aortic layers to the media. Hematoma formation may extend along the media, evolving into a dissection. Sometimes, the extension of the hematoma elicits progressive stretching of the impaired aortic wall with subsequent formation of a saccular aortic aneurysm. The aortic aneurysm and dissection may eventually rupture.

1.1.4 Predisposing conditions for acute aortic syndromes

Several conditions predispose an individual to develop an AAS, either through weakening of the aortic media or by exposing the wall of the aorta to increased pulsatile pressure (Table 1.II).[20]

1.1.4.1 Mechanisms weakening the medial layer of the aorta

Aortic wall structural abnormalities are well-established risk factors for AAS. Histopathological analyses have revealed degenerative lesions of the medial aortic layer underlying these diseases. In 1930, Erdheim *et al.*[21] first defined this tissue alterations as "aortic idiopathic cystic medial necrosis." Over the years, the perception of aortic diseases as a genetics-based issue has increased. Patients with connective tissue disorders such as Ehlers-Danlos and Marfan Syndromes are prone to develop medial degeneration of the aortic wall. Marfan Syndrome accounts for 5% of all AD and is the leading cause of AD in patients <40 years old.[22] However, a degenerative process of medial collagen and elastin fibers can happen independently, and AAS or aortic aneurysms may occur in a normal aorta.[23]

Table 1.II. Predisposing conditions for acute aortic syndromes.

Mechanisms weakening the medial layer of the aorta	Mechanisms inducing high wall stress on the aorta
Connective tissue disorders including Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome; bicuspid aortic valve; coarctation of the aorta	Arterial hypertension, particularly if uncontrolled
Vascular inflammation (giant cell arteritis, Takayasu arteritis, Behcet's disease, syphilis, Ormond's disease)	Smoking; use of sympathomimetic agents such as cocaine, ecstasy, or energy drinks
Infection involving the aortic wall either from bacteremia or extension of adjacent infection.	Weightlifting or another Valsalva maneuver
Atherosclerosis	Trauma (*e.g.*, deceleration or torsion injuries, motor vehicle accident, fall)
Preexisting aortic aneurysm	Pregnancy and delivery
	Iatrogenic factors such as catheter intervention (percutaneous stenting or catheter insertion), surgery (ascending aorta surgery, valvular surgery, coronary artery bypass graft, side, or cross-clamping of the aorta)

Atherosclerosis also represents a risk factor for aortic aneurysms. The International Registry of Acute Aortic Dissection (IRAD) data reveal that a history of atherosclerosis is present in 31% of patients.[24] A medial inflammatory response to atherosclerosis leads to negative histological remodeling of the aortic wall: irregular thickening of the intima, massive fibrosis and calcification, and increased amounts of extracellular fatty acids. The intimal integrity can be compromised by the extracellular matrix being degraded by histiocytic cells. Additional degenerative changes can reduce cellularity and collagen hyalinization. Both mechanisms may lead to intimal rupture, most often at the edges of plaques.[25]

Inflammatory diseases can destroy the inner layers of the aortic wall, leading to a progressive aortic impairment, speeding up vessel expansion and causing higher wall stress. Suppurative bacterial or fungal aortitis is rare. It can cause focal destruction of the vessel wall with subsequent aneurysm formation and/or rupture.[24] Autoimmune diseases of the aorta can severely affect the vasa vasorum and decrease the blood supply of the media. Furthermore, inflammatory lesions – namely inflammatory infiltrates, smooth muscle and fibroblast necrosis, and fibrosis of the vessel wall – may develop

inside the aortic wall. Inflammation related to infectious diseases, such as luetic aortitis, can lead to similar alterations.

All mechanisms that weaken the aortic wall, particularly the medial layer, lead to higher wall stress, which can induce aortic dilatation and aneurysm formation, eventually resulting in AD or aortic rupture.

1.1.4.2 Mechanisms inducing high wall stress on the aorta

An initial event such as systolic hypertension peak usually triggers AAS. Hypertension is recognized as one of the most significant risk factors for AAS. Based on IRAD data, most patients had a history of systemic hypertension (72%).[24] Antihypertensive therapy is pivotal to control AAS to reduce mortality. Another risk factor is smoking, a bad habit with a harmful effect on the aortic wall. Tobacco use can lead to catecholamine release and exacerbate dissections. Furthermore, IRAD data reveal that cocaine use led to AAS in 1.8% of patients with AAS, particularly in young African American males.[26]

In addition, after motor vehicle accidents, thoracic blunt trauma usually causes dissection of the aorta, especially in the region of the ligamentum Botalli at the aortic isthmus (92%). However, aortic injuries can also occur in the ascending aorta (3%), in the arch (4%) and in the distal descending aorta (1%). The descending aorta is fixed to the spine by the mediastinal pleura, intercostal arteries, and the ligamentum Botalli, whereas the arch and ascending aorta are more mobile, resulting in a focus of stress at the isthmus. The mechanism of blunt traumatic aortic injuries is a complex combination of motion of the structures within the thorax, and local loading of the tissues, either as a result of their anatomy or due to the nature of the impact.[27]

Pregnancy and delivery can also trigger aortic complications, from dissection to rupture, even in women without other risk factors.[28]

The IRAD registry shows that 4% of AAS were due to iatrogenic causes. Physicians should be aware of the possibility of iatrogenic AD after invasive vascular procedures or cardiac surgery. In the Registry on Aortic Iatrogenic Dissection (RAID), the incidence of iatrogenic ascending aorta dissection was very low (0.06%); it carries an excellent short- and long-term prognosis with the adoption of a conservative approach.[29] However, prior heart surgery is another risk factor occurring in 18% of patients with AAS. AD may be observed in patients who had previously undergone aortic valve replacement. The interval between valve replacement and dissection also varies according to the genetic risk factors. Patients with Marfan Syndrome have higher long-term rates of aortic complications after isolated aortic valve replacement.[30]

1.2 Epidemiology

Despite the known morbidity of these pathologies, the current epidemiology of AAS is unknown. Studies may underestimate the incidence due to incomplete inclusion of

deaths before hospital admission: More than one third of them are never diagnosed.[31-33] People can die from unrecognized AD that can be found postmortem at autopsy. In fact, AD prevalence varied from 0.2% to 0.8% in large series of autopsies.[34, 35] Almost 50% of patients with AD die at home or before reaching the hospital.[36, 37] Therefore, existing registries underestimate the incidence of AAS.

The incidence of AAS is mostly related to the prevalence of risk factors. In their analysis of data collected over a 15-year study period (1980-1994), Clouse *et al.*[31] reported that the annual incidence of thoracic aortic aneurysm rupture was 3.4 per 100,000 person-years in a White population from the United States. Their study also highlighted that AD and ruptured degenerative aortic aneurysm occurred with similar frequency but less commonly than ruptured abdominal aortic aneurysms. In a recent epidemiological analysis with a 10-year study period (1995-2015), De Martino *et al.*[38] identified that the average age of a patient with AAS was 72 years, and they were typically male. Their results confirmed other evidence in literature.[39] Men are more often affected than women, and the rate ranges from 2:1 to 5:1.[40, 41] IRAD data indicate that women with AD have a different clinical presentation than men. They reach the hospital later and with a worse clinical status (coma and tamponade) than men.[39] Therefore, women have a higher mortality rate than men and die before reaching the hospital more often than men.

Although women are less frequently affected by AD, they are significantly older than men.[39] The mean age for the occurrence of ascending AD varies from 50 to 55 years of age. Distal dissection usually occurs in older patients, from 60 to 70 years old. Young patients (<40 years old) with AD are mostly patients with Marfan Syndrome or with other connective tissue disorders.[42] In an Italian study by Pacini *et al.*,[43] the authors found that AD also occurred in the ultra-octogenarian population who had received either medical therapy or endovascular or surgical treatment. Although hazardous, selected senile patients without additional risk factors could receive a surgical treatment for AD with satisfactory outcomes, avoiding an aggressive approach. On the other hand, compassionate case should be managed medically.[44]

The incidence of AAS was 7.7 per 100,000 person-years; it was higher for men and increased with age. The incidence of AD was the highest among AAS: 4.4 per 100,000 person-years.[38] The incidence of PAU and IMH was lower (2.1 and 1.2 per 100,000 person-years, respectively).[38] Although there have been advances in AAS management and improved diagnostic technologies, the incidence of AD and IMH have remained stable over time. The incidence of PAU seems to have increased over the years, although its symptomatic presentation has been similar over time (40%). A reason for this finding could be the incidental identification of asymptomatic PAU.[38] Increased mortality associated with AD was noted to be within 14 days and has defined the acute period. However, the risk of death increases up to 90 days, confirming that the subacute phase is affected by an additional mortality risk.[38]

1.3 Classification

There are several classifications for AAS. These systems are based on the anatomy, the time of symptom onset, and the underlying pathology and complications.

1.3.1 Anatomical classification

Anatomically, there are two commonly used classification schemes for AD. In 1965, De Bakey *et al.*[8] proposed a classification according to the entry tear location in the thoracic aorta:

- type 1 – the dissection process arises in the ascending aorta extending distally for a variable distance. It includes at least the aortic arch and typically the descending aorta;
- type 2 – the dissection tear is limited to the ascending aorta;
- type 3 –the dissecting process arises in the descending thoracic aorta at or distally to the origin of the left subclavian artery. It extends distally for varying distances. Type 3 can be distinguished in type 3a or 3b according to the origin of the dissection – above or below the diaphragm, respectively.

In 1970, from the standpoint of surgical treatment, Daily *et al.*[45] simplified De Bakey's classification according to involvement of the ascending aorta in the dissection process (Figure 1.2; Table 1.III). The so-called Stanford classification discriminates between two types of dissection:[45]

- type A – all dissections involving the ascending aorta irrespective of the site of tear;
- type B – all dissections that do not involve the ascending aorta.

The Stanford classification arose from the recognition that prognosis was largely dependent on the involvement or not of the ascending aorta in the dissection process. The therapeutic treatment varied accordingly. Surgery is mandatory for the type A AD, whereas a conservative strategy only with medical therapy could be sufficient for the type B AD.

The Stanford classification fails to consider the variations of thoracic aortic

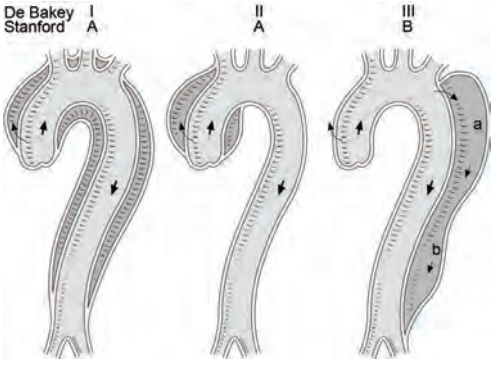

Figure 1.2. De Bakey and Stanford classification for aortic dissection.
Modified from Erbel *et al.*[12]