



Current imaging techniques and potential biomarkers in the diagnosis of acute aortic dissection

Dave R Listijono¹ • John R Pepper²

¹Liverpool Hospital, Sydney, New South Wales 2052, Australia

²Royal Brompton and Harefield NHS Foundation Trust, London, SW3 6NP, UK

Correspondence to: Dave Listijono. Email: dave.listijono@gmail.com

DECLARATIONS

Competing interest

None declared

Funding

None

Ethical approval

None

Guarantor

DRL

Contributorship

DRL performed the literature review, planned and drafted the paper. JRP initiated, designed and edited the paper. DRL and JRP both revised the final paper

Acknowledgements

The authors would like to thank Manju Shah for her assistance

Summary

Acute dissection of the thoracic aorta (AAD) is a potentially catastrophic disease, with significant morbidity and mortality, which remain unchanged over the last decade. Survival rate has been shown to be directly related to prompt diagnosis and precise management; however diagnosis of the disease remains time-consuming, not readily available, and lacking in sensitivity and specificity. The current approach when diagnosing AAD relies heavily on various imaging techniques, including chest radiograph, echocardiography, computed tomography and magnetic resonance imaging scans. Nevertheless, the door remains open for the incorporation of biochemical tests to aid in detecting AAD. This article will review the imaging modalities currently employed in the management of AAD, as well as a discussion of the potential role of several biomarkers in AAD. To date, imaging is the diagnostic tool for AAD however, technical and logistical limitations limit the use of imaging in various circumstances. Current available biomarkers such as D-dimer and C-reactive protein are under-utilized in many cases, mainly due to their non-specificity in diagnosing AAD. Over the last decade, many biomarkers have been proposed for use in AAD, with several showing promising results – including: smooth muscle myosin heavy chain, calponin, soluble elastin fragments and transforming growth factor β . Extensive research is being undertaken to define the roles of these novel biomarkers in the management of AAD.

Introduction

Acute dissection of the thoracic aorta (AAD) is a potentially catastrophic cardiovascular disease. Despite advances in medical, surgical and endovascular management of AAD, the morbidity and mortality remain significant, with recent studies reporting early mortality rates of 18–25%, which have remained unchanged over the last decade.^{1,2} Survival rate has been shown to be heavily dependent on undelayed diagnosis and prompt management, potentially allowing

a 30-day survival rate of more than 90%.³ However, current diagnostic algorithms, which usually involve having a degree of clinical suspicion from the presenting symptoms and clinical findings, and subsequently employing various imaging techniques such as chest radiograph, echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI), are often time-consuming, not readily available at bedside or emergency room, and lack sensitivity and specificity.^{3–5} Thus the door is open for an approach to management of AAD that allows

a more rapid and accurate diagnosis. Research has been made into identifying suitable biomarkers to allow their incorporation into the management algorithm of AAD. This article will review the imaging modalities currently employed in the management of AAD, as well as a discussion of the potential role of several biomarkers in AAD.

Methods

The main source of materials evaluated in this review article was electronic journal articles. A vast review of the literature was initially undertaken, where we performed a Medline search using the following keywords: 'acute aortic dissection', 'biomarkers', 'imaging'. Relevant articles were selected based on appropriateness of their contents related to the topic, publication date and, where able, journal reputation.

Pathogenesis

Aside from traumatic causes, the main pathological process of AAD involves degeneration of the tunica media layer of the aortic wall, leading to diminished compliance and subsequent increased rigidity, eventually placing the aorta at a significant risk of shear stress when there is a sudden surge in pressure. The most common histological finding in the aorta of patients with acute dissection is cystic medial necrosis. Chronic aneurysm and dissection of the aorta is also closely related to a number of connective tissue diseases, including Marfan syndrome (MS) and the less common Loey-Dietz syndrome. The pathophysiology underlying the formation of aortic aneurysm, and subsequent aortic rupture, in these conditions is known to involve an over-abundance of transforming growth factor β (TGF- β), which has led to recent research involving TGF- β 1 as a potential biomarker and also a therapeutic target in both MS and non-MS patients with AD.^{6,7} These will be discussed in subsequent sections.

Imaging

Chest radiograph

The initial imaging performed is usually a chest radiograph. Previous studies have reported that

widening of the mediastinum and the aortic knuckle on chest X-rays are associated with 39–90% of dissections.⁸ However, additional images were obtained in up to 98% of patients in the International Registry of Acute Aortic Dissection (IRAD) study due to the limited sensitivity of the chest radiograph, especially in type B dissections.^{1,9,10}

Echocardiography

Transthoracic echocardiography (TTE) has limited diagnostic utility in AAD due to its inability to adequately visualize the distal ascending, transverse and descending aorta, such that although approximately 50% of type A dissections can be identified by TTE, it carries a high false-negative rate. Its use is mainly confined as a screening investigation providing information on ventricular and valvular functions, and presence of pericardial effusion. Transoesophageal echocardiography has become the investigation of choice because of its improved sensitivity, ability to detect tear sites and blood flow in the false lumen, and portability for use in the Emergency Department. Biplane and multiplane TEE may allow visualizations of portions of the aorta previously limiting TTE, in addition to its high sensitivity and specificity.¹¹ However, its use may be limited by the need for sedation and oesophageal intubation, along with operator expertise and experience to ascertain accurate results. Thus, an alternative rapid diagnostic test is necessary.

Computed tomography

A standard CT study with contrast, with the addition of the improved multislice technology, allows for a highly sensitive and specific imaging option,¹² and can provide a definitive diagnosis of dissection. It accurately demonstrates the extent of periaortic haematoma, and is effective in identifying a dilated aorta, true and false lumens and an intimal flap. Its widespread round-the-clock availability has resulted in most patients having this investigation done before referral to a cardiothoracic centre.¹³ However, the disadvantages of CT imaging include its inability to diagnose aortic regurgitation and adequately assess the relationship of the dissection to major

aortic branches. In addition, other potential limitations to CT imaging include: the need for potentially nephrotoxic contrast and the importance of having an experienced radiologist to ensure appropriate electrocardiogram gating and image interpretation.

Magnetic resonance imaging

MRI has a high sensitivity and specificity in diagnosing AAD, with the ability to diagnose aortic regurgitation.¹⁴ It is a valuable tool for long-term follow-up of patients, useful in accurately assessing changes over time in the size and contour of the dissected aorta. However, its use in the acute settings is limited by the absolute contraindication of ferro-magnetic object presence and a prolonged study duration, both of which are rarely avoidable or practical in the management of unstable patients.

Biomarkers

The potential for biomarkers to be incorporated in the diagnosis algorithm of AAD has been extensively researched, especially given the need for a convenient, reliable and accurate test to aid in rapid diagnosis of AAD.

D-Dimer

D-Dimer (DD) is currently the most widely available and reliable biomarker used in AAD.¹⁵ DD is a degradation product of fibrin cross-linking. In the setting of AAD, aortic injury results in release of tissue factor into the circulation, with subsequent activation of the extrinsic pathway of the coagulation cascade leading to fibrin formation. Fibrinolytic pathway is then activated, resulting in degradation of cross-linked fibrin. The IRAD substudy on biomarkers (IRAD-Bio)¹⁶ found that, at a cut-off value of 500 ng/mL within 24 h of symptom onset, DD has a sensitivity and specificity of 96.6% and 46.6% versus controls, along with a negative predictive value of 95%. Of particular note, the 'controls' used in the IRAD-Bio study were patients with suspicion of AD. Its poor specificity may be due to its elevated levels in other conditions such as: pulmonary embolism (PE), deep vein thrombosis, trauma,

recent surgery and so on. The IRAD-Bio study showed a significantly elevated (5- to 10-fold greater) DD levels in AD patients compared with other diagnoses, including PE, in the first six hours; however, this finding may be considered anecdotal given the small number of PE patients ($n = 2$). As yet, DD levels cannot differentiate between AD and PE; however, a highly elevated level of DD may prompt an urgent contrast-enhanced CT, allowing confirmation or exclusion of both AD and PE.¹⁷ Studies have also shown correlation between lower levels of DD and thrombosis of false lumen.^{16,18} This is important because of the potential adverse outcome of a dissection with partially thrombosed, compared with a patent, false lumen.¹⁹ In addition to its high sensitivity, the measurement of DD technically requires only 10 min with a rapid enzyme-linked immunosorbent assay; DD may thus be a useful rule-out tool and, at higher levels in patients presenting within six hours of symptoms onset, may be used to rule in AD. However, the latter needs to be further substantiated with larger studies involving appropriate control subjects.

Smooth muscle myosin heavy chain

Smooth muscle myosin heavy chain (sm-MHC) is a major component of smooth muscle, which is released into circulation upon damage of smooth muscle cells, as in the case in aortic dissection where the damage occurs to the aortic medial smooth muscle. It is also present in uterine and intestinal smooth muscle, and thus may be elevated in conditions involving these systems.²⁰ Suzuki *et al.* has developed a rapid 30-min assay for sm-MHC which is, as yet, unavailable for clinical use. Preliminary clinical testing has demonstrated sensitivity and specificity of 90% and 97% respectively, with a diagnostic accuracy of 96%, at a cut-off value of 2.5 $\mu\text{g/L}$, if performed within the first three hours of symptom onset.²¹ These values significantly decline with time, with sensitivities of 72.4% and 30.3% at six and nine hours respectively, potentially limiting its use only on patients with early presentation. This assay may be a useful tool for differentiating between AAD and acute myocardial infarction (AMI), with the former displaying significantly

higher levels of circulating sm-MHC, with a specificity of 83%.²¹ In addition, levels of sm-MHC exceeding 10 µg/L showed 100% specificity for AD. Furthermore, differing values of this assay may allow differentiation between proximal and distal aortic lesion. Patients with DeBakey I or II lesions were more likely to show assay levels exceeding the clinical limit of 2.5 µg/L, compared with DeBakey III lesions, possibly reflecting the lower smooth muscle content of the abdominal aorta, compared with thoracic aorta. Thus, given its relatively fast testing time, high sensitivity and specificity, and known time-course of release, the sm-MHC assay is a promising tool to aid in the rapid diagnosis of AAD, especially in the early phase of presentation.

Calponin

Calponin is essentially a 'cardiac troponin' counterpart to vascular smooth and non-muscle cells.²² It is a type of calcium-binding protein responsible for the regulation of the calcium-calmodulin-dependent phosphorylation of myosin.²³ There are three isoforms of calponin: acidic, basic (also known as 'h1') and neutral ('h2'). Basic calponin is the most abundant and specific to smooth muscle, compared with its two other counterparts. A recent multicentre international study has developed assays for all three isoforms of calponin and assessed its diagnostic value as a biomarker in acute AD.²² The study found a profound lack of correlation between neutral calponin and aortic dissection, and the assay was not subsequently pursued. Acidic calponin displayed a higher than two-fold increase in levels for all dissection types, more so for type A (4.70 ng/mL, *n* = 12; normal reference: 2.04 ng/mL) patients, compared with type B (2.84 ng/mL), presenting within six hours of symptom onset. This pattern was maintained for type A (5.08 ng/mL) patients for the next 6–12 h time range; however, it was not the case with type B (2.43 ng/mL) patients, whose levels were no longer significantly elevated in that time range. Basic calponin levels were increased three folds (377.56 ng/mL, *n* = 16; normal reference: 123.31 ng/mL) for all dissections presenting within six hours of symptom onset, similar for both type A and B dissections. This pattern was maintained in the 6–12 h

window for type A (348.79 ng/mL, *n* = 16) patients but not for type B (171.96 ng/mL, *n* = 2). Compared with acidic calponin, the marked increase in basic calponin levels was expected, given it is the most specific and abundant isoform in smooth muscle. For both acidic and basic calponin assays, none of the patients without AD show elevations at any time points. Notably, all patients enrolled in the study were under clinical suspicion of AAD aortic dissection, thus imitating real-world situations to a reasonable degree. Importantly, this study demonstrated the diagnostic value of calponin (basic isoform, especially) in detecting aortic dissection with delayed presentation (up to 12 h postsymptom onset), which is one of the shortcomings of the previously mentioned biomarker sm-MHC, whose accuracy was limited to patients presenting early (within 6h of onset).

C-reactive protein

The acute phase reactant C-reactive protein (CRP) is a sensitive and non-specific marker of inflammation produced in the liver in response to stimulation by various cytokines. It has been previously studied as a prognostic biomarker in AAD, with research suggesting CRP levels above 6.3 mg/dL associated with significantly increased short-term mortality rate.²⁴ Elevated plasma concentration of CRP has also been implicated with complications of AAD such as impaired oxygenation, pleural effusion, and increased risk of in-hospital death.^{17,25,26} Despite its potential utility to measure prognosis, the use of CRP in settings of AAD have been hampered by its temporal release profile, where patients with early presentation rarely displayed elevation, compared with late presenters.²⁴ CRP levels have also been shown to be elevated in chronic aneurysm and aneurysm formation,²⁷ which may preclude its use in patients with those pre-existing conditions presenting with acute dissection.

Soluble elastin fragments

Elastin is a major component of the aortic wall, arranged in a framework of laminae interconnected with interlaminae fibres. In AD, external insult on the endothelium of the aorta and subsequent damage to the medial layer disrupts

this arrangement, triggering inflammation and activation of proteolytic enzymes, ultimately resulting in the release of soluble elastin fragments (sELAF) into the circulation.²⁸ Shinohara *et al.*²⁸ found that AD patients, with a patent or partially patent false lumen, who presented within 48 hours of symptom onset, displayed elevated levels of serum sELAF. Increasing levels of serum sELAF were also associated with advancing age in healthy controls. With a cut-off point set at +3 SD above the mean for each age group in the control subjects, 64% of AD patients displayed positivity to the assay, with a specificity of 99.8%. In addition, the positive and negative predictive values were 94.1% and 98.1% respectively. The study also suggested the potential for sELAF in differentiating between AAD and AMI, with the former being associated with significantly higher levels (114.7 ± 56.9 versus 56.1 ± 14.9 ng/mL). However, the sELAF assay did not show any positivity for AD patients with a thrombosed false lumen and, with the addition of a three-hour-long measurement time, thus its role in the rapid diagnosis of AD may be questionable, at least until new methods are developed to shorten its assay processing time.

Transforming growth factor β

TGF- β is a signalling molecule bound to an extracellular matrix protein fibrillin-1.²⁹ Studies conducted in rodent models have shown that instances where deficiency of fibrillin-1 exists in the extracellular matrix, for example in patients with MS, lead to an over-signalling of TGF- β , resulting in vascular-related sequelae, such as aortic re-modelling.³⁰ Recent studies have discovered that angiotensin II-receptor blockers, such as Losartan, reduce the aberrant signalling of TGF- β in patients with MS, resulting in significantly reduced rate of aortic dilation.^{6,29} Subsequently, a small preliminary study involving non-MS patients presenting with AAD have also shown significant elevation in TGF- β levels, compared with normal controls, with type A patients (28.5 ± 14.7 ng/mL, $n = 20$) displaying two-fold elevations compared with Type B patients (14.4 ± 6.1 ng/mL, $n = 8$).⁷ These findings suggest the potential of TGF- β as a biomarker in the settings of AAD in non-MS adult patients.

Conclusion

The potentially catastrophic nature of acute aortic dissection calls for a rapid and accurate diagnostic approach. The rapid progress in development of biomarkers in the last decade, for sole or combined use with imaging techniques, may soon allow them to be incorporated into the diagnostic algorithm and therefore offer clinicians an additional effective tool as an approach to patients with suspected acute aortic dissection.

References

- Hagan PG, Nienaber CA, Isselbacher EM, *et al.* The International Registry of Acute Aortic Dissection (IRAD). *JAMA* 2000;**283**:897–903
- Narayan P, Rogers CA, Davies I, Angelini GD, Bryan AJ. Type A aortic dissection: has surgical outcome improved with time? *J Thorac Cardiovasc Surg* 2008;**136**:1172–7
- Nienaber CA, von Kodolitsch Y, Petersen B, *et al.* Intramural hemorrhage of the thoracic aorta: diagnostic and therapeutic implications. *Circulation* 1995;**92**:1465–72
- Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. *N Engl J Med* 1997;**336**:1876–88
- Nienaber CA, von Kodolitsch Y, Nicolas V, *et al.* The diagnosis of thoracic aortic dissections by noninvasive imaging procedures. *N Engl J Med* 1993;**328**:1–9
- Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008;**358**:2787–95
- Suzuki T, Trimarchi S, Sawaki D, *et al.* Circulating transforming growth factor-beta levels in acute aortic dissection. *J Am Coll Cardiol* 2011;**58**:775
- Spittell PC, Spittell JAJ, Joyce JW, *et al.* Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990). *Mayo Clin Proc* 1993;**68**:642–51
- Suzuki T, Mehta RH, Ince H, *et al.* Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). *Circulation* 2003;**108**(Supp 1):II312–7
- von Kodolitsch Y, Nienaber CA, Dieckmann C, *et al.* Chest radiography for the diagnosis of acute aortic syndrome. *Am J Med* 2004;**116**:73–7
- Pepi M, Campodonico J, Galli C, *et al.* Rapid diagnosis and management of thoracic aortic dissection and intramural haematoma: a prospective study of advantages of multiplane vs. biplane transoesophageal echocardiography. *Eur J Echocardiography* 2000;**1**:72–9
- Sommer T, Fehske W, Holzknicht N, *et al.* Aortic dissection: a comparative study of diagnosis with spiral CT, multiplanar transoesophageal echocardiography, and MR imaging. *Radiology* 1996;**199**:347–52
- Prendergast BD, Boon NA, Buckenham T. Aortic dissection: advances in imaging and endoluminal repair. *Cardiovasc Intervent Radiol* 2002;**25**:85–97
- Erbel R, Alfonso F, Boileau C, *et al.* Diagnosis and management of aortic dissection: recommendations of the

- Task Force on Aortic Dissection, European Society of Cardiology. *Eur Heart J* 2001;**22**:1642–81
- 15 Suzuki T, Distanto A, Eagle K. Biomarker-assisted diagnosis of acute aortic dissection: how far we have come and what to expect. *Curr Opin Cardiol* 2010;**25**:541–5
 - 16 Suzuki T, Distanto A, Zizza A, *et al.* Diagnosis of acute aortic dissection by D-Dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. *Circulation* 2009;**119**:2702–7
 - 17 Eggebrecht H, Naber CK, Bruch C, *et al.* Value of plasma fibrin D-Dimers for detection of acute aortic dissection. *JACC* 2004;**44**:804–9
 - 18 Hazui H, Fukumoto H, Negoro N, *et al.* Simple and useful test in discriminating between acute aortic dissection of the ascending aorta and acute myocardial infarction in the emergency setting. *Circulation* 2005;**69**:677–82
 - 19 Tsai TT, Evangelista A, Nienaber CA, *et al.* Partial thrombosis of false lumen in patients with acute type b aortic dissection. *N Engl J Med* 2007;**357**:349–59
 - 20 Katoh H, Suzuki T, Yokomori K, *et al.* A novel immunoassay of smooth muscle myosin heavy chain in serum. *J Immunol Methods* 1995;**185**:57–63
 - 21 Suzuki T, Katoh H, Tsuchio Y, *et al.* Diagnostic implications of elevated levels of smooth-muscle myosin heavy-chain protein in acute aortic dissection. *Ann Intern Med* 2000;**133**:537–41
 - 22 Suzuki T, Distanto A, Zizza A, *et al.* Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection. *Eur Heart J* 2008;**29**:1439–45
 - 23 Winder SJ, Allen BG, Clement-Chomienne O, Walsh MP. Regulation of smooth muscle actin-myosin interaction and force by calponin. *Acta Physiol Scand* 1998;**164**:415–26
 - 24 Schillinger M, Domanovits H, Bayegan K, *et al.* C-reactive protein and mortality in patients with acute aortic disease. *Intensive Care Med* 2002;**28**:740–5
 - 25 Hata N, Tanaka K, Imaizumi T, *et al.* Clinical significance of pleural effusion in acute aortic dissection. *Chest* 2002;**121**:825–30
 - 26 Sugano Y, Anzai T, Yoshikawa T, *et al.* Serum c-reactive protein elevation predicts poor clinical outcome in patients with distal type acute aortic dissection: associate with the occurrence of oxygenation impairment. *Int J Cardiol* 2005;**102**:39–45
 - 27 Vainas T, Lubbers T, Stassen FRM, *et al.* Serum c-reactive protein level is associated abdominal aortic aneurysm size and may be produced by aneurysmal tissue. *Circulation* 2003;**107**:1103–5
 - 28 Shinohara T, Suzuki K, Okada M, *et al.* Soluble elastin fragments in serum are elevated in acute aortic dissection. *Arterioscler Thromb Vasc Biol* 2003;**23**:1839–44
 - 29 Matt P, Schoenhoff F, Habashi JP, *et al.* Circulating transforming growth factor- β in Marfan Syndrome. *Circulation* 2009;**120**:526–32
 - 30 Gelb BD. Marfan's syndrome and related disorders - more tightly connected than we thought. *N Engl J Med* 2006;**355**:841–4

© 2012 Royal Society of Medicine Press

This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by-nc/2.0/>), which permits non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.