A killer at large: acute aortic dissection

Acute aortic dissection is one of the most fatal acute cardiovascular disorders that has challenged physicians and surgeons for decades. This article provides an up-to-date overview of the aetiology, pathophysiology, diagnosis and treatment of this condition.

'And in the trunk of the aorta we found a transverse tear' is an excerpt from the post-mortem report of King George II, who is now believed to be the first documented death from aortic dissection (Burchell and Keys, 1942). Acute aortic dissection is both a medical and a surgical emergency which begins when a tear in the intimal layer of the ascending or the descending thoracic aorta allows blood to enter and dissect through the layers of the aortic wall thus creating two lumina: a true lumen and a false lumen separated by a dissection flap (Prêtre and Von Segesser, 1997). The aorta gives rise to many important branches that supply oxygenated blood to the heart, brain, arms, spinal cord, viscera, kidneys and extremities (Golledge and Eagle, 2008). Any of these branches, from the coronaries distally, can be compromised by the dissection leading to end-organ ischaemia with disastrous consequences. Delay in diagnosis and misdiagnosis of acute aortic dissection, coupled with a high mortality in untreated patients often reported as 1–3% per hour during the first 48 hours (Svensson and Labib, 1994; Siegal, 2006), make this condition one of the most lethal acute cardiovascular disorders. Although dissection can affect any part of the aorta, the term 'acute aortic dissection' has been synonymous with acute dissection of the thoracic aorta.

Clear understanding of the pathophysiological mechanisms associated with acute aortic dissection forms the basis of early diagnosis, selection of appropriate imaging studies, and prompt provision of medical or surgical care for patients with this condition. This article reviews the aetiology, pathophysiology, diagnosis and treatment of acute aortic dissection, concentrating on developments since the last article on this topic in the *British Journal of Hospital Medicine* (Aziz and Ramsdale, 2004).

Aetiology and pathophysiology

Traditionally, acute aortic dissection occurs when two conditions exist in the aorta: weakness of the aortic wall resulting mainly from medial degeneration, and increased shear stress across the aortic lumen (Siegal, 2006; Golledge and Eagle, 2008). Aortic dissection often starts with an intimal tear (entry point) which is an important initial event that allows blood to enter into the aortic wall leading to dissection of the medial layer (Golledge and Eagle, 2008; Wong et al, 2008). Consequently, two lumina coexist in the aorta: the aortic true lumen and the newly created channel within the aortic wall which is known as the false lumen. Within the false lumen, blood can travel in an antegrade or retrograde direction, or both, before re-entering the arterial lumen (Golledge and Eagle, 2008). Such propagation of blood is responsible for the significant morbidity and mortality associated with acute aortic dissection which may result from disruption of blood flow across important aortic branches, acute aortic valve regurgitation and cardiac tamponade (Mukherjee and Eagle, 2005; Siegal, 2006).

The effect of dissection on the perfusion of aortic branches is complex; it depends on whether the artery is perfused by the false or true lumen, the degree of blood flow through the true lumen, and the relationship of the dissection flap to the individual aortic branch (Golledge and Eagle, 2008). The true lumen is usually compressed by the often larger and highly pressurized false lumen (Erbel et al, 2001). Continued expansion of the false lumen may later lead to aneurysm formation if the patient survives the initial event (Golledge and Eagle, 2008). Finally, a breach of the adventitial layer may result in a slow contained leak or frank aortic rupture with sudden fatal consequences (Wong et al, 2008).

Risk factors

Acquired

A number of inherited and acquired conditions are known to predispose to acute aortic dissection (*Table 1*). Aortic aneurysm and dissection seem to share some of the risk factors, at least in adult patients with an ageing aorta (Erbel et al, 2001; Golledge and Eagle, 2008). For example, increasing age and male sex are recognized risk factors for aortic dissection (Hagan et al, 2000; Erbel et al, 2001). Systemic hypertension, however, is the most common risk factor. The International Registry of Acute Aortic Dissection (IRAD) analysed the data of 464 patients who presented with acute aortic dissection to 12 international referral centres over a 2-year period (Hagan et al, 2000). In this study, hypertension was present in over 70% of patients.

Chronic hypertension affects the three layers of the aortic wall resulting in intimal thickening, fibrosis and calcification, medial extracellular matrix degradation, and adventitial fibrosis. These changes result in poor

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oxygen and nutrient supply to the aortic wall, vascular smooth muscle necrosis, and fibrosis of the elastic structures of the arterial wall. The consequent weakness and increased wall stress are common ground for both aneurysmal degeneration and aortic dissection (Erbel et al, 2001; Mukherjee and Eagle, 2005). Smoking and hypercholesterolaemia are additional factors bringing about atherosclerotic changes to the aortic wall seen in hypertensive patients (Mukherjee and Eagle, 2005).

Inherited

Connective tissue disorders have long been recognized as an important group of conditions that predispose the aortic wall to dissection (*Table 1*). Of these, Marfan's syndrome is probably the most studied. Marfan's syndrome is an autosomal dominant disorder with high penetrance that affects both sexes equally and has an estimated incidence of one in 5000 (Callewaert et al, 2008). Cardiovascular pathology is the leading cause of mortality and morbidity in Marfan's syndrome (Callewaert et al, 2008).

The manifestations of Marfan's syndrome are caused by mutations in the FBN-1 gene which encodes for an important extracellular matrix protein, fibrillin-1 (Dietz et al, 1991). This protein forms fibrils in the extracellular matrix, so mutations are thought to rob elastic tissue of a key building material (Travis, 2006). Indeed, fibrillin-1 mutations lead to structural weakening of the extracellular matrix at several sites including the cardiovascular, ocular and skeletal systems with resultant aortic root dilatation, aortic dissection, ocular lens dislocation (ectopia lentis) and bone overgrowth (Callewaert et al, 2008). However, several lines of evidence support an additional role of fibrillin-1 as a regulator of the transforming growth factor-β (TGF-β) family of cytokines (Habashi et al, 2006). Mutant fibrillin-1 protein may therefore lead to increased TGF-β activity and the consequent systemic disorders associated with Marfan's syndrome (Wong et al, 2008). Losartan, an angiotensin-receptor blocker commonly used to treat hypertension, has been shown to prevent aneurysmal growth in a mouse model of Marfan's syndrome as a result of its antagonistic effect on TGF-β (Habashi et al, 2006). A therapeutic benefit from this finding may exist in the future which could have a positive impact on the cardiovascular morbidity and mortality in patients with Marfan's syndrome.

Another connective tissue disorder, Ehlers–Danlos syndrome, is in fact a heterogeneous group of disorders characterized by joint hypermobility, skin hyperextensibility and tissue fragility (Erbel et al, 2001). Ehlers–Danlos syndrome type IV is an autosomal dominant defect in the synthesis of type III collagen which is associated with structural changes in elastic arteries, particularly the aorta, with resultant weakness and increased wall stress. These changes are important in promoting aortic dissection (Golledge and Eagle, 2008). In fact, 40% of Ehlers–Danlos syndrome type IV patients have dissection and arterial rupture by 40 years of age (Golledge and Eagle, 2008).

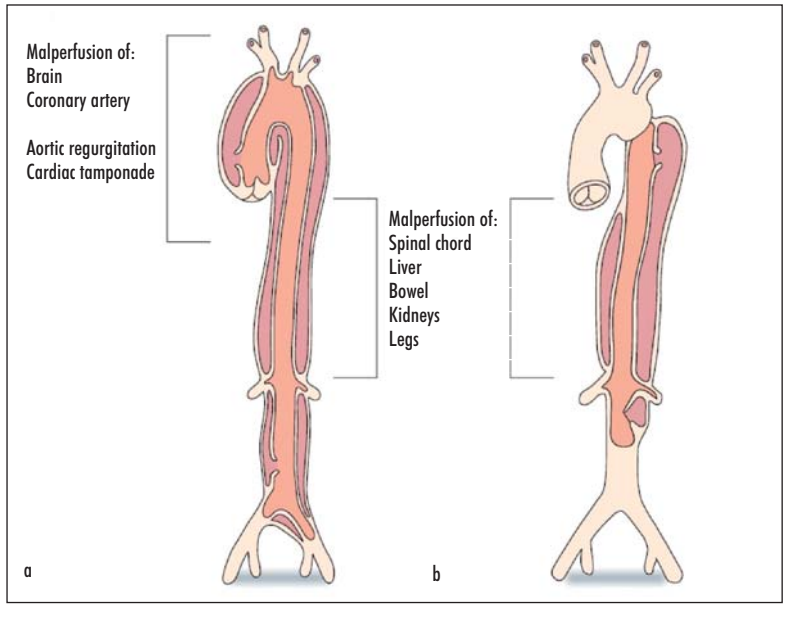
Classification

There are two traditional classification systems for acute aortic dissection: the Stanford classification and the DeBakey classification (*Figure 1*). Both systems are based on the site of the intimal tear and the extent of the dissecting haematoma (*Table 2*). Recent advances in imag-

Table 1. Risk factors for acute aortic dissection

Acquired	Hypertension	
	Atherosclerosis	
	Previous cardiac surgery	
	Previous aortic dissection	
	Thoracic aortic aneurysm	
	Cocaine abuse	
	Blunt chest trauma	
	Iatrogenic, e.g. coronary catheterization	
Inherited	Connective tissue disorders	Marfan's syndrome
		Ehlers–Danlos syndrome type IV
		Familial aortic dissection
		Turner's syndrome
	Cardiovascular disorders	Coarctation of the aorta
		Bicuspid aortic valve
Others	Giant cell arteritis	
	Takayasu's arteritis	
	Behçet's disease	

Figure 1. Classification and complications of acute aortic dissection. a. Stanford type A involves the ascending aorta either alone (DeBakey type II, not shown) or with the descending aorta (DeBakey type I, shown). b. In Stanford type B, the ascending aorta is spared (DeBakey type III). From Golledge and Eagle (2008).



ing technology have led to the identification of pathological changes of the thoracic aortic wall which may be related to dissection (Golledge and Eagle, 2008; Wong et al, 2008). Consequently, the term acute aortic syndrome has been used to encompass classic aortic dissection, aortic intramural haematoma and penetrating atherosclerotic ulcer (Vilacosta and Román, 2001).

An intramural haematoma occurs when blood collects within the aortic media without an intimal tear. The source of the haematoma is presumed to be ruptured vasa vasorum (Wong et al, 2008). The prevalence of intramural haematoma in patients with suspected aortic dissection ranges from 10–30% (Mukherjee and Eagle, 2005). Penetrating atherosclerotic ulcer, on the other hand, is a break in an intimal atherosclerotic plaque which occurs most commonly in the descending thoracic aorta and can lead to an intramural haematoma, or aortic rupture if it progresses to the adventitia (Ahmad et al, 2006). In fact, penetrating atherosclerotic ulcer has the highest rate of aortic rupture when compared to intramural haematoma or classic dissection (Ahmad et al, 2006).

Although many dissections develop without preceding penetrating atherosclerotic ulcer or intramural haematoma, the exact sequence of events associated with acute dissection is still controversial (Golledge and Eagle, 2008). A third classification system by Svensson et al (1999), based on aortic wall pathology, has therefore been introduced (*Table 2*). Because of its simplicity and surgical relevance, the Stanford classification will be used for the rest of this discussion.

Diagnosis

The main challenge in managing patients with acute aortic dissection stretches beyond its high mortality rate; it is a condition that has been traditionally plagued with diagnostic difficulties owing to its varied modes of presentation which usually mimic other disorders. Therefore, clinical suspicion of aortic dissection is crucial to the rapid diagnosis, prompt treatment and potentially improved survival (Hagan et al, 2000).

Table 2. Classification of acute aortic dissection

Stanford	Type A: ascending aorta affected
	Type B: ascending aorta not affected
DeBakey	Type I: entire aorta affected
	Type II: ascending aorta affected
	Type III: descending aorta affected
Svensson	Class 1: classic dissection with an intimal flap between true and false lumen
	Class 2: intramural haematoma or haemorrhage
	Class 3: subtle dissection with an eccentric bulge at intimal tear site
	Class 4: penetrating atherosclerotic ulcer as a result of plaque rupture
	Class 5: iatrogenic or traumatic dissection

Clinical presentation

By definition, acute aortic dissection occurs less than 14 days from the onset of symptoms. The typical patient with acute dissection is a male in his sixties or seventies with a history of hypertension presenting with an abrupt onset of chest pain (Hagan et al, 2000; Erbel et al, 2001). Female patients tend to present later in life and their symptoms are less typical (Nienaber et al, 2004).

Symptoms

Approximately 8% of emergency department visits are the result of chest pain (Golledge and Eagle, 2008). Pain that is sudden, severe, tearing or ripping, with maximum intensity at its onset, is characteristic of acute aortic dissection (Erbel et al, 2001). Patients with type A dissection usually have anterior chest pain while patients with type B dissection usually have posterior interscapular pain. With extension of the dissection, the pain may change its location accordingly; this migratory pain, although typical for aortic dissection, was found in only 16% of patients in the IRAD study (Hagan et al, 2000). Pain may also be absent in 10% of cases (Hagan et al, 2000).

In addition, patients can present with features attributable to aortic branch occlusion such as syncope caused by acute aortic valve regurgitation, acute myocardial infarction or cardiac tamponade, stroke as a result of cerebral ischaemia, paraplegia from spinal cord ischaemia, abdominal pain as a result of acute mesenteric vascular occlusion, and upper or lower limb ischaemic symptoms (Erbel et al, 2001; Mukherjee and Eagle, 2005).

Signs

As mentioned earlier, hypertension is the most common risk factor for aortic dissection (Hagan et al, 2000) and its presence can be established from the history or the examination. Patients with type A dissection, however, can present with hypotension or shock as a result of cardiac tamponade, acute aortic regurgitation, myocardial infarction, spinal shock or aortic rupture (Erbel et al, 2001; Siegal, 2006). Differences in pulse timing and volume (pulse deficits) have been long associated with aortic dissection. This finding was observed in 50% of patients in their seventies with type A dissection (Svensson and Labib, 1994). More recently, however, the IRAD reported pulse deficits in less than 20% of their patients (Hagan et al, 2000). Cardiac auscultation can reveal a diastolic murmur in 40–50% of patients with type A dissection as a result of acute aortic regurgitation (Nienaber and Eagle, 2003a). Finally, features of an underlying connective tissue disorder, such as Marfan's syndrome, should be borne in mind when dealing with younger patients with suspected aortic dissection.

Differential diagnosis

Aortic dissection can masquerade as many cardiac and occasionally non-cardiac conditions. As a result, initial misdiagnosis of dissection occurs in up to 30% of

patients (Mukherjee and Eagle, 2005). Acute coronary syndrome, pulmonary embolism, pericarditis, pneumothorax, pneumonia, non-dissecting thoracic aneurysms, aortic stenosis, and oesophageal spasm or perforation are conditions that may be confused with aortic dissection (Erbel et al, 2001; Mukherjee and Eagle, 2005; Siegal, 2006). All these conditions can present with chest pain; aortic dissection should therefore be suspected in patients with additional findings attributable to dissection such as syncope, stroke, acute heart failure, and acute mesenteric or limb ischaemia (Erbel et al, 2001).

Investigations

Electrocardiogram

An electrocardiogram (ECG) can help distinguish aortic dissection from acute coronary syndrome to avoid giving a patient with dissection antiplatelets, anticoagulants or thrombolytic agents. This is especially important for type A dissection, as the definitive treatment is emergency surgery (Ringstrom and Freedman, 2006). Unfortunately, 20% of patients with type A dissection have ECG evidence of myocardial ischaemia or infarction as a result of extension of the dissection proximally into the coronary arteries, making it impossible to differentiate between the two conditions on the basis of ECG alone (Erbel et al, 2001).

Chest X-ray

The classic chest X-ray signs of acute aortic dissection are a widened mediastinum (>8 cm) and an abnormal aortic contour (Mukherjee and Eagle, 2005; Siegal, 2006). Mediastinal widening was present in approximately 63% of patients with type A dissection and 56% of type B patients in the IRAD study (Hagan et al, 2000). In a more recent study, the sensitivity of chest X-ray for type A dissection was only 47% compared to 77% for type B disease (von Kodolitsch et al, 2004). The authors' view of the poor sensitivity of chest X-ray in acute aortic disease is shared by others (Golledge and Eagle, 2008). With the widespread availability of better imaging techniques, a patient with suspected aortic dissection should immediately undergo a highly sensitive imaging study, as a normal chest X-ray does not rule out aortic dissection.

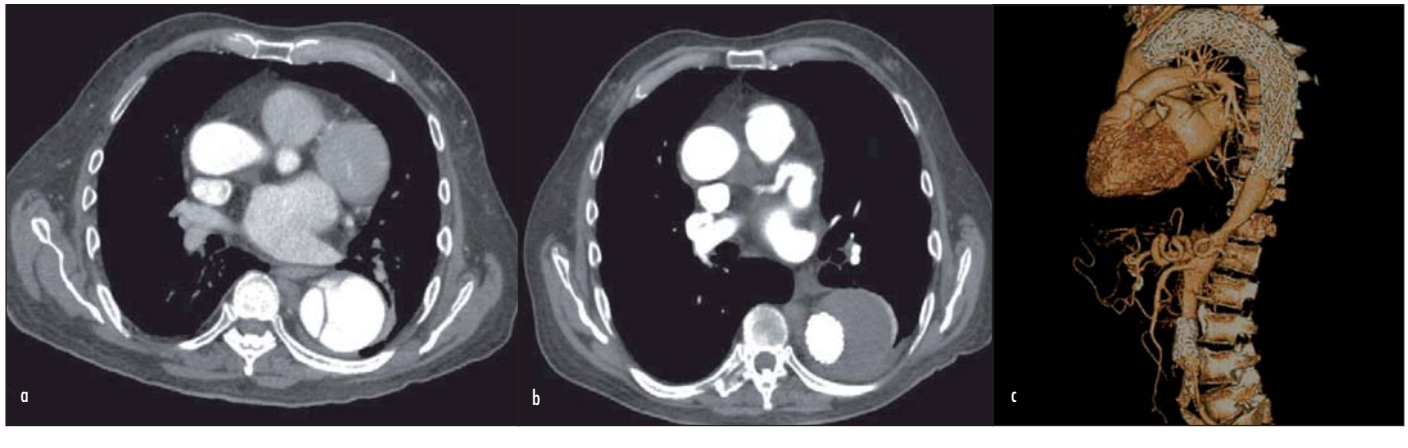
Computed tomography

Computed tomography (CT) scan is currently the most commonly selected imaging modality for diagnosing aortic dissection (Moore et al, 2002). Advances in CT technology, such as multidetector CT, permit scanners to acquire multiple images quickly and simultaneously with a slice thickness of <1 mm and reduced artefacts (Smith and Schoenhagen, 2008). In aortic dissection, visualization of the true lumen separated from the false lumen by the dissection flap confirms the diagnosis (Erbel et al, 2001; Mukherjee and Eagle, 2005) (*Figure 2*). Additional information regarding the extent of the dissection and aortic branch compromise can also be provided by CT (Golledge and Eagle, 2008). The sensitivity of CT in diagnosing both types of aortic dissection was 93% in a report from the IRAD (Moore et al, 2002). Owing to its highly sensitive and specific resolution capabilities, ECG-gated contrast-enhanced multidetector CT allows differentiation between the three causes of acute chest pain with the highest morbidity and mortality: myocardial infarction, pulmonary embolism and acute aortic dissection (Runza et al, 2007). Careful clinical evaluation and strict criteria for patient selection are important to avoid an unjustified risk of radiation equivalent to at least 400 chest X-rays with this imaging procedure (Runza et al, 2007).

Echocardiography

Both transthoracic and transoesophageal echocardiography can be used to diagnose aortic dissection (Nienaber and Eagle, 2003a). They are quick, non-invasive, and can be used in haemodynamically unstable patients by the bedside (transthoracic echocardiography) or in the operating theatre (transoesophageal echocardiography)

Figure 2. Computed tomography (CT) findings from a patient after stent–graft repair of aortic dissection. a. Axial CT image showing a huge false and collapsed true lumen after aortic dissection. b. Axial CT image showing a stent graft within the true lumen and thrombosed false lumen. c. Three-dimensional reconstruction showing many stent grafts, which were placed in this patient to treat an acute aortic dissection (most proximally but also one distally). A residual stenosis is present within the proximal abdominal aorta. From Golledge and Eagle (2008).



(Nienaber and Eagle, 2003a). Echocardiography can be used to diagnose acute aortic regurgitation (Moore et al, 2002); however, transoesophageal echocardiography is better than transthoracic echocardiography in visualizing the descending aorta but does not visualize the abdominal aorta (Wong et al, 2008).

Magnetic resonance imaging

Although magnetic resonance imaging (MRI), with its newer gadolinium-enhanced three-dimensional angiography, provides superb images of the thoracic and abdominal aorta, its use is limited in emergency situations because of lack of availability, in addition to problems caused by patient factors such as haemodynamic instability and metal implants (Mukherjee and Eagle, 2005). MRI is mainly used for follow up of patients who survive the acute attack and develop chronic dissections (>14 days from onset of symptoms) (Golledge and Eagle, 2008). It is therefore clear that the choice of imaging method depends on the patient's presentation, local availability and experienced staff (Golledge and Eagle, 2008).

Biochemical markers

Modelled on myocardial infarction, there has been a growing interest in the diagnosis of acute aortic dissection using one or more biomarkers. Blood levels of smooth muscle myosin heavy chains (Suzuki et al, 2000), D-dimers (Weber et al, 2003) and soluble elastin fragments (Shinohara et al, 2003) have been assessed in patients with aortic dissection. With promising early results, these biomarkers offer the potential for quick, non-invasive and inexpensive diagnosis of a condition that is highly lethal. For example, the sensitivity and specificity of smooth muscle myosin heavy chains were 98% and 83% respectively (Suzuki et al, 2000). This is an area of research that promises the development of at least one clinically useful biomarker in the near future (Apostolakis and Akinosoglou, 2007).

Treatment

There are no randomized trials to guide the treatment of acute aortic dissection. The European Society of Cardiology published the only society-based guidelines for the management of aortic dissection (Erbel et al, 2001). As in all acute medical and surgical emergencies, time is of the essence. Once a patient is suspected of having an acute aortic dissection, immediate admission to an intensive care or similar unit is mandatory while diagnostic procedures are undertaken (Erbel et al, 2001).

Initial management

Initial management of type A and type B dissection involves prompt reduction of the systolic blood pressure to limit the extent of the dissection, avoid expansion of the false lumen and decrease the risk of rupture (Erbel et al, 2001). Parenteral β-blockers (propranolol, esmolol, metoprolol, labetalol) are the most commonly used drugs to achieve this objective. In patients with severe systolic blood pressure elevation, or in resistant cases, vasodilators (e.g. sodium nitroprusside) are used in combination with β-blockers. The European Society of Cardiology recommended that the systolic blood pressure should be titrated to 100–120 mmHg (Erbel et al, 2001). Other groups suggest a more aggressive approach aimed at a mean arterial pressure of 60–80 mmHg (Wong et al, 2008).

Stanford type A dissection

Any patient with a suspected type A dissection should be immediately referred to a cardiac surgeon as the unacceptably high mortality (>50%) associated with non-operative management of these patients, either as a result of frailty or refusal of an operation, makes emergency surgical resection of the ascending aorta, with or without the aortic arch, the treatment of choice in type A dissection (Golledge and Eagle, 2008; Wong et al, 2008). The aim of surgery is to prevent rupture and to relieve the fatal complications associated with the extension of dissection to the aortic valve, the coronary arteries, the pericardium or arch arteries (Wong et al, 2008). Replacement or resuspension of the aortic valve, each with its advantages and disadvantages, depends on the condition of the valve at the time of surgery (Wong et al, 2008).

Stanford type B dissection

Medical treatment is the treatment of choice in uncomplicated type B dissection (Erbel et al, 2001; Wong et al, 2008). The IRAD reported a 30-day survival rate of approximately 90% in patients treated medically (Erbel et al, 2001). An emergency intervention is indicated in the presence of complications such as malperfusion syndrome (organ or limb ischaemia) or aortic rupture as the mortality rate in those cases is consistently >50% (Svensson et al, 2008). Some consider intractable pain, persistent hypertension and dissection of an already aneurysmal aorta as additional indications for intervention (Erbel et al, 2001; Wong et al, 2008).

With the advent of minimally invasive vascular techniques, the currently available options for type B patients who require an emergency intervention have greatly expanded beyond open surgery such that percutaneous interventions have now become the first-line therapy in most patients with malperfusion syndrome (Wong et al, 2008). An example of such interventions is balloon fenestration of the dissection flap to re-establish flow in the true lumen and improve aortic branch perfusion. Thoracic aortic endovascular stent–graft placement can be concomitantly used with fenestration, or to treat impending or actual aortic rupture. The stent–graft seals the intimal tear thus inducing thrombosis of the false lumen and re-expands the true lumen (Wong et al, 2008). Examples of open surgical operations include femoro-femoral bypass, replacement of the dissected aorta with a prosthetic graft, and open fenestration. These techniques are mainly used if endovascular techniques fail (Wong et al, 2008) or are unavailable.

Long-term outcome

Aortic rupture of the weakened dilated false lumen, recurrent dissection, and refractory hypertension are the main concerns during long-term follow up (Golledge and Eagle, 2008). Approximately one third of patients surviving initial treatment for acute dissection will experience either dissection extension or aortic rupture, or will require surgery for aortic aneurysm formation within 5 years of presentation. Furthermore, this risk is substantial in the first few months after initial therapy. (Nienaber and Eagle, 2003b). Therefore, the mainstay of long-term management of patients who survive acute aortic dissection is blood pressure control using β-blockers to reduce the blood pressure to <130/80 mmHg (Golledge and Eagle, 2008), and surveillance of the aorta using CT or MRI scans at 1, 3, 6, and 12 months, then annually thereafter (Erbel et al, 2001).

An important point to remember is that in acute dissection survivors the entire aorta and potentially its branches are susceptible to dissection, aneurysm and rupture, making thorough long-term follow up a necessity (Nienaber and Eagle, 2003b).

Conclusions

Acute aortic dissection remains a challenging cardiovascular disorder with high mortality and morbidity rates. A high level of suspicion in the appropriate clinical setting is the basis of rapid diagnosis and institution of suitable treatment. It is likely that better understanding of the pathophysiological mechanisms underlying aortic dissection will lead to the identification of a biochemical marker analogous to myocardial infarction. At the molecular level, targeted drug therapy may alter the effects of connective tissue disorders, such as Marfan's syndrome, on the aortic wall. Finally, continued advances in imaging technology and endovascular surgical techniques provide hope for better management of aortic dissection in years to come. **BJHM**

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KEY POINTS

- Acute aortic dissection is associated with high mortality and morbidity rates.
- Medical treatment is the treatment of choice in type A dissection.
- Emergency surgical treatment is the treatment of choice in type B dissection.
- Research aimed at developing novel biochemical markers for early detection of acute aortic dissection is ongoing.