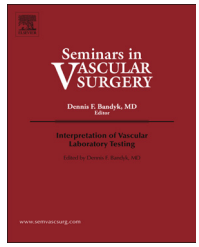
Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semvascsurg



Biomarkers in descending thoracic aortic dissection

Sherene Shalhub, MD, MPH[a,*], *Anahita Dua, MD, MS, MBA*[b], *and Jared Brooks, BA*[a]

[a]*Division of Vascular Surgery, Department of Surgery, University of Washington, 1959 NE Pacific Street, Box 356410, Seattle, WA 98195-6410*

[b]*Department of Surgery, Medical College of Wisconsin, Milwaukee, WI*

ARTICLE INFO

ABSTRACT

The clinical application of serum biomarkers (D-dimer, C-reactive protein) to predict the natural history of descending thoracic aortic dissection remains elusive. In this review, our current understanding of biomarkers in descending thoracic aortic dissection detection, predicting complications, and aiding in patient management is discussed.

1. Introduction

Aortic dissection (AD) starts as an initial intimal tear, followed by the rapid growth of an intramural hematoma that dissects the media within the aortic wall leading to blood flow through a double-barrel aorta with a true and false lumen [1]. Diagnosis of AD and prognosis prediction remain a challenge. The most sensitive clinical test for AD diagnosis is sudden onset of severe ripping pain in the chest, back, or upper abdomen [2]. This can be absent in 5% to 20% of patients [1,2]. In terms of prognosis, the estimated 3-year mortality of descending thoracic aortic (DTA) AD, also known as Stanford Type B AD or DeBakey III AD, is 20%. The ability to predict the natural history of DTA AD in any given patient for future risk stratification remains elusive [3].

The role of biomarkers has been investigated both in diagnosis and identifying progression of DTA AD. The biomarkers studied were selected based on the understanding of the natural history of DTA AD. It is hypothesized that the acute dissection process activates the extrinsic pathway of the coagulation cascade due to release of tissue factor from the injured aortic wall along the length of the false lumen [4]. False lumen thrombosis is hypothesized to activate the intrinsic pathway of the coagulation cascade and subsequently the fibrinolytic system is activated. The cross-linked fibrin is degraded and then D-dimer is formed [5]. Additionally, an inflammatory response has been described to be associated with AD [6]. DTA AD can lead to complications in the short term, such as aortic rupture; refractory pain; and spinal, visceral, renal, and extremity malperfusion. In the subacute and chronic phase of aortic dissection, aortic remodeling begins. Aortic remodeling is characterized by ongoing fibrinolysis, and active proteolysis of the extracellular matrix [4,5,7]. Over the long term, the aorta can undergo gradual dilation and aneurysmal degeneration.

This review was undertaken to discern the current understanding of biomarkers in DTA AD detection and complications prediction.

2. Biomarkers in the detection of descending Thoracic Aortic Dissection

The utilization of biomarkers in AD diagnosis has been investigated as a screening test to direct further imaging in a manner similar to venous thromboembolic disease. Several biomarkers have been investigated for that purpose; the most widely studied biomarker to date has been serum D-dimer.

* *Corresponding author.*
E-mail address: shalhub@uw.edu (S. Shalhub).

http://dx.doi.org/10.1053/j.semvascsurg.2015.01.001
0895-7967/$ - see front matter © 2015 Elsevier Inc. All rights reserved.

D-dimer, the degradation product of cross-linked fibrin, is an indirect marker of the coagulation system activation. Serum D-dimer levels have been reported to be elevated in cases of thromboembolic disease, liver disease, pregnancy-related complications, malignancy, or generalized inflammation [8]. The testing is inexpensive, widely available, and can be completed expeditiously [9]. In AD, serum D-dimer has been shown to be elevated as much as 20 times that of a normal subject. This is similar to the levels detected in pulmonary embolism cases [4,5,10,11]. In general, serum D-dimer levels in acute AD are higher than in cases with acute myocardial infarction and in those with chronic AD [4]. Two large meta-analysis studies evaluated the utility of D-dimer as a test to detect AD in patients with chest pain and thus direct further aortic imaging. The positive test threshold was set at the threshold for pulmonary embolism detection. These meta-analyses showed that serum D-dimer had a sensitivity of 94% to 95% and a specificity ranging between 40% and 100% for AD detection [10,12]. Serum D-dimer levels show a trend for gradual decrease within the first few days of AD, thus it has been proposed as a biomarker to differentiate acute AD from chronic AD [4]. Given the high sensitivity and low specificity of the test, it is useful as a screening test in patients with low clinical probability of acute AD [10].

Serum D-dimer levels appear to be correlated to the anatomic extent of AD with higher levels detected in Stanford Type A AD and in those with larger aortic diameters [9]. In studies where the extent of the dissection was classified according to the DeBakey classification, the highest levels of serum D-dimers in the acute phase were detected in DeBakey I AD, followed by DeBakey III AD then DeBakey II AD [5,13]. This led to the hypothesis that the extent of coagulation and fibrinolysis pathways activation is proportionately related to the surface of contact between the bloodstream and the exposed thrombogenic elements in the false lumen. The finding was not replicated in a smaller study (n = 18) comparing D-dimer levels between Stanford Type A and B AD [11]. Additionally, this finding has not been replicated in Stanford Type B specifically. In a study of 30 patients with Stanford Type B AD, no significant correlation was found between admission serum D-dimer levels and extent of dissection as classified according to the DeBakey classification IIIa versus IIIb [14]. D-dimer levels have been shown to be significantly lower in cases of false lumen thrombosis and intramural hematoma. The latter entities lack a patent false lumen and have a smaller anatomic extension compared to a classic AD [13,14]. Given these results, the use of serum D-dimer testing as a singular test modality in cases with high index of clinical suspicion for AD cannot be recommended [15].

Several other biomarkers have been studied as diagnostic for AD. These include plasma smooth muscle myosin heavy chains, soluble elastin fragments, and calponin, a smooth muscle troponin-like protein. These biomarkers are thought to be released from the injured aortic media during AD and have been shown in small studies to detect AD with high sensitivity and specificity, although at this time they remain impractical in the clinical emergency setting [16–18].

Plasma N-terminal pro-B-type natriuretic peptide (BNP) levels were also evaluated. In a prospective study, in 18 patients with acute AD (13 Stanford Type A AD, 5 Stanford Type B AD), plasma BNP levels were found to be elevated in acute AD compared to normal controls [11]. A potential hypothesis to explain this finding is the associated history of long-standing hypertension in patients with AD, as plasma BNP levels have been shown to be elevated in patients with essential hypertension and diastolic dysfunction. This is supported by the finding in the same study that plasma BNP levels were also increased in patients with chronic thoracic aneurysms [11].

3. Biomarkers in predicting descending Thoracic Aortic dissection prognosis

The utilization of biomarkers has been investigated as prognostic indicator in the short and long term. Candidate biomarkers include serum D-dimer, C-reactive protein (CRP), metalloproteinases, and genetic markers.

D-dimer levels have been demonstrated to be predictive of hospital short-term mortality [4,9]. In a prospective study of 114 patients with acute AD (64 Stanford Type A AD, 50 Stanford Type B AD), elevated admission plasma D-dimer levels were associated with high risk of short-term mortality [9]. D-dimer levels have also been evaluated as a marker for early in-hospital complications. In a retrospective study of 16 patients with acute AD (6 Stanford Type A AD, 10 Stanford Type B AD), complicated AD cases, as defined by contained aortic rupture and tamponade, had higher serum D-dimer levels compared to uncomplicated cases [4]. In a prospective study of 30 patients with Stanford Type B AD focused on serial D-dimer measurements, re-elevation of D-dimer during hospitalization was associated with complications defined as re-dissection in (n = 3) and venous thromboembolic events (n = 4) during hospitalization [14].

The acute-phase reactant CRP is a biomarker of systemic inflammation that is produced mainly by the liver. Elevation of plasma CRP levels and leukocytosis have been described in acute AD with plasma CRP levels increased by more than five times compared to normal subjects [11]. Plasma CRP levels in AD have been demonstrated to be time dependent, with a rapid rise in the first 4 to 6 hours, reaching a peak between 36 hours and 6 days post AD, and then followed by a decline in the chronic phase [19,20]. The use of CRP testing in evaluating the severity of AD was first described in 1991 in a cohort of 42 cases of DTA AD [21]. The marker was followed during hospital admission for medical management of the DTA AD and the patients were discharged once the levels had normalized. A second peak was noted in 26% of the patients and the majority of these patients had either progression of the AD or recurrent pain [21]. In a prospective study of 114 patients with AD (64 Stanford Type A AD, 50 Stanford Type B AD), elevated admission plasma CRP levels (>6.3 mg/dL) have been associated with high risk of short-term mortality in the acute phase. In a retrospective study of 255 consecutive patients with symptomatic thoracic, abdominal aortic aneurysms, and AD (including 27 patients with DTA AD), the highest serum CRP quartile level was an independent predictor of mortality, with a 2.6× increase in mortality after adjusting for age, sex, aortic rupture, shock, mechanical