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Biomarkers in Acute Aortic Dissection and Other Aortic Syndromes

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Acute aortic syndromes have an incidence of >30 per million per annum and a high mortality without definitive treatment. Survival may relate to the speed of diagnosis. Although pain is the most common symptom, there is a large fraction of patients in whom the diagnosis may be mistaken or overlooked. Currently, a high index of clinical suspicion is the chief prompt that diverts a patient into a definitive algorithm of imaging investigations. Although there is no point-of-care biochemical test that can be reliably used to positively identify dissection, biomarkers are available that could accelerate the diagnostic pathway and thereby expedite treatment.
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Acute aortic dissection (AAD) is the most common thoracic aortic emergency and may be rapidly fatal without early diagnosis and appropriate management (1,2). Symptoms, signs, electrocardiograms (ECGs), and chest X-rays lack sensitivity and specificity (1). Diagnosis is therefore not immediate; definitive confirmatory investigation may not available in the emergency room (ER), and the varied presentation allows the diagnosis to be missed, misdiagnosed, or overlooked in up to 40% of cases (3), sometimes only being established at post-mortem (4,5).

The 2 common classifications of AAD are the DeBakey and Stanford classifications. The Stanford type A and DeBakey I and II variants involve the ascending aorta, whereas type B dissection (DeBakey III) involves the descending aorta only. Acute type A dissection is highly lethal, but a rapid diagnosis may allow life-saving surgical repair. Untreated mortality may approximate 1% to 2%/h following symptom onset with the majority of patients succumbing within 30 days (6–8). Surgical repair transforms the high mortality risk to a greater than 70% survival chance in the short term. This survival advantage of surgery continues in the longer term with outcomes vastly superior to those achieved by conservative management (9).

The initiating event of AAD may relate to medial hematoma bursting inwards through the media or the development of an intimomedial tear due to shear forces within the aortic lumen with propagation of a cleavage line within the media for a varying extent of the aortic wall (4,10). Other acute aortic syndromes (AAS), intramural hematoma, and deep penetrating ulcers may have similar presentations and prognosis but may cause less medial disruption (4). All aortic syndromes generate a vascular medial injury, and some generate an additional intimal lesion. Exposure of the media to blood elements initiates the coagulation cascade and generates a consumption coagulopathy. The degree of this coagulopathy will depend upon the surface area of tissue exposure and whether false luminal thrombosis occurs.

For all AAS, reduction in overall patient mortality might be best achieved by shortening the time from symptoms to treatment. Notwithstanding several recommendations and guidelines, the evidence suggests that definitive management is delayed for several hours while diagnostic evaluation is completed. Approximately 75% of patients with acute dissection have their initial diagnosis made in a nonspecialist hospital (11). The time from initial symptoms to hospital presentation is approximately 1 to 2 h, but the time to diagnosis varies considerably (12). Fifty percent of patients have a time to diagnosis of >6 h in Europe and >15 h in the U.S.; 75% of patients have diagnostic times >3 to 4 h (11). In type A dissection, the time duration between presentation and definitive management is >12 h in the majority of patients and has been reported as being >24 h in 20% to 50% in some series (9,13,14). In type B dissection, the mainstay of treatment is initial medical therapy with antihypertensive management. Patients presenting with atypical symptoms are at increased risk of in-hospital mortality, which may be related to diagnostic delay, prolonging the institution of treatments that may affect the disease's natural history, particularly dissection propagation (15). Delays in instigating blood pressure control in type B dissection may be >24 h after the initiating event, a period during which the natural history of the dissection is defined.

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JACC Vol. 56, No. 19, 2010
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Abbreviations and Acronyms

AAD = acute aortic dissection
AAS = acute aortic syndrome(s)
AMI = acute myocardial infarction
CRP = C-reactive protein
DD = D-dimer(s)
ECG = electrocardiogram
ER = emergency room
PE = pulmonary embolism
sELAF = soluble elastin fragments
smMHC = smooth muscle myosin heavy chain

Therefore, the prognostic significance of accelerating diagnosis is evident.

Diagnostic delay is exacerbated by nonclassical presentations that do not evoke clinical suspicion such as painless malperfusion phenomena, dypsnea due to heart failure or pleural effusion, troponin positivity, acute coronary syndrome–like ECG, limb ischemia, or abdominal pain, all of which are associated with longer in-hospital diagnostic times (14,16,17).

The challenge is therefore to accurately diagnose the condition as early as possible. The primary presentation of AAD to the ER is most commonly an elderly male, with hypertension and sudden onset chest pain (1), and the much more common acute coronary syndrome is an important differential diagnosis. Any lack of suspicion of AAD will fail to trigger investigation, delaying diagnosis (3). In the absence of a rapid, accurate, and readily available diagnostic test, the current diagnosis of AAD requires definitive imaging such as computed tomography (CT), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI), (18) but the use of each investigation is based on an index of clinical suspicion, and each incurs a further logistical delay in patient management.

Myocardial ischemia has the diagnostic advantages of the ECG and troponin estimation, allowing risk stratification and emergency treatment. AAS have no such rapidly available diagnostic tools. However, the higher and early mortality of these conditions appeals for a rapid, sensitive, and specific point-of-care diagnostic test that could be undertaken as a point-of-care assessment in the ambulance or ER, allowing direction towards imaging and definitive treatment. Other advantages would include:

1. An ability to reliably exclude an AAS, allowing diversion of investigative resources in different directions.
2. An ability to place an AAS as a likely diagnosis, accelerating the patient's progression to treatment in an appropriate medical center.
3. An enhanced high index of suspicion of an AAS, allowing pre-formal diagnosis delivery of blood pressure–reducing and anti-impulse therapy.
4. Prevention of inappropriate therapy (e.g., thrombolysis and antiplatelet agents).

Thus, there is a need for a specific biomarker test or array that can reliably include or exclude AAD and other AAS as a diagnostic possibility. Such a test would necessarily have need to distinguish other possible diagnoses, in particular the possibility of troponin-positive dissections in the presence of coronary malperfusion and acute abdomen biomarkers when visceral malperfusion occurs.

Potential Biomarkers in AAD

As dissection is a disease of the aortic medial layer, the search for biomarkers has been concentrated upon markers reflecting injury to vascular smooth muscle (smooth muscle myosin), the vascular interstitium (calponin), the elastic laminae (soluble elastin fragments [sELAF]) of the aorta, or secondary phenomena due to exposure of blood to nonintimal vascular surfaces (D-dimers [DD]) (19). For a biomarker to be acceptable for the paramedic or physician to employ, it must fulfill a number of criteria (20):

- Widely commercially available;
- Easy to use and fast;
- High sensitivity (identify all cases of AAD);
- High specificity (identify all cases that are not AAD);
- Release should be temporally related to presentation of event; and
- Have an acceptable cost.

No current biomarkers fit this profile, but we review the strengths and weaknesses of biomarkers studied to date.

Biomarkers for diagnosis of AAD. SMOOTH MUSCLE MYOSIN HEAVY CHAIN (smMHC). Smooth muscle myosin is a major component of smooth muscle. It is also present in uterine and intestinal smooth muscle and potentially could be elevated in conditions involving these systems. Preliminary experience by Katoh et al. in 1995 (21,22) suggested that smMHC is elevated within the first 24 h following AAD. Suzuki et al. (23) enrolled 27 patients with AAD (type A, n = 16), investigated 6.0 ± 1.3 h after symptom onset. Serum samples were obtained at 12-h intervals for the first 3 days and then at 24-h intervals for the next 7 days, for analysis of smMHC. Peak levels of smMHC were noted at initial testing with a rapid reduction in the first 24 h (Fig. 1). At a cutoff value of 2.5 $ng \cdot ml^{-1}$, the sensitivity of the assay was 90% and 85% at 12 and 24 h, respectively. All patients with values less than the cutoff value had type B or DeBakey III pathology, and this may be related to differential expression in different parts of the aorta. Patients with acute myocardial infarction (AMI) did not demonstrate any increase in smMHC levels in this group of patients (23).

As the initial assay time for smMHC was 5 h, the authors developed a rapid 30-min assay (24) and tested this in a multicenter study recruiting 95 patients with AAD (presenting within 24 h of symptom onset), 48 with AMI, and 131 healthy volunteers. Levels of smMHC were significantly higher for patients with AAD compared with healthy volunteers, and values were highest in patients presenting within the first 3 h. A significant reduction in levels occurred after 3 h, diminishing sensitivity. At a cutoff level of 2.5 $ng \cdot ml^{-1}$, sensitivity was 90.9% in the first 3 h, 72.4% in the subsequent 3 h, and 30.3% thereafter. When comparing the levels of smMHC in patients presenting within

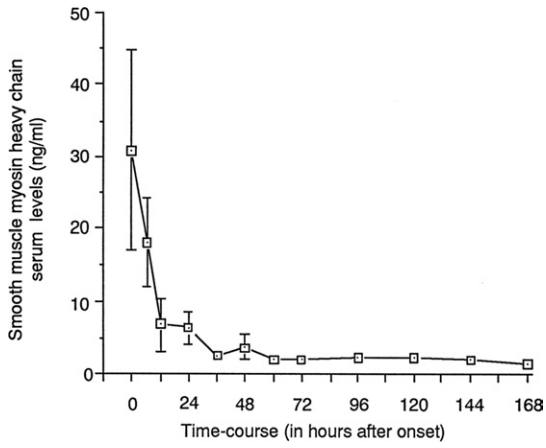

Figure 1 **The Time Course of smMHC Levels in Patients With Aortic Dissection (n = 27)**

Peak levels are at symptom onset. Thereafter, a rapid decline is noted over time (23). Reprinted, with permission, from Suzuki et al (23). smMHC = smooth muscle myosin heavy chain.

3 h following AMI, the assay had a specificity of 83% at the 2.5 $ng \cdot ml^{-1}$ cutoff level. Levels of smMHC greater than 10 $ng \cdot ml^{-1}$ demonstrated a specificity of 100% for detecting AAD. Levels were significantly higher in proximal compared with distal lesions; and in patients with distal lesions (DeBakey III), even if presenting within the first 3 h of symptom onset, smMHC levels were not >2.5 $ng \cdot ml^{-1}$ (24). smHMC is not currently available as a point-of-care test.

In summary, smMHC is elevated in the first hours following AAD, but levels rapidly decrease in the first 24 h. It is not elevated in the setting of AMI. The smMHC elevation is greater in proximal versus distal dissection. This investigation could have utility if administered at initial presentation but rapidly loses sensitivity as time after symptom onset increases.

CALPONIN. In cardiac muscle, contraction is regulated by the troponin-tropomyosin system, allowing the development of troponin assays as sensitive and specific biomarkers of myocardial injury (25,26). Contraction of smooth muscle is regulated primarily by the reversible calcium-calmodulin–dependent phosphorylation of myosin; however, contraction can be modulated by other signal transduction pathways, one of which involves the thin filament-associated protein calponin (27). Within vascular smooth muscle, calponin, a 34-kDa protein that is a troponin counterpart of smooth muscle (28), has previously been isolated and purified (29). Calponin has 3 isoforms: basic (also termed h1), acidic, and neutral (termed h2), with the basic isoform being the most abundant and specific to smooth muscle. This protein has recently been the focus of recent study in AAD (30). After developing calponin assays for all 3 isoforms, 217 patients with a high suspicion of AAD (high enough to request definitive imaging by which confirmation of diagnosis was obtained) were studied. Of the total study population, 59 (27.2%) had confirmed AAD (72.9% type A), 44.9% had cardiac disease, 10.8% thoracic aneurysm (nondissecting), 1.9% pulmonary embolism, and 42.4% had an uncertain diagnosis but not AAD. Acidic calponin showed a >2-fold increase for all dissections within the first 6 h of symptom onset (more notable for type A versus B). In both the 6- to 12-h and 12- to 24-h time periods, type A dissections demonstrated acidic calponin levels continued to increase, albeit with a reduced rate of rise. Within the first 6 h, basic calponin demonstrated a greater than 3-fold increase for all dissections (similar for both type A and B). In the 6- to 12-h period, type A dissections still demonstrated a greater than 3-fold increase (there was, however, a drop-off for type B). Both type A and B were still elevated at 12 to 24 h but continued to fall compared with previous time intervals. Neutral calponin did not demonstrate any elevation at any of the time points studied. None of the 3 isoforms of calponin were elevated at any of the examined time points in non-AAD patients.

During the first 6 h using an optimal value of 2.3 $ng \cdot ml^{-1}$ (acidic) and 159 $ng \cdot ml^{-1}$ (basic) resulted in a sensitivity of 50% and 63% and specificity of 87% and 73% for acidic and basic calponins, respectively. For the initial 24-h period, using values of 2.3 $ng \cdot ml^{-1}$ (acidic) and 139 $ng \cdot ml^{-1}$ (basic) led to a sensitivity of 58% and specificity of 72% (acidic) and a sensitivity of 50% and specificity of 66% (basic). Predictive values (negative and positive, respectively) were 0.84 and 0.56 in the first 6 h, and 0.84 and 0.41 in the initial 24 h for acidic calponin. For basic calponin, predictive values were 0.86 and 0.44 in the first 6 h, and 0.80 and 0.33 in the initial 24 h. A strength of this study was that it contained patients in whom a diagnosis of AAD was being actively pursued (and not utilizing healthy individuals), a situation more applicable to the ER and biomarker validation. Calponin assays are not currently available as point-of-care tests.

In summary, calponin has 3 isoforms, the basic isoform being the most extensively studied. Its levels are elevated in the setting of both proximal and distal aortic disease within the first 24 h. Although calponin has satisfactory negative predictive value during the first 24 h, its positive predictive value is poor. The high specificity of acidic calponin in the early period after symptom onset could be of utility if administered as part of a biomarker array at presentation but would require further development and refinement of available assays as point-of-care tests.

sELAF. Elastin is one of the main structural components of the arterial wall (31), and mature elastin is composed of soluble elastin subunits. As one of the main pathological features of the aortic media in AAD is elastin lamellar disruption (32,33), elastin degradation products (sELAF) could potentially be released into the circulation at the time of AAD (3). Shinohara et al. (34) developed an enzyme-linked immunoassay (ELISA) system to measure the con-

JACC Vol. 56, No. 19, 2010
November 2, 2010:1535–41

centration of sELAF in serum. The study comprised 25 patients with AAD, 50 patients with AMI, 20 patients with chest pain (AAD and AMI excluded), 40 nontreated hypertensive subjects, and 474 healthy controls. The first 3 groups were all recruited to the study within 48 h of symptom onset. In 474 healthy controls, sELAF was demonstrated to increase with advancing age, but no gender differences were noted. In patients with AAD, sELAF (mean ± SD) was 114.7 ± 56.9 ng·ml^{-1} compared with 56.1 ± 14.9 ng·ml^{-1}, 47.3 ± 13.5 ng·ml^{-1}, and 47.7 ± 22.3 ng·ml^{-1} for AMI, chest pain (AAD/AMI excluded), and nontreated hypertensive groups, respectively (Fig. 2). With a cutoff point for positivity set at 3 standard deviations above the mean in healthy subjects at each age, 16 patients (64.0%) with AAD were positive, with a specificity of 99.8%. The positive and negative predictive values were 94.1% and 98.1%, respectively.

For patients with AAD and a patent or partially thrombosed false lumen, 88.9% were positive for sELAF. In the group of patients with a completely thrombosed false lumen, sELAF assays were negative, a clear limitation of the marker. The difference in sELAF between patent/partially occluded and occluded false lumens was 135.4 ± 53.2 ng·ml^{-1} versus 60.3 ± 15.6 ng·ml^{-1}, $p < 0.005$, respectively. However, when serial sELAF serum levels were measured (n = 5, open/partially occluded), results suggested that sELAF remain elevated for a period of >72 h (34).

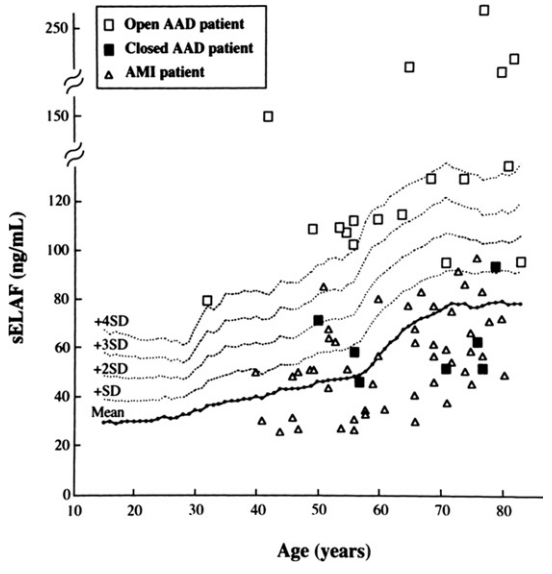

Figure 2 Serum sELAF Levels in Patients With AAD or AMI

The **continuous lines** represent mean and **dashed lines** up to 4 SDs above mean values for healthy controls. **Open squares** indicate AAD with patent false lumen, **closed squares** indicate AAD with thrombosed lumen. **Open triangles** indicate AMI patients. Reprinted, with permission, from Shinohara et al. (34). AAD = acute aortic dissection; AMI = acute myocardial infarction; sELAF = soluble elastin fragments.

Soluble elastin fragment assays are not currently available as a point-of-care tests.

In summary, sELAF elevation is sustained for quite long periods (up to 72 h) post-AAD. It has excellent positive and negative predictive values for AAD with perfused false lumen, but levels are reduced with partial and negative with complete false lumen thrombosis. It could however have utility as part of a biomarker array for AAD.

C-REACTIVE PROTEIN (CRP). CRP is an acute phase protein produced in the liver that is nonspecifically elevated in a number of conditions (including AAD) in response to inflammatory processes. In 255 patients admitted with symptomatic aneurysmal disease or AAD, Schillinger et al. (35) measured CRP levels on admission to the ER. CRP levels were temporally related to onset of symptoms, with patients with a shorter duration of pain (under 8 h) having a significantly lower CRP than those with longer symptom onset (>24 h). Both CRP and white blood cell counts are higher in chest pain patients with dissection versus other diagnoses, but differences are not sufficient to affect the diagnostic algorithm.

D-DIMER (DD). DD is a fibrin degradation product, present in the circulation following fibrinolysis of thrombus. It was first introduced in the 1990s as a diagnostic aid for thromboembolic disorders such as deep venous thrombosis and pulmonary embolus, for which they have a high negative predictive value but a low specificity (36,37). Elevated levels of DD can be found in a number of disease states, including malignancy, disseminated intravascular coagulation, recent trauma or surgery, deep venous thrombosis, PE, and AAD. Following an incidental observation, Weber et al. (38) investigated the relationship of elevated DD levels and AAD. They prospectively evaluated DD levels in 10 patients with confirmed AAD (as well as 14 retrospective cases) and compared these with 35 consecutive admissions with acute chest pain without AAD. Out of the 35 controls, 20 (57.1%) had an acute cardiac cause for chest pain, and only 1 patient had a diagnosis of PE. DD levels were positive in all AAD patients, and values were higher in more extensive disease. With a cutoff value of 0.5 μg·ml^{-1}, DD had a sensitivity of 100% and a specificity of 68.6% (38) in positively detecting AAD.

Eggebrecht et al. (39) studied 64 consecutive chest pain patients (16 AAD, 16 PE, 16 AMI, 16 noncardiac), assessing DD levels within 48 h of symptom onset. DD levels were elevated in all patients with AAD, significantly so versus AMI and noncardiac chest pain, but no different when compared with PE. A negative correlation was noted between the DD value and time of symptom onset. With a cutoff value of 0.62 μg·ml^{-1}, sensitivity and specificity were 100% and 73%, respectively. At a cutoff value of 0.5 μg·ml^{-1}, sensitivity and specificity were 100% and 67%, respectively (39).

There are a number of different assays available to test DD levels, and it is important that cutoff values and sensitivities are reported for individual assays. Akutsu et al. compared a rapid DD test (which returns a DD value from whole blood within 10 min) with a standard latex agglutination assay for screening clinically suspected AAD (40). In the study cohort of 78 patients, 30 had AAD, and of the remaining 48, 7 (14.6%) had nondissecting aneurismal disease and 2 (4.1%) had PE. All patients with AAD had a DD value >0.5 $\mu g \cdot ml^{-1}$, and the new, rapid bed-side test correlated well with the standard latex agglutination assay. With a cutoff value of 0.5 $\mu g \cdot ml^{-1}$, sensitivity was 100% and specificity 54% (40). In an attempt to improve specificity, Akutsu et al. next looked at DD estimation in conjunction with hypertension on admission (systolic blood pressure greater than 180 mm Hg). Although this combination of variables improved the specificity (96%) with a positive predictive value of 86%, sensitivity fell to 40% (40).

In a single-center, retrospective case-control study, Ohlmann et al. (41) also assessed the usefulness of measuring DD in managing patients with AAD. Out of 94 patients with AAD, 93 had levels >0.4 $\mu g \cdot ml^{-1}$. DD levels were positively correlated with the anatomical extent of dissection and in-hospital mortality. With a cutoff value of 0.4 $\mu g \cdot ml^{-1}$, sensitivity and specificity were 99% and 34%, respectively. In a multivariate analysis, independent predictors of in-hospital mortality were pericardial effusion (odds ratio [OR]: 6.80 [95% confidence interval (CI): 1.87 to 27.60]), female sex (OR: 4.96 [95% CI: 1.39 to 19.95]), and DD levels >5.2 $\mu g \cdot ml^{-1}$ (OR: 5.38 [95% CI: 1.27 to 30.87]) (41). Weber et al. (42) have also reported the prognostic relevance of DD measurement in a cohort of 27 patients with AAD. Nonsurvivors in patients with AAD were demonstrated to have significantly higher DD levels than survivors in both patients who were surgically or medically managed.

Sodeck et al. (43) performed a systematic review and prospective cohort study of use of DD as a biomarker in excluding AAD. In a total of 16 studies reviewed (n = 437), only 15 of 437 (3.4%) patients with AAD were DD negative. Their meta-analysis demonstrated that DD yielded a high sensitivity and negative likelihood ratios (with narrow CIs), implying that a negative DD is likely to exclude the diagnosis of AAD; however, pooled specificities and positive likelihood ratios did not increase the ability to diagnose AAD. In their cohort of 65 patients with a median (interquartile range) symptom onset of 4.8 (2.4 to 16) h, the sensitivity of initial DD levels for excluding the diagnosis of AAD at cutoff values of 0.1, 0.5, and 0.9 $\mu g \cdot ml^{-1}$ were 100%, 98%, and 86%, respectively (43).

Recently, the IRAD-Bio (International Registry of Acute Aortic Dissection Substudy on Biomarkers) study reported on the use of DD assessment in AAD diagnosis (44). The study recruited 220 patients with clinical suspicion of AAD within the first 24 h following symptom onset (Fig. 3). Of the 220 patients, 87 (39.5%) had a radiographically con-

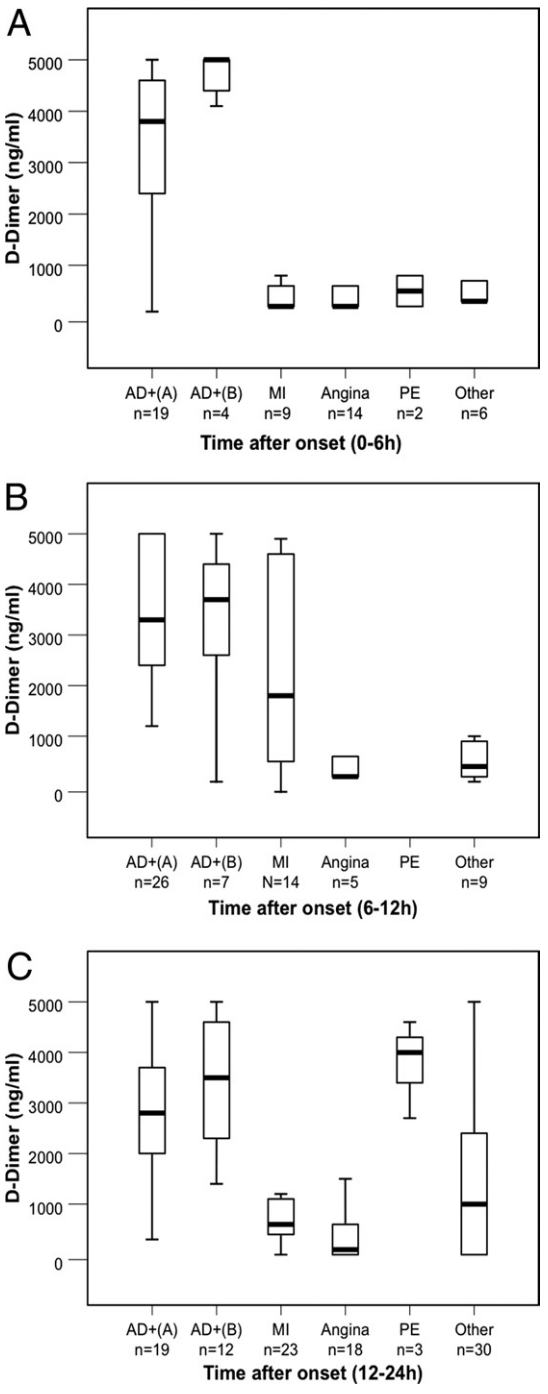

Figure 3 **DD Levels From Time of Symptom Onset in Patients From the IRAD Biomarkers Study**

D-dimer (DD) levels were 5- to 10-fold greater for patients with dissection compared with other diagnoses in the first 6 h. In the 12- to 24-h period, a comparable elevation of DD was noted in patients with a diagnosis of pulmonary embolus. **(A)** 0- to 6-h time period; **(B)** 6- to 12-h time period; and **(C)** 12- to 24-h time period. Reprinted, with permission, from Suzuki et al. (44). AD+(A) = positive for aortic dissection, type A; AD+(B) = positive for aortic dissection, type B; IRAD = International Registry of Acute Aortic Dissection; MI = myocardial infarction; PE = pulmonary embolism.

JACC Vol. 56, No. 19, 2010
November 2, 2010:1535–41

firmed diagnosis of AAD (type A, n = 64). Of the remaining 133, diagnoses were: myocardial ischemia, 83 (37.7%); PE, 5 (2.3%); and uncertain (AAD excluded) diagnosis, 45 (20.5%). DD values demonstrated favorable overall diagnostic performance (area under the curve on receiver operating characteristic curve analysis) compared with the control group (0.84) and when analyzed according to the diagnosis of angina (0.93), uncertain diagnosis (0.82), MI (0.81), and PE (0.65). At a cutoff value of 0.5 $\mu g \cdot ml^{-1}$ versus controls, sensitivity and specificity were 96.6% and 46.6%, respectively. Compared with angina, uncertain diagnosis, MI, and PE, specificities were 62.2%, 44.4%, 39.1%, and 20.0%, respectively (44). Thus, DD assessment may have an important role in the investigational triage of patients with suspected AAD.

However, despite the excellent sensitivities associated with DD estimation in the aforementioned studies, some patient subgroups can generate a false negative result (i.e., a low or equivocal DD level in the presence of AAD). Hazui et al. (45) found that absolute DD values are lower in patients with thrombosed false lumen, shorter dissection lengths, and younger age groups, and such patients could be misdiagnosed if DD assays were used in isolation. Reduced sensitivity and absolute DD levels in patients with thrombosed false lumen have also been reported by Akutsu et al. (40).

In summary, DD levels have an excellent sensitivity for the detection of AAD and could be used to triage patients towards definitive imaging for diagnosis of AAD even in the presence of troponin positivity. The test is easily employed within the ER. When DD elevation is present, an important differential diagnosis is acute PE. However, as suspicion of both AAD and acute PE direct the patient towards definitive imaging studies, this lack of specificity is not necessarily a disadvantage. However, as DD may lack sensitivity for certain AAD subtypes, a high index of clinical suspicion should overrule equivocal DD levels in directing a patient towards definitive imaging.

Summary of Biomarkers Used in AAD

There are a number of biomarkers that have potential to accelerate diagnosis in AAD, but none is yet completely validated, and combination biomarker arrays have yet to be investigated. Each have difficulty in recognizing patients with a thrombosed false lumen or limited disease extent, and most have limited half-lives. Of those discussed, there is little experience with other AAS, intramural hematoma, and acute penetrating ulcers that have not progressed to dissection. Although smMHC demonstrates good early sensitivity for detection of AAD, levels quickly fall and are reduced in more distal disease. Experience with calponin is limited, but assays need further development to improve sensitivity and specificity. Levels of sELAF remain elevated for up to 72 h and are better at detecting proximal than distal disease; however, sELAF is not detected in the presence of a thrombosed false lumen. Estimation of DD has an excellent sensitivity for AAD, but moderate specificity, and may be helpful in imaging investigation triage. However, false negative low DD levels have been reported in patients with thrombosed false lumen, less extensive disease, and younger age groups. Physicians should be aware that DD assessment cannot completely rule out dissection or other AAS, and that in equivocal cases with a high index of clinical suspicion, imaging should still be rapidly performed if these diagnoses are not to be overlooked.

What Is Needed?

The management of AAS patients is dependent upon their anatomical characterization and type and presence of complications, including rupture, rupture risk, and malperfusion phenomena; imaging, therefore, plays a key role. The importance of a diagnostic biomarker in AAS is to allow triage of patients who should undergo rapid imaging, allowing the prompt initiation of treatment algorithms. This would reduce delays in diagnosis and increase the number of patients diagnosed and treated, potentially improving the prognosis of patients with these conditions. The data presented suggest that there are a number of candidate biomarkers that could prove of value particularly if used in combination. Consider, for instance, a patient with type A dissection complicated by coronary malperfusion whose symptomatology and preliminary investigations would be consistent with acute ST-segment elevation myocardial infarction. Such an AAD patient should not receive high-dose antiplatelet agents, undergo thrombolysis, or proceed to primary angioplasty, but rather should undergo AAD imaging and prompt surgical repair. Although a positive troponin study might be expected, a course of investigation that included DD and vascular smooth muscle injury marker assessment might better direct this patient management. Much more information is needed. Not only do we need identification and characterization of further candidate biomarkers, we also need validation in prospective cohorts of patients presenting with chest pain. Most biomarker assessment has been undertaken in patients in whom the diagnosis is known, and results have often been compared from normal control patients without chest pain morbidities. As the relative frequencies of AAS to acute coronary syndromes approximate 1 in 1,000, prospective studies to allow earlier diagnosis are difficult to design but nevertheless necessary. Recent reports have demonstrated that such studies are possible, and more are urgently required (44).

Conclusions

There is currently no single biomarker that can positively identify AAD or other AAS. Of those studied, DD analysis has sufficient predictive value to facilitate imaging investigation triage with some caveats. Research is necessary to further determine the role of DD assessment and to discover and characterize other candidate biomarkers that could be

used alone or in combination as point-of-care assessments in the diagnostic algorithm.

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