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Diagnostic Testing in Acute Aortic Dissection

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Abstract Acute aortic dissection (AAD) is the most common catastrophe to involve the aorta, resulting in high morbidity and mortality. Delayed diagnosis can adversely affect patient outcome, therefore a high clinical index of suspicion is the first step. Absence of the classical signs such as pulse defecit and chest radiograph changes should not falsely reassure clinicians. Availability of a biomarker to expedite and improve diagnosis of AAD would greatly benefit emergency department clinicians. Some promising novel biomarkers include calponin and elastin, but their use in everyday practice is still some time away. Bedside imaging including transthoracic and transesophageal echo is being increasingly used in the unstable patient suspected of AAD, while computed tomography (CT) appears to be the most accurate rapid imaging modality for its diagnosis. Expeditious diagnosis is crucial to improve patient survival allowing for better outomes.

Keywords Acute aortic dissection · Biomarkers · Imaging · TEE · MRI

Introduction

Acute aortic dissection (AAD) as a clinical emergency was first described by Morgagni more than 200 years ago [1]. The early detection of AAD is paramount given its significant morbidity and mortality. Recent studies have reported early mortality rates in the region of 18–25 % with little change over the past decade despite increasing technology [2]. Calculating the true incidence of AAD is difficult due to the number of aortic catastrophies that result in sudden death and go undiagnosed. A large Swedish population-based study (1982–2002) has placed the incidence over a 16-year period at 3.4 cases per 100,000 per year [3]. Early diagnosis and instigation of treatment is hampered by delayed or misdiagnosis in up to 40 % of cases. This may be due to the lack of specificity and sensitivity of symptoms, signs, EKG and chest radiographs [4]. For Type A dissection, the untreated mortality is currently 1–2 %/h with a 30-day mortality rate for the majority of patients approaching 100 % [2]. Current evidence purports that diagnostic evaluation of patients further delays the definitive diagnosis by a number of hours, thereby increasing mortality [5].

This article aims to review the current evidence regarding the diagnosis of AAD in order to improve our management of this important condition.

History and Clinical Diagnosis

Although often presenting with the classical tearing chest pain radiating through to the back, AAD can present in any number of guises making it a challenging clinical diagnosis. Other symptoms and signs are often secondary to vascular compromise including pulse deficits, renal impairment and neurological signs, which can often mimic acute stroke. Less common symptoms include syncope, acute congestive heart failure and evidence of myocardial ischemia [2]. Risk factors for AAD must be taken into

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account on initial presentation and heighten clinical suspicion if present.

The most commonly associated factors are hypertension, atherosclerosis and previous cardiovascular surgery. Howard et al., in a population-based study of aortic dissection, reported 67.3 % of their study population having a known history of hypertension [6••]. AAD is more frequent in the 60th decade of life with a mean age of 63 at the time of diagnosis [2]. Men are more commonly affected, accounting for 2/3 of patients in the IRAD cohort (International Registry of Acute Aortic Dissection). Marfan's disease results in approximately 5 % of all cases of aortic dissection, with a small number of other collagen vascular diseases (including Ehler–Danlos syndrome) causing an even smaller percentage of aortic dissections. Bicuspid aortic disease also carries a high lifetime risk of AAD with 1 in 20 patients with a bicuspid aortic valve developing AAD [7]. Cocaine has been recognized as a cause of AAD with the proposed mechanism mediated through profound catecholamine-induced elevation of the BP resulting in intimal tear [8].

Abrupt onset pain still remains the most common presenting clinical symptom. Hagan et al. conducted a case series from 1996–1998 in which patients with AAD at presentation were enrolled from 12 international centers. Of the 464 patients enrolled in this study, 84.8 % of patients reported abrupt onset pain. The majority of patients complained of chest pain (72.7 %). Anterior chest pain was typical in patients with type A dissection, whereas patients with type B dissection more often experienced pain in the back and abdomen, although there was substantial overlap ($P < 0.001$) [2].

A recent study by Lovy et al. sought clinical and diagnostic criteria to identify low-risk patients as an initial step in developing a clinical decision rule in Acute Aortic Syndome (AAS). AAS included aortic dissection, rupture, intramural hematoma, and penetrating atherosclerotic ulcer. They retrospectively reviewed their institutional database for all adults initially presenting from January 1, 2006, to August 1, 2010, who underwent a CT scan for suspected AAS and who did not have a history of trauma, AAS, or aortic surgery. A total of 1,465 patients were included.

Chest pain, acute onset of pain, radiation to the back, and severe pain were all significant positive predictors of AAS. Acute chest pain had a sensitivity of 82.9 % with CI 66.4–94.4 %, a specificity of 70.7 %, a positive predictive value (PPV) of 0.07 % and a negative predictive value (NPV) of 99 % [9••]. A review paper by Golledge et al. demonstrated similar results with 85 % of the patients included presenting with chest or back pain [10].

Pulse deficits and the murmur of aortic regurgitation are clinical signs which are classically associated with AAD. Pulse deficit was reported in 44 % of the review patients [10]. Chua et al. conducted a retrospective chart review of 68 patients with AAD, highlighting that 63.8 % did not display a pulse deficit on clinical examination. This study also showed that emergency physicians are more likely to miss the diagnosis of AAD when pulse deficit was not detected on examination (OR 35.76; 95 % CI 3.70–345.34) [11•]. From IRAD aortic regurgitation and pulse deficit were noted in only 31.6 % and 15.1 % of patients, respectively [2]

Hypertension is a common presenting finding however inter-arm blood pressure differences are not commonly recorded. IRAD reported 49 % of patients were hypertensive at presentation with hypertension at initial presentation being more common among patients with type B dissection (70.1 vs 35.7 %, $P < 0.001$) [2].

Neurological deficit is widely reported with some cases presenting with acute neurological findings in the absence of pain [12, 13]. IRAD reports overall figures of 4.7 % of patients with an acute neurological deficit at presentation [2] with similar studies reporting figures of 12 % [10].

In isolation, chest pain and indeed the nature of the pain may not be useful in aiding clinical diagnosis, but, in correlation, other clinical findings, patient risk factors such as known hypertension or the presence of conditions such as Marfans' syndrome and X-ray findings may aid diagnosis. Attempts have been made to formulate pathways to identify high-risk patients that require imaging. The American Heart Association have published guidelines which identify high-risk clinical features to expedite a diagnosis [14•]. This grouped risk factors (e.g. Marfan syndrome) with clinical features (tearing chest pain) and signs (pulse deficit) to risk stratify patients to immediate imaging. This guideline has since been applied to the IRAD database and is highly sensitive. However, this study did not allow for any testing of the specificity of the study. Widespread implementation of such a guideline may result in over-investigation of patients [15••].

As AAD has many mimics and up to 10 % of patients may be pain free at presentation, a high clinical index of suspicion must be kept. The presence of signs such as pulse deficits, neurological symptoms and interim BP difference all raise the clinical suspicion of AAD; however, their absence does not exclude the diagnosis as evidenced by the relevant figures above.

Investigations

A high index of clinical suspicion currently remains key to the diagnosis of AAD. There is no point of care biochemical test available at present to accurately diagnose aortic dissection. Some novel biomarkers are currently

showing promise but are unlikely to impact on improving the time to diagnosis.

Current Biomarkers

C Reactive Protein (CRP)

This is an acute phase protein which rises in response to inflammatory processes. Schillinger et al. found that CRP (and white cell count) were higher in those patients presenting with chest pain and subsequently diagnosed with AAD. However, due to its poor specificity, the rise was not found to be sufficient to alter diagnostic pathways [16].

D-Dimer

The likely usefulness of this fibrin degradation product is in its "rule out" and risk stratification ability. When the dissection involves a coronary ostium and results in myocardial infarction (MI), elevated troponin and characteristic EKG changes may force the ED physician into treatment of an MI with anticoagulation therapy which would be disastrous for an AAD. The elevation of D-dimers coupled with an elevation in troponin should force the physician to rethink the diagnosis. This is because an analysis of more than 700 patients with MI showed no correlation between raised D-dimers and MI [17].

The sensitivity of this biomarker has frequently been reported as approaching 100 % with a NPV of >97 % [18]. A recent meta-analysis of 349 cases provided a pooled sensitivity result of 94 % [19]. False negatives were most likely in patients under 70, dissections which are shorter in length, and those with a thrombosed false lumen [20].

Despite its limitations, the use of D-dimer testing is recommended by the task force of European Society of Cardiology in the initial workup of those patients suspected of AAD [4]. A new point of care rapid latex agglutination test of whole blood providing a result within 10 min was shown to correlate well with laboratory testing [21]. This could have practical applications for usage within the ED as a screening tool when combined with an appropriate clinical presentation. Such a strategy will require research and validation before it is adopted given the likely utilization of resources.

Potential New Biomarkers

Smooth Muscle Myosin Heavy Chain (smMHC)

Research as early as 1995 by Katoh et al. suggested the use of this biomarker as a diagnostic tool for AAD [22, 23]. Levels rose rapidly within the first 24 h and ,when a cutoff value of 2.5 ng/l was used, the specificity was 90 % at 12 h and 85 % at 24 h. Those below the cutoff value who were subsequently diagnosed with AAD had DeBakey type B aortic dissection. At the 2.5-ng/ml cutoff, the biomarker had a specificity of 83 %, but at 10 ng/ml the specificity rose to 100 %. Interestingly, acute MI was found not to cause a rise in smMHC [24]. It must be noted that smMHC is present in uterine and intestinal smooth muscle. Theoretically, it could therefore be raised in conditions affecting these organs.

Calponin

Of the three isoforms (acidic, basic and neutral), two have shown some potential. During the first 6 h after AAD acidic calponin, at a value of 2.3 ng/ml, demonstrated a sensitivity of 50 % and specificity of 87 %, while the basic isoform provided sensitivity of 63 % and specificity of 73 % when using a cutoff value of 159 ng/ml. The PPV were 0.56 and 0.44 for acidic and basic calponin, respectively, at 6 h. The NPV of 0.84 (acidic) and 0.86 (basic) were of more clinical significance [25]. A drawback of the acidic isoform is its presence in neurological tissue, which therefore limits its accuracy for diagnosis in those with neurological signs.

Elastin (sELAF)

This biomarker measures the degradation product of elastin, one of the arterial wall's main structural components. The study used a cutoff level of 3 standard deviations above mean at all ages and resulted in a specificity of 99.8 %. However, this figure fell to 88.9 % for those with a patent or partially thrombosed false lumen. Of significance, sELAF was negative in those with a completely thrombosed false lumen. This was one of the marker's greatest limitations. A clear benefit above calponin and smMHC was that sELAF remained raised for up to 72 h post-dissection [26].

Novel biomarkers are unlikely to be available to EDs in the near future, and thus are unlikely to impact significantly on early diagnosis of AAD. Of those biochemical markers readily available, D-dimer would appear to be of sufficient specificity to prompt further diagnostic evaluation and imaging to facilitate expeditious diagnosis and treatment [27].

EKG

The EKG is often the first piece of diagnostic information obtained on patients with potential AAD. In IRAD, the EKG was reported as normal in 31 % of its 464 patients. Nonspecific ST and T wave changes were demonstrated in 42 % with evidence of ST elevation in 5 % of cases [2]. A

retrospective study of 233 cases further confirms these findings. It demonstrated acute ST elevation in 4 % of cases. ST segment depression or T wave inversion were seen in 47 % of cases [28], while 30 % of EKGs had no significant finding. The main pitfall of misdiagnosing AAD as ACS include the instigation of potentially harmful interventions such as anticoagulation, antiplatelet therapy and emergency catheter intervention. The mortality can climb to over 70 % from administration of thrombolytic agents, manifested mainly by hemorrhage into the pericardial sac resulting in cardiac tamponade [29].

The underlying cause of EKG abnormalities involves hypoperfusion of the coronary arteries. A number of mechanisms have been suggested. These include a bulging false lumen which can cause occlusion of the coronary orifice, a dissection which can extend into the wall of the coronary artery, or the coronary artery itself can detach from the aortic root. In attempting to identify the vessel involved, retrospective studies have broken down the cases of ST elevation to suggest mainly right coronary artery and left main branch involvement [28].

An important aspect of EKG changes in the setting of aortic dissection is their implication for the patient's outcome. Patients with ST segment changes had a higher prevalence of pericardial effusion, cardiac tamponade, moderate/severe aortic regurgitation, and shock on admission, resulting in higher in-hospital mortality. On multivariate analysis, EKG changes were the only independent predictor of mortality. Even when the cases with ST elevation were removed from the equation, there remained an association with EKG changes and a higher in-hospital mortality [30•].

Imaging

The implications of a diagnosis of aortic dissection mandates that the imaging technique used be highly specific and sensitive. It should also provide adequate information to plan for an emergent therapeutic strategy. Planning for a therapeutic strategy depends not only on the type of dissection but also on the site of entry, the extent of dissection, the involvement of the coronary arteries, arch branches, or visceral arteries, the involvement of the aortic valve, the presence and extent of pericardial effusion, false lumen patency, and the presence of thrombus in the false lumen. Therefore, delineation of these features should be an important part of the diagnostic workup for patients with suspected aortic dissections. Imaging techniques range from the initial radiograph through to MRI.

Chest X-ray

The classic finding with aortic dissection on x-ray is mediastinal widening. The mediastinum can be seen to bulge to the right with dissection of the ascending aorta and to the left with dissection of the thoracic aorta. Multiple other signs have been reported in cases of aortic dissection including widening of the aortic knob, aortic wall thickness, double aortic shadow and the presence of a pleural effusion, mainly on the left [31, 32]. However, while the absence of findings on a chest x-ray lowers the likelihood of the disease, it does not exclude its presence. In IRAD, absence of mediastinal widening was noted in 37.4 % of patients presenting with type A aortic dissection. No chest x-ray abnormality was noted in 12.4 % of patients [2]. Pooled data from 10 studies placed the predictive sensitivity of a widened mediastinum and abnormal aortic contour at 64 and 71 %, respectively. If all chest x-ray abnormalities were included, this increased the sensitivity to 90 %; however, this included minor chest x-ray changes including small pleural effusions [33]. A further prospective trial showed that the specificity of a chest radiograph for significant aortic disease was 86 % [34].

These studies demonstrate that the absence of chest x-ray abnormalities makes the likelihood of significant aortic disease less likely. However, it is not powerful enough to be used alone as a rule-out test. Additional studies are required in almost all patients. In unstable patients, obtaining a chest x-ray can further delay the institution of appropriate imaging and treatment

CT

CT is well established as the most used diagnostic modality in cases of suspected AAD. IRAD reported CT as the first imaging modality used in 61 % of cases [2]. Advantages of CT include its near universal availability and its speed of diagnosis. It can also delineate branch vessel involvement and visualize the entire aorta. A further plus of CT is that an alternative cause for chest pain has been reported in up to 21 % of cases scanned for suspected AAD [35].

Non-helical CT scanners were more than capable of diagnosing aortic dissection in the past. However, these machines were relatively slow and any patient motion resulted in significant artefact. The sensitivity of studies using non-helical CT have been shown as close to 100 % but the specificity ranges from 87 to 100 %. The use of helical CT has improved this reported specificity. A systematic review of 1,139 patients in 16 studies suggested that helical CT had a sensitivity of 100 % and a specificity of 98 % in the diagnosis of aortic dissection [36]. Multidetector CT (MDCT) has added further speed and thus improved the use of CT as a diagnostic tool. This involves using multiple detectors to obtain simultaneous images of any part of the body in a single breath-hold. MDCT allows accurate imaging of a large area in a short acquisition time with high resolution. This improves the visualization of

vascular structures as compared with conventional CT. It also facilitates breath holding, thus minimizing artefacts on images. A study on 57 patients showed sensitivities and specificities of up to 100 % with MDCT [37].

A further advancement on CT imaging has been the use of EKG gating. Movement of the heart throughout the cardiac cycle can produce motion artefacts in the image. The difficulty with interpreting cardiac motion can be helped with EKG gating. This is where data are only acquired during a specified portion of the cardiac cycle, typically during diastole. Images are created over a sequence of cardiac cycles, e.g., R to R intervals. This has been shown to be valuable for reducing ascending aortic motion artefacts that can mimic dissection without increasing imaging time [38, 39].

Triple rule-out CTs are being used more and more by various institutions allowing visualization of pulmonary arteries, aorta and coronary arteries in a single exam. This modality may safely eliminate the need for further investigation in 75 % of patients in the appropriate population [40]. The major disadvantages of this protocol are the use of increased contrast with a higher radiation dose. This limits its applicability to a unique subset of patients in which AAD, pulmonary embolism and acute coronary syndrome cannot be reliably distinguished based on clinical history. Most triple rule-out CTs also do not include the abdominal aorta, thus the extent of a descending AAD may not be visualized. Continued clinical research is needed to ascertain the place of triple rule-out CTs in the investigation of chest pain and AAD.

CT is an effective method of diagnosing an AAD with the completion of studies analyzing its effectiveness failing to maintain pace with the speed of increasing technology.

MRI

MRA can be considered a very accurate tool for the diagnosis of AAD allowing the visualization of the aorta without the need for ionizing radiation. Both the sensitivity and specificity have been reported as 100 % [36]. It is extremely accurate at identifying the site of entry, identifying thrombus and the presence of a pericardial effusion. Advantages include the assessment of functional cardiac information including left ventricular function and aortic regurgitation. There are significant limitations in the use of MRA as a first-line diagnostic tool, resulting in its use in only 1 % of cases in IRAD [2]. The availability of MRI and the length of time needed for a scan limit its use in everyday practice. The monitoring of critically ill patients is also much more difficult in the MRI environment. Faster scanners are currently being explored and, as the new generations of scanners are developed, MRA may be expected to play a more prominent role [41].

Transthoracic Echo

Although the current guidelines from the AHA would point to CT as the modality of choice in ruling out AAD [4], transthoracic echo can often be overlooked as a screening tool. It is portable, inexpensive, safe and can be of particular benefit in the patient who is hemodynamically unstable. While an ascending aortic flap is diagnostic of AAD, other 'high-risk' features include aortic regurgitation, dilated aortic root (especially with a pericardial effusion), inferior hypokinesia, and a bicuspid aortic valve. As well as establishing a diagnosis of AAD, it can detect signs suggestive of an alternative diagnosis such as pericardial effusions, right heart dilatation (pulmonary embolus), and regional wall abnormalities (MI) [42].

High-risk features for type A dissection on echo can prompt ED physicians to make timely referrals to cardiothoracic surgery or arrange urgent transfer to an appropriate center. This minimizes delays in transfer of the patient within a facility, such as to and from the radiology department, which is of particular importance in the hemodynamically unstable patient, in smaller centers with no cardiothoracic unit, and in those centers with limited access to CT scanners.

For the most time-critical dissection, type A, sensitivity is 78–100 %. For the less urgent type B dissection, sensitivity decreases to 31–55 % [43, 44].

Transesophageal Echo (TEE)

The current guidelines from the European Society of Cardiology advocate the use of transesophageal echo for those hemodynamically unstable patients either prior to transfer or on arrival in the operating theatre [4]. The paradigm of AAD on TEE is an intimal flap. Reverberation artefacts have been reported to cause some misdiagnosis; however, the use of color flow imaging can help to recognize reverberation artefacts [42]. For those patients with Type A dissection, TEE can provide additional information to assist in preoperative planning. This includes coronary, head or neck vessel involvement, presence of aortic regurgitation, site of entry tear, and the proximal extent of the dissection flap. It may also detect pericardial effusion or cardiac tamponade and make an assessment of left ventricular function [45].

The sensitivity of TEE is 94–100 % with a specificity of 77–100 % for identifying the intimal flap. One meta-analysis concluded it had similar sensitivity and specificity for AAD detection of helical CT and MRI [36]. However, the accuracy of TEE is also dependent on the operator with its availability limited in many settings.

It must be emphasized that the absence of such factors does not rule out the presence of an aortic dissection.

The imaging modality of choice remains CT. MRI has a higher sensitivity but its availability in the emergency situation results in CT becoming a more amenable diagnostic tool. TTE and TEE have been included in AHA and European society of Cardiology guidelines as a tool in the unstable patient. However, this is dependent on the operator and availability with a high level of skill involved.

Conclusion

The diagnosis of AAD is challenging for the emergency physician with potentially devastating consequences. A high index of suspicion must be maintained in order to ensure expedient and accurate diagnosis. The presence of risk factors and signs including pulse deficits or neurological symptoms propel the clinician to investigate further. There is currently no single biomarker that can be used to diagnose aortic dissection, but the judicious use of D-Dimers can aid clinicians in risk stratification and research is ongoing in this field. The future may allow novel biomarkers to be incorporated into a guideline with known risk factors and clinical features. This would significantly expedite and reduce mortality from AAD. CT remains the imaging of choice with increasing input from TTE.

Compliance with Ethics Guidelines

Conflicts of Interest All authors have declared no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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