Significance of Biomarker Panel Including Cardiac Troponin I, D-dimer, and B-Type Natriuretic Peptide in Acute Aortic Dissection

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Abstract: We assessed whether elevated serum cardiac troponin I (cTnI), D-dimer and B-type natriuretic peptide were associated with short-term mortality in patients with acute aortic dissection (AAD).From 2010 to 2011, 6455 consecutive patients with acute chest pain were admitted to our emergency department, 15 (0.23%) of whom had AAD diagnosed and biomarker data collected. AAD was confirmed on transthoracic esophageal echocardiogram and computed tomography. Patients with abnormal cTnI concentrations had a higher rate of mortality. In univariate analysis, elevated cTnI was an independent predictor of in-hospital mortality (relative risk 27.46, 95% confidence interval 1.20–629.31). No relationship between mortality and D-dimer, B-type natriuretic peptide or the DeBakeyclassifications was identified. In conclusion, elevated serum cTnI identifiesAAD patients at high risk of in-hospital mortality. These findings suggest that cTnI may be a promising tool for rapid risk stratification of patients with AAD.

Keywords: Acute aortic dissection, B-type natriuretic peptide, D-dimer, cardiac troponin I, risk stratification.

INTRODUCTION

Acute aortic syndrome is a contemporary term used to describe interrelated emergency aortic conditions with similar clinical characteristics and challenges [1]. Among these, acute aortic dissection (AAD) is a life-threatening cardiovascular emergency with a high mortality rate early after symptom onset, increasing by 1–2% per hour, and with survival related to the speed of diagnosis [2]. A high clinical suspicion – dependent upon individual expertise, characteristics of chest pain and a critically elevated D-dimer level – should trigger a definitive algorithm of imaging investigations for confirmation of diagnosis [1, 2]. Prognostic stratification based on clinical predictors [1] and D-dimer [3] has been crucial to tailor in-hospital management and potentially improve clinical outcome. Whether point-of-care, multi-marker strategies, including cardiac troponin I (cTnI), D-dimer and B-type natriuretic peptide (BNP), could improve prognostic stratification is unknown. We undertook a prospective study to determine whether elevated concentrations of serum cTnI, BNP andD-dimer are associated with in-hospital mortality in a prospective cohort of patients with AAD.

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METHODS

Study Population

The study population comprised a consecutive, prospective cohort of patients with AAD admitted to a teaching hospital. Patients admitted to the emergency department (ED) with a high clinical suspicion of AAD and subsequently proven diagnosis, and who had a biomarker panel obtained in the ED were eligible for inclusion. High clinical suspicion of AAD included at least one risk condition i.e. long-standing arterial hypertension, smoking, dyslipidemia, and cocaine/ crack or amphetamine users; connective tissue disorders i.e. hereditary fibrillinopathies, Ehlers-Danlos syndrome, etc; hereditary vascular diseases: bicuspid aortic valve, aortic coarctation; vascular inflammation i.e. auto immune disorders, giant cell arteritis, Takayasu arteritis, etc. associated with clinical presentation driven by thoracic or abdominal pain [1, 4]. AAD dissections were classified at presentation on the basis of false lumen propagation to the ascending aorta (DeBakey I, II and III). The DeBakey I and II variants involve the ascending aorta, and DeBakey III involves the descending aorta I or II dissection was defined as instantaneous onset of severe chest pain and/or syncope and/or tamponade associated or not with aortic insufficiency, collapse, pulse differential, myocardial ischemia or neurologic signs. III dissection

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was defined as instantaneous onset of severe chest or back pain, with migrating pain or distal pulse differential, with or without high blood pressure, renal insufficiency, claudication or distal malperfusion [1, 4]. The diagnosis of AAD was proved using standard criteria for TEE, computed tomography scanning, magnetic resonance imaging, angiography [4, 5] or at autopsy. Patients ineligible for inclusion were those in whom a diagnosis of AAD was excluded; patients with AAD secondary to iatrogenic factors or deceleration trauma; with a previous arterial and/or venous puncture; a history of heart failure syndrome, with or without preserved ejection fraction; and with previous venous thromboembolism, acute coronary syndrome or another acute thrombotic vascular syndrome.

Patients with a high clinical suspicion of AAD underwent fast-track assessment by an experienced physician, including a medical history, physical examination, electrocardiogram, pulse oximetry, blood tests, bedside transthoracic echocardiogram (TTE), and chest X-ray. The DeBakey I, II and III classification was used. Transesophageal echocardiography (TEE) was available, excluding routine "off-shift" night time and weekend hours. The diagnosis and therapeutic approaches were decided by the physicians in charge and were not driven by the biomarker results.

The study was approved by the ethics committee of the hospital, and all patients or relatives provided written informed consent to participate.

Biomarker Assessments

Blood samples were obtained on admission. D-dimer, BNP and cTnI concentrations were measured once, as most patients received vasoactive drugs and underwent invasive procedures and/or surgery. All biomarkers were assayed by fluorescence immunoassay through quantitative tests with a 225μL blood sample and time to result of approximately 15 minutes (Triage® Meter Plus with Triage Profiler SOB Panel, Biosite Incorporated, 9975 Summers Ridge Rd. San Diego CA, 92121, USA). Values judged to be normal for the biomarkers were < 500 ng/mL for D-dimer, < 100 pg/mL for BNP and < 0.05 ng/mL for cTnI.

Statistical Analysis

Continuous variables in the subgroup of patients who survived versus those who died were compared using an unpaired *t* test. Nominal values were compared using the χ^2 test or Fisher's exact test. A Cox regression model was performed for prediction of in-hospital death in the total population, with variables that were most strongly associated with in-hospital death included in the model. Variables significant in the univariate analysis were retained as predictive factors in the multivariable analysis. Kaplan–Meier survival curves were obtained and compared using the log-rank test The relative risk and associated 95% confidence intervals for the various potential risk factors were calculated. A *P*-value < 0.05 was considered to be statistically significant. All results are expressed as absolute number or mean ± standard deviation. Statistical analyses were made using PASW 20, 2011.

RESULTS

From 2010 to 2011, 6455 consecutive patients with acute chest pain were admitted to the ED, 15 (0.23%) of whom met the inclusion criteria. AAD was suspected on clinical grounds and was confirmed by TEE in 15 patients and by computed tomography in 8 patients.

Patients' demographic and presenting Characteristics are shown in Table **1**. AAD patients were young and predominantly male. Risk factors as long-standing smoking, artery hypertension, and dislipidemia were frequent. Eleven patients had the index event at home and 4 patients in-hospital. AAD was characterized most frequently by sudden acute dyspnea, acute severe chest pain or blood pressure asymmetry.

A high proportion of the patients arrived at the ED with clinical stability. Nine patients were classified as DeBakey type I, 2 patients as DeBakey type II and 4 patients as DeBakey type III (Table **1**).

The results of hospital investigations are shown in Table **2**. Electrocardiographic findings were negative T-waves in 11 patients, ST-segment depression in 7 patients and ST-segment elevation in 3 patients. All patients had an abnormal chest X-ray; the main finding was an enlarged mediastinum and 3 patients had pleural effusion. Aortic hematoma was observed in 5 patients. Most patients had preserved ejection fraction, 7 had severe aortic regurgitation and 4 mild aortic regurgitation.

Serum levels of D-dimer, BNP and cTnI, leucocytes and fibrinogen are shown in Table **3**. D-dimer levels showed a non-significant trend towards higher values in patients who died compared with those who survived (2801 ± 1884 ng/mL vs 2279 ± 1805 ng/mL, P= .59;

Table 1: Patient Baseline Characteristics and Clinical Presentation

Variable	Mean ± SD or absolute number (n = 15)
Age, years	49 ± 21
Male gender	10
Smoking	8
Artery hypertension	6
Dyslipidemia	4
Diabetes mellitus	1
Clinical Presentation	
Acute sudden dyspnea	13
Acute sudden thoracic pain	11
Severe thoracic pain	10
Back pain	5
Acute heart failure syndrome	5
Pulse deficit	7
Syncope	2
Presyncope	3
Dizziness	2
Abdominal pain	1
Shock	1
Dysphonia and cough	1
Focal neurologic deficit	0
Blood pressure asymmetry	10
Systolic blood pressure mmHg	137 ± 30
Hypertensive > 150 mmHg	8
Normotensive 100–149 mmHg	6
Hypotensive < 100 mmHg	1
DeBakey classification	
I	9
II	2
III	4

Table 2: Results of Hospital Investigations and Clinical Outcomes

Variable	Mean ± SD or absolute number (n = 15)
Electrocardiographic findings	
Negative T-waves	11
ST-segment depression	7
ST-segment elevation	3
Chest X-ray results	
Enlarged mediastinum	15
Pleural effusion	3
Transesophageal echocardiogram findings	
Aortic regurgitation grade III–IV	7
Mild aortic regurgitation	4
No aortic regurgitation	4
Intramural hematoma	5
Pericardial effusion	1
Diameter of the aorta (mm)	40.8 ± 15.7
Ejection fraction	51.5 ± 12
Ejection fraction ≥ 50%	11
In-hospital outcome	
Surgery	6
Discharged alive	7
Mortality	8

Table **4**). Three patients had abnormal troponin levels (1.12 ng/mL, 1.27 ng/mL, 2.4 ng/mL), 2 of them had ST depression and elevation on ECG.

Among the 15 AAD patients, 6 underwent surgery during hospitalization. Overall, 8 patients died and 7 were discharged alive from hospital (Table **2**). Univariate analysis results in patients who died and in those who survived are shown in Table **4**. cTnI was an independent predictor of in-hospital mortality (relative risk 27.46, 95% confidence interval 1.20–629.31). Patients with an abnormal cTnI concentration had a higher mortality rate than those with a normal concentration (Figure **1**). We did not find any relationship among, gender, clinical presentation, surgery, mortality and troponin levels.None of the other biomarkers, either alone or in combination, or the DeBakey classification was independently predictive of increased in-hospital mortality.

DISCUSSION

The results from this single-center study provide several insights into the use of a biomarker panel in patients with AAD and risk factors associated with chronic endothelial dysfunction and vascular inflammation. Firstly, in male patients with predominantly ascending AAD and clinical stability, elevated serum cTnI was associated with short-term mortality (Figure **1**). Secondly, the presence of abnormal BNP concentrations may increase the diagnostic accuracy of clinical judgment, identifying patients with an early stage of acute heart failure

Table 3: Concentrations of Biomarkers, Leucocytes and Fibrinogen

Variable	Mean ± SD	Normal range
Cardiac troponin I (ng/mL)	0.36 ± 0.69	< 0.05 ng/mL
D-dimer (ng/mL)	2523 ± 1795	< 500 ng/mL
B-type natriuretic peptide (pg/mL)	709 ± 990	< 100 pg/mL
Leucocytes (K/uL)	7285 ± 3590	≤10000 K/ul
Fibrinogen (mg/dL)	627 ± 203	< 300 mg/dL

Table 4: Univariate Analysis

Variable	Patients Who Died (n = 8)	Patients Discharged Alive (n = 7)	*P*-Value	RR	CI 95%	*P*-Value
D-dimer (ng/mL)	2801 ± 1884	2279 ± 1805	.59	1	1−1.001	.54
BNP (pg/dL)	922 ± 1373	523 ± 510	.45	1	0.999-1.001	.32
cTnI (ng/dL)	3 patients (43%)	0 patients	.03	27.4	1.20−629.31	.03

Abbreviations: CI, confidence interval; cTnI, cardiac troponin I; BNP, B-type natriuretic peptide; RR, relative risk.

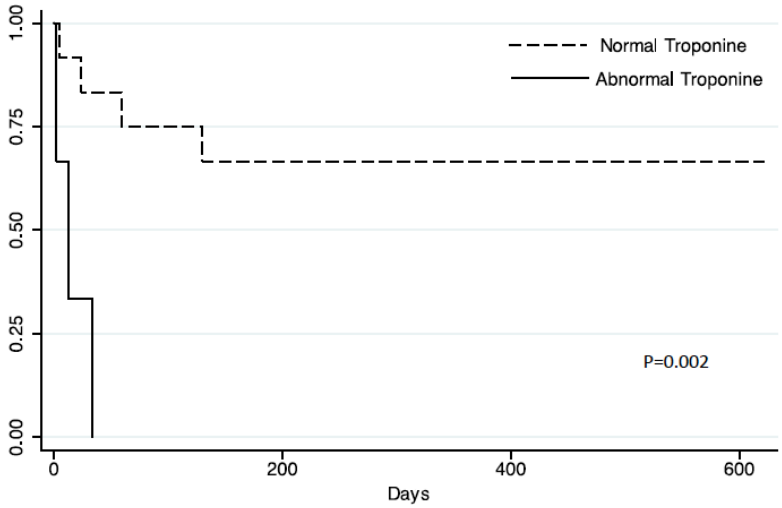

Figure 1: Survival of Data 1: Survival proportions. Kaplan–Meier survival curves in patients with acute aortic dissection with abnormal or elevated cardiac troponin I.

syndrome, including those with preserved ejection fraction. Lastly, a high clinical suspicion associated to critically elevated D-dimer level was a trigger to start a definitive algorithm of imaging investigations for confirmation of diagnosis.

Cardiac troponins are the most sensitive and specific biochemical markers of acute cardiomyocyte injury. In specific cases, however, increased demand ischemia, myocardial strain because of volume and pressure overload or disturbance of cardiomyocyte cell membrane integrity due to systemic inflammatory response or apoptosis as an alternative Mechanisms should be considered[6]. At the present time, irrespective of the clinical condition [6-8], cardiac troponin expression (detectable or elevated concentrations [7]) is related to poor outcome. Currently, no guidelines are available on the treatment of patients with abnormal measurements, with the exception of those with non-ST elevation acute coronary syndromes or pulmonary embolism; furthermore, only treatment of the underlying cause is recommended in such cases [7].

Our present data show that elevated cTnI concentration is a predictor of short-term mortality, in contrast to the results of a French study by Bonnefoy *et*

al. [9]. These authors showed a high prevalence (24%) of increased cTnI above the myocardial infarction threshold. However, in multivariable analysis no relationship with mortality or cardiovascular adverse events was observed. In our patients, considering age, cardiovascular risk factors and clinical and electrocardiographic findings, it is possible that cTnI concentrations were due to the expression of different stages of myocardial infarction type II or I [7, 8]. Several mechanisms, including coronary malperfusion, adrenergic, renin–angiotensin–aldosterone systems and vasopressin activation and/or coronary artery disease (7 patients were> 50 years of age), acute pericardial effusion and global myocardial ischemia have also to be considered. The results suggest that elevated cTnI identifies a subgroup at high risk of in-hospital mortality, as has been observed in other cardiovascular or non-cardiovascular conditions [8]. It is possible that in the setting of AAD, cTnI measurements could establish a fast-track process for early transportation from community or urban hospitals to hospitals with access to surgery or endovascular approaches, thus improving patient care.

BNP, which is secreted by the atria and ventricles, is part of an intricate homeostatic network that regulates the circulating blood volume. BNP concentrations rise under conditions of increased wall stress, resulting from increased preload or afterload or systolic or diastolic dysfunction. Its value in the identification of different ventricular dysfunction stages or mortality risk in adult patients [10, 11] and in pediatric populations [12] has been well established.

Currently, the search for biomarkers in acute aortic syndromes has concentrated towards two groups [13]: a) markers reflecting injury to vascular smooth muscle, the vascular interstitium and the elastic laminae of the aorta; and b) those reproducing secondary phenomena due to exposures of blood to nonintimal vascular surfaces (D-dimer). Frequently, an acute heart failure syndrome is a clinical complication of patients with proximal AAD [4]; BNP could offer a secondary phenomenon biomarker to better understand this complication [10, 11]. Recent evidence linking BNP and AAD showed high plasma concentrations in patients with AAD (667 ± 703 pg/mL) or chronic aneurysm (593 ± 964 pg/mL) compared with a control group [14]. Among these patients, most had aortic regurgitation; however, no information about the clinical characteristics or ejection fraction was reported. In this study BNP values did not distinguish AAD from chronic aneurysm.

Considering the clinical characteristics and echocardiographic findings (Tables **1** and **2**), plasma BNP concentrations identified a subgroup with acute heart failure syndrome and preserved ejection fraction. BNP concentrations established severe ventricular dysfunction and adrenergic, renin–angiotensin–aldosterone systems and vasopressin activation in some patients, but not in others. Although abnormal BNP concentrations could be attributed to heart failure secondary to aortic valve disruption and/or acute ischemia, long standing hypertension and advanced age [15] have to be considered in some cases. Diagnosis of heart failure with preserved ejection fraction could be established through normal ejection fraction and elevated plasma BNP concentrations [16]. Although BPN determination does not replace echocardiography in the diagnostic approach to AAD, adding a rapid plasma BNP assay could be useful for detecting early ventricular dysfunction stages when an echocardiogram is not available or the ejection fraction is normal. Although BNP values had no relationship with in-hospital mortality, our results, to the best of our knowledge, could be the first clinical evidence linking BNP and ejection fraction in AAD patients.

D-dimer is a byproduct of fibrin degradation and a useful biomarker in AAD [3]. If D-dimer concentration is not elevated, we can rule out aortic dissection. The extent of D-dimer elevation reflects the longitudinal extent of AAD, predicts mortality, and possibly differentiates it from myocardial infarction. Considering that D-dimer elevation occurs after the dissection, it is not useful as a predictor [3].

In our study, we observed concentrations above the upper limit of the assay in all patients except one, who had localized intramural hematoma. As previously reported [2], a trend towards higher D-dimer levels in patients who died was detected; however, no relationship with mortality was observed. Our results confirm previous observations [2, 3, 13] and suggest that testing for D-dimer should become part of initial screening of patients with the suspicion of AAD. A negative test result makes the presence of the disease unlikely.

Currently, despite the introduction during the past decade of new imaging modalities, the mortality rate remains high and diagnosis is missed or overlooked in up to 38% of cases presenting to the ED [2]. In our patients, clinical suspicion was driven by chest pain characteristics and chest X-ray abnormalities. Adding a biomarker panel to available noninvasive bedside tests

before more accurate and semi-invasive tests helped us to drive patients into a definitive algorithm of imaging investigations, and identify the main pathophysiologic mechanism and myocardial complications. Although there is no point-of-care biochemical test that can be reliably used to positively identify dissection, a biomarker panel in the ambulance or in community hospitals could accelerate the diagnostic pathway and thereby expedite treatment, ultimately improving patient care and outcomes.

LIMITATIONS

These results can be considered as preliminary only due to the limited sample size. Contemporary cTnI assays are often not elevated during the initial hour after symptom onset [7]. Anatomical extension and D-dimer values were not compared. cTnI as a mortality predictor had wide confidence intervals. Considering the clinical suspicion, an echocardiogram was conducted to identify AAD and not to obtain specific data to establish diastolic dysfunction [16].Previous therapy and characteristics of unstable patients were not obtained. The main limitation – the small sample size – is the rule in previous publications, which can be overcome only by a multicenter study.

CONCLUSION

Serum cTnI measurements could identify a subgroup of patients with AAD at high risk of in-hospital mortality. These findings may suggest this biomarker as a promising tool for rapid risk stratification.

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