Cardiac Troponins as Prognostic Markers in Acute Heart Failure

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ABSTRACT:

BACKGROUND:

Cardiac troponins provide diagnostic and prognostic information in acute coronary syndromes, but their role in acute decompensated heart failure is unclear.

OBJECTIVE:

Describe the association between elevated cardiac troponin levels and adverse events in patients hospitalized with acute decompensated heart failure.

METHODS:

Troponin was measured at the time of admission in 340 patients who were hospitalized to Baghdad Teaching Hospital for acute decompensated heart failure between October 2007 and October 2008. A positive troponin test was defined as a cardiac troponin I level of 0.5 ng/mL or higher.

RESULTS:

Overall, 30 patients (8.8%) were positive for troponin. Patients who were positive for troponin had lower systolic blood pressure on admission [138±30 vs. 144±30 mmHg, P value 0.01], a lower left ventricular ejection fraction [mean 33±15 % vs. 38±16%, P value 0.002] and higher in-hospital mortality [3 patients (10%) vs 8 patients (2.58%), P value 0.001] than those who were negative for troponin. The adjusted odds ratio for death in the group of patients with a positive troponin test was 2.45 (95% confidence interval [CI], 2.14 to 2.79; P<0.001) by the Wald test).

CONCLUSION:

In patients with acute decompensated heart failure, a positive cardiac troponin test is associated with higher in-hospital mortality, independently of other predictive variables.

KEYWORDS: cardiac troponin, heart failure

INTRODUCTION:

Heart failure is currently epidemic in many countries. Most patients with heart failure are admitted to the hospital from the emergency department, where a comprehensive evaluation is required to determine the precipitating cause of the condition. Unfortunately, the definition of a comprehensive evaluation has not been established [(1)]. Since coronary artery disease is the most common cause of heart failure, it is appropriate to evaluate patients with heart failure for myocardial ischemia. Initial evaluation of patients who present with heart failure often includes a focused history, physical examination, electrocardiography, and measurement of biomarkers. Although this approach is well validated for the evaluation of acute coronary syndromes, except for specific laboratory-based investigations, an objective risk-stratification process for the evaluation of acute decompensated heart failure is lacking. The value of measuring serum cardiac troponin when a patient presents with acute decompensated heart failure remains uncertain. Although several limited analyses suggest that an increase in serum cardiac troponin levels is associated with adverse long-term outcomes [(2,5)], the short-term implications are less clearly defined. Some small trials involving patients with heart failure have shown that increases in troponin levels, even in the absence of chest pain or an acute coronary syndrome, correlate with a poor prognosis[(5,7)] and that detectable troponin, at any level, is associated with impaired hemodynamics, a progressive decline in left ventricular systolic function, and shortened survival[(5-9)]. This study was conducted to describe short-term outcomes associated with elevated troponin levels on admission in hospitalized patients with acute decompensated heart failure.

METHODS:

We analyzed outcomes associated with elevated troponin levels in patients with acute decompensated heart failure. Troponin was measured at the time of admission in 340 patients who were hospitalized in Baghdad Teaching Hospital for acute decompensated

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heart failure between October 2007 and October 2008. Ischemic heart failure was defined as the cause of the acute decompensated heart failure if the patient reported a history of coronary artery disease or myocardial infarction and / or electrocardiography showed evidence of that.

Troponin Measurements

We used DECISION Point™ Myoglobin/Troponin I/CK-MB test which is a solid-phase chromatographic immunoassay which can qualitatively detect CK-MB, myoglobin, and cardiac toponin I (cTnI) in heparinized whole blood. It was manufactured by Nanogen Point of Care, Toronto, Canada. If the concentration of cTnI is 0.5 ng/mL, which is the established cut-off value by the manufacturer, or more, a visible pinkish-purple band will appear in the test area.

Statistical Analysis

The primary outcome was in-hospital mortality from all causes, and the secondary outcomes included differences in medical management, and length of stay between the troponin-positive and troponin-negative groups. All outcomes were specified before the data were examined. We also examined associations between therapy and mortality, controlling for troponin in patients who received inotropes or vasodilators, but not both. Analysis of variance, Wilcoxon rank-sum tests, or chi-square tests were used for univariate analyses. All reported P values were two-sided. Because of anticipated differences between troponin-positive and troponin-negative groups with respect to medical history and clinical characteristics at presentation, mortality was adjusted for relevant prognostic factors. Analyses were performed with the use of SPSS (Statistical Package for Social Sciences).

RESULTS:

Troponin Levels and Characteristics of the Patients

Troponin levels were measured at the time of admission in 340 hospitalized patients with acute decompensated heart failure. Overall, 30 patients (8.8%) were positive for troponin on admission. Characteristics of the patients according to whether they were positive or negative for troponin are summarized in Table 1. There were small but significant differences between the two troponin groups. On admission, troponin-positive patients had lower systolic blood pressure and lower ejection fractions but were less likely to have atrial fibrillation.

There were also differences in treatment and resource utilization according to treatment between the two troponin groups (Tables 2 and 3).

In-Hospital Mortality

Overall, troponin-positive patients had a higher rate of in-hospital mortality than troponin-negative patients [3 patients (10%) vs. 8 patients (2.58%), P value 0.001]. Actuarial analysis showed that within 1 day after admission, in-hospital mortality was higher for troponin positive than for troponin-negative patients. The adjusted odds ratio for death among patients with a positive troponin test was 2.45 (95% confidence interval [CI], 2.14 to 2.79; P<0.001). Ischemic heart failure, which was reported as the cause of the acute decompensated heart failure in 56.66% and 51.93% of troponin-positive and troponin-negative patients, respectively, was not a useful discriminator of troponin status, nor was it predictive of mortality. Among troponin-positive patients, mortality was 10.8% for those with ischemic heart failure and 9.4% for those without ischemic heart failure; among troponin-negative patients, mortality was 2.8% and 2.4%, respectively, for these groups.

DISCUSSION:

This study included 340 hospitalized patients with acute decompensated heart failure in whom troponin was measured. Of these patients, 8.8% were found to be positive for troponin, including those with and those without a history of coronary artery disease or myocardial infarction. Like patients presenting with an acute coronary syndrome, patients presenting with acute decompensated heart failure and a positive troponin status were found to be a high-risk group. Patients in this group, as compared with those who were negative for troponin, required longer hospitalization and had a higher risk of in-hospital death, even after adjustment for other risk factors. These results suggest that measurement of troponin adds important prognostic information to the initial evaluation of patients with acute decompensated heart failure and should be considered as part of an early assessment of risk. Since patients who are positive for troponin have a disproportionately high mortality, an association independent of other well-validated risk factors for acute decompensated heart failure, the results of troponin tests should be parts of decisions that are made with respect to triage and management. Although we did not study differential management, this study may indicate that patients with an increased risk of death should undergo more intensive cardiovascular monitoring; they may require admission to a critical care unit or cardiac telemetry if feasible. The study findings add to the existing risk-stratification data for predicting the short-term risk of death among patients with acute decompensated heart failure. Patients with an initial

blood urea level of more than 70 mg per deciliter, systolic blood pressure of less than 115 mm Hg, or a creatinine level of more than 2.75 mg per deciliter have high short-term mortality, exceeding 24% if all three factors are present[10]. Since these mortality

Table 1: Patient Characteristics and Treatment According to Troponin Status.

	Positive for Troponin	Negative for Troponin	
Characteristic	(N = 30)	(N = 310)	P Value
Age (yr)	65.3±14.0	64.9±14.0	0.05
Male sex (% of patients)	16 (53.33)	145 (46.77)	0.01
Heart failure due to ischemia (% of patients)	16 (53.33)	142 (45.8)	0.01
Hospitalization for heart failure within the past 6 mo	10 (33.33)	121 (39.03)	0.02
(% of patients)			
Medical conditions (% of patients)			
Atrial fibrillation	7 (23.33)	93 (30)	0.001
Coronary artery disease	17 (56.66)	161 (51.93)	0.02
Prior myocardial infarction	12 (40)	96 (30.96)	0.01
Prior coronary artery disease or myocardial infarction	18 (60)	171 (55.16)	0.02
Chronic obstructive pulmonary disease or asthma	8 (26.66)	103 (33.22)	0.01
Ventricular tachycardia or ventricular fibrillation	2 (6.66)	28 (9.03)	0.04
Diabetes mellitus	13 (43.33)	130 (41.93)	0.19
Hypertension	22 (73.33)	235 (75.8)	0.54
Hyperlipidemia	12 (40)	109 (35.16)	0.03
Smoking	6 (20)	40 (12.9)	0.01
Peripheral vascular disease	6 (20)	47 (15.1)	0.03
Condition requiring placement of a pacemaker	3 (10)	53 (17.09)	0.01
Symptoms on presentation (% of patients)			
Dyspnea	26 (86.66)	288 (92.9)	0.01
Leg edema	18 (60)	208 (67.09)	0.01
Fatigue	10 (33.33)	99 (31.9)	0.66
Pulmonary edema	26 (86.66)	267 (86.12)	0.32
Rales	23 (76.66)	217 (70)	0.03
Initial clinical findings			
Mean systolic pressure (mm Hg)	138±30	144±30	0.01
Left ventricular ejection fraction			
Mean (%)	33±15	38±16	0.002
<40% or moderate or severe (% of patients)	59	50	0.001
Initial electrocardiogram			
QRS duration (msec)	108.4±36.5	112.8±40.0	0.04
QRS >120 msec (% of patients)	8 (26.66)	105 (33.87)	0.01

Table 2: Patient Treatment According to Troponin Status.

Characteristic	Positive for Troponin	Negative for Troponin	P Value
Interval to first diuretic (hr)	(N = 30)	(N = 310)	
Median	2.4	2.2	0.04
Interquartile range	1.0−6.8	1.0−5.1	
Diuretics (% of patients)	27 (90)	295(95.16)	0.02
Interval to first vasoactive agent (hr)			
Median	6.3	6.5	0.785
Interquartile range	1.3−22.5	1.2−29.6	
Inotropes (% of patients)			
Any	6 (20)	28 (9.03)	0.001
Dobutamine	3 (10)	18 (5.8)	0.002
Dopamine	4 (13.33)	19 (6.12)	0.001
Nitroglycerin (% of patients)	6 (20)	34 (10.69)	0.002

Table 3: Resource Utilization According to Troponin Status.

	Positive for Troponin	Negative for Troponin	
Resource	(N = 30)	(N = 310)	P Value
Stay in coronary care unit			
Any time — no. (%)	13 (43.3)	51 (16.45)	0.001
Median days (IQR)	2.7 (1.4−4.8)	2.1(1−3.9)	0.003
Adjusted mean days	3.7	3.2	0.005
Stay in hospital — days			
Median stay (IQR)	6.1 (3.1−9.2)	5.1 (2.7−7.6)	0.002
Adjusted mean stay	6.7	5.8	0.003

rates are higher than those that are associated with most episodes of acute myocardial infarction, a more aggressive therapeutic approach is justified. A positive troponin status adds incremental prognostic information to that obtained from vital signs and other laboratory data. Conversely, we found that a negative troponin status was associated with a short-term mortality rate that was nearly two thirds lower than the rate with a positive troponin level. Although the absence of high-risk predictors does not mean low risk, the absence of detectable troponin may be helpful in planning management. When considered in association with other predictors of low risk, a negative troponin test may aid in the identification of patients for whom less intense monitoring and therapy are appropriate. Few studies have examined predictors of low risk in patients with acute decompensated heart failure. In a study of patients with acute decompensated heart failure who were in an emergency department observation unit[11], an elevated blood pressure (>160 mm Hg) or a negative troponin test was associated with discharge from the hospital within 24 hours and an absence of adverse outcomes within 30 days. Another analysis showed that a blood urea level of less than 55 mg per deciliter was associated with successful treatment in a short-stay unit [12]. These analyses suggest that initial blood pressure, renal function, and troponin status are the most useful risk-stratification data in patients presenting with acute decompensated heart failure. In the present study, patients who were positive for troponin took more time to receive diuretics, although they had more severe symptoms and had lower left ventricular ejection fraction. This may require reevaluation of the management steps done for patients so that those patients with the more severe symptoms receive essential treatments (including diuretics) relatively early. In the present study, patients who were positive for troponin required longer hospitalization and greater use of

resources. Since hospitalization and length of stay in an intensive care unit are important determinants of cost, if the cost is taken into consideration, early identification of patients who will require greater resources could allow early implementation of aggressive therapy. The impact of early risk stratification has been supported in other studies of acute decompensated heart failure. In the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) trial[13], simply establishing an early, accurate diagnosis of heart failure decreased both length of stay and costs. Early risk stratification may help identify patients who are likely to receive the greatest benefit from early intensive therapy. In an analysis of subjects in the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, You et al. evaluated cardiac troponin I and mortality in 2025 patients who were hospitalized with heart failure[14]. They reported that levels of cardiac troponin I higher than 0.5 μg per liter, which were present in 34.5% of the patients, were an independent predictor of short-term death, with a dose–response relationship. Smaller studies of patients with heart failure have shown similar implications of elevated troponin levels with respect to short-term morbidity and mortality. In 98 consecutive patients admitted for worsening heart failure, in-hospital death from cardiac causes occurred in 10 of 45 patients (22%) who had cardiac troponin T levels higher than 0.033 μg per liter, as compared with 4 of 53 (8%) who had lower cardiac troponin T levels ($P = 0.04$)[3]. Cardiac troponin T and brain natriuretic peptide, when considered together, identified patients at low risk (3%), intermediate risk (11%), and high risk (31%) for in-hospital death ($P = 0.006$). A study of 159 patients with acute decompensated heart failure showed that 24 patients (15%) had high levels of troponin[16]. Of these patients, 20.8% died during hospitalization or had refractory heart failure, as compared with 3.7% of those with low troponin levels (odds ratio, 6.8; 95% CI, 1.5 to 31.2). Finally, in a subgroup analysis of 133 patients in the Randomized Intravenous TeZosentan 4 (RITZ-4) study, which involved patients with acute decompensated heart failure or an acute coronary syndrome, an elevated cardiac troponin I level before randomization was associated with an increased rate of the composite end point of death, worsening heart failure, recurrent ischemia, or new myocardial infarction within 72 hours (odds ratio, 1.15; 95% CI, 1.01 to 1.32)[17]. In hospitalized patients with acute decompensated heart failure, but without classic signs of acute myocardial infarction, troponin is correlated with several physiological variables [4,18]. In 26 hospitalized patients with heart failure, a significant correlation was found between cardiac troponin T status and the left-ventricular-mass index[4]. In a study involving 40 hospitalized patients with heart failure[18], troponin status was correlated with blood pressure and the presence or absence of left ventricular hypertrophy as assessed by electrocardiography. Several hypotheses, including sub-endocardial ischemia due to a mismatch between myocardial oxygen supply and demand, have been proposed as explanations for these associations, but the mechanisms by which these features cause increases in troponin levels in the absence of an acute coronary syndrome remain uncertain. An elevation in cardiac troponin can indicate the presence of myocyte injury or death[19]. This model recognizes progressive myocyte loss as a prominent pathophysiological mechanism in the evolution of cardiac dysfunction and acute decompensated heart failure[20]. The pathophysiological factors that are thought to be responsible for ongoing myocyte injury or cell death include excessive adrenergic stimulation through renin, angiotensin, aldosterone, or endothelin signaling pathways, abnormalities in calcium handling, inflammatory cytokines, nitric oxide, and oxidative and mechanical stress[6]. Some guidelines for the evaluation of an acute coronary syndrome recommend that levels of cardiac troponin and brain natriuretic peptide or N-terminal pro–brain natriuretic peptide be used for prognosis and risk stratification. Current guidelines for the evaluation of heart failure do not mention troponin and recommend the measurement of brain natriuretic peptide only in cases in which the diagnosis is uncertain[21]. Our data suggest that the measurement of troponin levels in patients who present with heart failure provides independent prognostic information regarding in-hospital death and other clinical outcomes and can be useful for risk stratification of such patients. The current study has several limitations. Because troponin was measured only at the time of admission to the hospital, we cannot comment on the number of patients with an acute myocardial infarction, since a typical rise and fall of cardiac biomarkers was not recorded. Second, the prognostic information that can be gained from an analysis of the interaction of troponin with other biomarkers, such as brain natriuretic peptide, was not explored in this study. Because the diagnosis was not objectively ascertained, some patients with both heart failure and an acute coronary syndrome may have been included in our analysis. However, when only data from patients who were categorized as having non ischemic heart failure were analyzed, troponin levels

retained their prognostic significance. Consequently, the study findings may under-represent adverse outcomes, with possible prognostic implications, since others have found that mortality at 30 days may exceed in-hospital mortality[14].

CONCLUSION:

In hospitalized patients with acute decompensated heart failure, a positive troponin test is associated with more frequent adverse events, including increased in-hospital mortality, independently of treatment and other prognostic variables. Patients with heart failure who are positive for troponin require greater use of hospital resources, including longer stays in the hospital and in the intensive care unit.

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