High-Sensitivity Troponin I and the Risk of Flow Limiting Coronary Artery Disease in Non-ST Elevation Acute Coronary Syndrome (NSTEMI-ACS)

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Abstract

Background: In acute coronary syndrome, elevated troponins are associated with worse clinical outcomes. We examined the relationship between the level of troponin elevation and the presence of a flow-limiting lesion for patients with no history of coronary disease admitted with NSTEMI-ACS.

Methods: From January of 2010 until April of 2013, 561 patients received coronary angiography for new-onset NSTEMI-ACS. The Mann-Whitney Test, chi-square test, and Spearman correlation were used to examine relationships. Inferences were made at the 0.05 level of significance. The independent samples t test and the chi square test were used to identify predictors of LV systolic dysfunction- LVSD.

Results: The 430 patients with a flow-limiting coronary lesions had a higher troponin I level than the 131 patients without obstructive coronary disease (5.69 ng/ml vs. 2.85 ng/ml, $p=0.002$). Further, within troponin categories, those in the greater than 5.0 ng/ml group were more likely to have angiographically significant CAD than those in the less than 0.5 ng/ml group ($p=0.012$). Elevated troponins were also associated with increased thrombus burden, worse systolic function, higher complexity of the lesions, and worse post intervention TIMI flow. Cardiac troponin $>5\text{ng/ml}$ [odds ratio=2.13 (95%CI=1.22 to 3.70) $p=0.008$] and DM [odds ratio=1.74 (95%CI=1.02 to 2.97) $p=0.042$] were independent predictors of LVSD. Advanced LM disease and age were marginally significant.

Conclusion: The degree of cardiac troponin I elevation should be incorporated into the risk stratification models of NSTEMI-ACS to promptly triage high-risk patients to early

invasive strategies and tailored anticoagulant therapy to reduce troponin elevation and improve myocardial perfusion.

Background

Cardiac troponin is the main biomarker of myocardial ischemia. In acute coronary syndrome, elevated troponin levels are associated with complex obstructive coronary anatomy and impaired myocardial tissue perfusion. Elevated troponins can identify high-risk patients with non-ST elevation acute coronary syndrome (NSTEMI), who may benefit from early invasive management. However, the degree of troponin elevation has not been incorporated in risk stratification models for NSTEMI. To triage patients for conservative versus invasive management strategies, we need to define the significance of the magnitude of troponin elevation following NSTEMI (1).

NSTEMI is the most common form of acute coronary syndrome. Troponin elevation signifies a delayed presentation in ST elevation MI not so for NSTEMI. The determination of ischemic injury timing becomes more challenging when NSTEMI patient present with variable levels of troponin elevation.

Thus, we examined the relationship between troponin levels and the extent of coronary disease and myocardial dysfunction, as assessed by coronary angiography, in a subset of patients with no history of coronary disease admitted with NSTEMI.

Methods

Study design

This is a retrospective study of a cohort admitted to a university-affiliated teaching hospital with highly specialized cardiovascular care over a period of 40 months. The data for this study were obtained from the National Cardiovascular Data Registry (NCDR) database and electronic chart review of study participants.

Serum cardiac troponin levels were measured using a high-sensitivity enzyme-linked immune-absorbent assay kit (VITROS® Troponin I ES Assay, © Ortho Clinical Diagnostics, Johnson & Johnson -Hong Kong- Ltd. 2003-2014). A level greater than 0.033 ng/ml is considered above the reference range and represents a positive test value. The highest troponin I level prior to coronary angiography was used in the analyses.

Selection of study participants

The study investigated the association of cardiac troponin I levels and the presence of a flow-limiting coronary arterial lesion; a flow-limiting lesion was defined as an angiographically significant coronary lesion warranting percutaneous and/or surgical revascularization. The study only included patients with new-onset (de novo) NSTEMI. Patients with a history of coronary artery disease, heart failure, and cardiac bypass were excluded.

Study Objectives and Data Analysis

In addition to determining the association between cardiac troponin I levels and the presence of flow-limiting coronary artery disease, the study also examined the relationship between cardiac troponin I levels and various other factors, including vascular anatomy, lesion complexity, success of percutaneous intervention (based on the post-intervention Thrombolysis In Myocardial Infarction - TIMI - study grading system of the coronary blood flow), and incidence of Left Ventricular Systolic Dysfunction (LVSD), defined by an ejection fraction of less than 40% on left ventriculogram, in de-novo NSTEMI-ACS patients.

Means and standard deviations are reported for continuous variables, and counts and percents for categorical variables. The independent samples Mann-Whitney Test (two groups), Kruskal-Wallis Test (three groups), one-way analysis of variance (ANOVA) with Least Significance Difference post hoc test, chi square test, and Spearman correlation were used to examine relationships. Inferences were made at the 0.05 level of significance with no corrections for multiple comparisons. Multivariable logistic regression was used to determine if troponin is an independent risk factor for LVSD. Analyses were conducted using IBM SPSS Statistics 22.0 (IBM, Armonk, NY).

Results

Baseline characteristics

From January 2010 through April 2013, 561 patients received coronary angiography for new onset NSTEMI-ACS. Of this total, 485 (86.5%) had left ventricular functional assessment at the time of cardiac catheterization. All patients were managed invasively.

Patients were divided into three groups according to the degree of troponin I elevation (mild <0.5 ng/ml [$n = 167$], moderate $0.5-5$ ng/ml [$n = 263$], and high >5 ng/ml [$n = 131$]). Table 1 shows that age differed among the three groups ($p = 0.008$): the moderate group was older than the mild group (mean age = 66.3 ± 13.9 vs. 62.2 ± 12.5) but not the high groups (64.1 ± 13.3).

Table 1. Characteristics of troponin groups.

Cardiac Troponin Groups	Mild c-Tn n = 167	Moderate c-Tn n = 263	High c-Tn n = 134	p value
Age (Years)	62.2 (SD=12.5)	66.3 (SD=13.9)	64.1 (SD=13.3)	0.008 ^a
Gender				0.18
Male	93 (55.7%)	128 (48.7%)	75 (55.9%)	
Female	74 (44.3%)	135 (51.3%)	59 (44.1%)	
Race				0.005 ^b
Caucasian	111 (66.5%)	205 (78.2%)	106 (81.5%)	
African American	54 (32.3%)	55 (21%)	23 (17.7%)	
Asian	2 (1.2%)	1 (0.4%)	1 (0.8%)	
Hispanic	0 (0%)	1 (0.4%)	0 (0%)	
Euro Score	4.38 (SD=2.8)	5.44 (SD=3.3)	5.98 (SD=6.1)	0.003 ^c
Diabetes Mellitus	51 (30.5%)	79 (30%)	38 (29%)	0.96
DM Therapy	6 (11.8%)	6 (7.7%)	1 (2.6%)	0.54
Diet	21 (41.2%)	37 (47.4%)	22 (57.9%)	
Oral	18 (35.3%)	28 (35.9%)	13 (34.2%)	
Hypoglycemic	6 (11.8%)	7 (9.0%)	2 (5.3%)	
Insulin Therapy				
No Therapy				
GFR <60 (estimated GFR)	37 (22.2%)	41 (15.6%)	30 (22.4%)	0.12
Intervention:				0.28
PCI	93 (55.7%)	132 (50.2%)	76 (58.0%)	
IABP	160 (96.8%)	257 (97.7%)	128 (97.7%)	0.49
Anticoagulation				0.01 ^d
UH	59 (35.4%)	92 (35.7%)	64 (48.2%)	
LMWH	26 (15.6%)	43 (16.4%)	17 (12.7%)	0.29
Bivalirudin	51 (30.5%)	66 (25.1%)	33 (24.6%)	0.34
Direct Thrombin Inhibitor	42 (25.2%)	73 (27.8%)	46 (34.5%)	0.12
PostOp complications:				0.39
Cardiogenic Shock	1 (0.6%)	5 (1.9%)	3 (2.3%)	
Heart Failure	1 (0.6%)	2 (0.8%)	1 (0.8%)	0.98
Stroke	2 (1.2%)	0 (0.0%)	2 (1.5%)	0.08
Hemodialysis	0 (0.0%)	1 (0.4%)	2 (1.5%)	0.17
Bleeding (within 72 hrs)	5 (3.0%)	7 (2.7%)	4 (3.1%)	0.97
Hospitalization (Days)	4.15 (SD=2.9)	4.53 (SD=3.3)	5.36 (SD=5.3)	0.12

Abbreviations - GFR: glomerular filtration rate; PCI: percutaneous coronary artery intervention; IABP: intra-aortic balloon pump; UH: unfractionated heparin; LMWH: low molecular weight heparin

^a The moderate group was older than the mild group (mean age = 66.3±13.9 vs. 62.2±12.5) but not the high group (64.1±13.3).

^b Patients were more likely to be Caucasian as troponin categories increased (66.5% for the <0.5 ng/ml group, 78.2% for the 0.5-5 ng/ml group, 81.5% for the >5.0 ng/ml group) and less likely to be African American as troponin categories increased (32.3% for the <0.5 ng/ml group, 21.0% for the 0.5-5 ng/ml group, 17.7% for the >5.0 ng/ml group); p value for chi square test excludes Asians and Hispanics due to low counts.

^c The moderate and high groups had a higher euroscore than the mild group (mean euroscore = 5.44±3.3 and 5.98±6.1 vs. 4.38±2.8).

^d Patients were more likely to receive unfractionated heparin as troponin categories increased (63.4% for the <0.5 ng/ml group, 69.7% for the 0.5-5 ng/ml group, 84.2% for the >5.0 ng/ml group).

Patients were *more likely* to be Caucasian as troponin categories increased (66.5% for the <0.5 ng/ml group, 78.2% for the 0.5-5 ng/ml group, 81.5% for the >5.0 ng/ml group) and *less likely* to be African American as troponin categories increased (32.3% for the <0.5 ng/ml group, 21.0% for the 0.5-5 ng/ml group, 17.7% for the >5.0 ng/ml group).

The moderate and high groups had a higher euro-score than the mild group (mean euro-score = 5.44 ± 3.3 and 5.98 ± 6.1 vs. 4.38 ± 2.8 $p = 0.003$). Patients were more likely to have been treated with unfractionated heparin as troponin levels increased (63.4% for the <0.5 ng/ml group, 69.7% for the 0.5-5 ng/ml group, 84.2% for the >5.0 ng/ml group ($p = 0.01$)).

Primary outcomes

Patients with flow-limiting coronary lesions ($n = 430$) had higher mean troponin I levels than patients without obstructive coronary disease ($n = 131$) [5.69 ± 12.57 ng/ml vs. 2.85 ± 5.76 ng/ml, $p = 0.002$]. More importantly, the proportion of patients with angiographically significant CAD increased as troponin levels increased (70.7% for the <0.5 ng/ml group, 77.2% for the 0.5-5 ng/ml group, 83.2% for the >5.0 ng/ml group ($p = 0.038$)) (Figure 1).

Figure 1. Troponin groups and the presence of flow-limiting CAD.

Secondary outcomes

Elevated troponin levels were associated with increased thrombus burden (8.34 ± 15.44 ng/ml for patients with intracoronary thrombus vs 5.29 ± 13.11 ng/dl for those without thrombotic lesions, $p = 0.001$), worse systolic function (6.62 ± 9.77 ng/dl for those with LVEF <40% compared to 4.42 ± 8.70 ng/dl for those with preserved LV function, $p = 0.003$), higher complexity of the lesions (patients with high - type C – lesions, per AHA/ACC classification, had mean troponin level of 8.38 ± 17.71 ng/ml vs 3.44 ± 7.7 ng/ml for those with non-high - type C - lesions, $p < 0.001$), and worse TIMI flow (patients with TIMI grade 0 flow post-intervention had mean troponin of 49.1 ± 71.99 ng/ml vs 5.16 ± 10.41 ng/ml for those with TIMI grade 3 flow, $p = 0.017$) post intervention.

Patients with LVSD were more likely to be older, have diabetes (DM), have more advanced left main coronary disease, and have cardiac troponin levels greater than 5 ng/ml. When the statistically significant predictors for LVSD ($p < 0.05$) from the univariate analysis were entered into a multivariable logistic regression model of analysis, cardiac troponin levels $> 5 \text{ ng/ml}$ [odds ratio = 2.13 (95%CI = 1.22 to 3.70) $p = .008$] and DM [odds ratio = 1.74 (95%CI = 1.02 to 2.97) $p = .042$] were found to be independent predictors for LVSD (Table 2). Age and left main coronary disease almost reached statistical significance.

Table 2. Independent predictors of LVSD.

Variables	Odds Ratio	95% Confidence Interval	p-value
C-Tn	2.13	1.22 to 3.70	0.008
DM	1.74	1.02 to 2.97	0.042
Age	1.02	1.00 to 1.04	0.054
LMCD	1.93	0.99 to 3.74	0.053

Discussion

The classic definition of myocardial infarction (MI) by the World Health Organization (WHO) is based on symptoms, electrocardiographic abnormalities, and elevated cardiac enzymes. However, over the past decade the Global MI Task Force has integrated new elements to the definition of MI based on the mechanisms of myocardial injury. Obstructive coronary lesion is the most clinically relevant form of injury and results in troponin release (2,3).

Routine detection of troponin levels using high sensitivity assays that yield a continuous gradient in apparently normal subjects makes it difficult to differentiate myocardial necrosis related to plaque rupture in ACS patients from necrosis in non-ACS patients. Newby et al. discussed the impact of improved test sensitivity on the interpretation of cardiac troponin and emphasized the value of pretest probability when interpreting troponin elevation (3).

The major findings of the present study were: 1) obstructive coronary lesions (flow-limiting) related myocardial injury resulted in greater troponin elevation when compared to other etiologies of myocardial injury, 2) in the context of a flow-limiting coronary artery disease, the degree of troponin elevation implies high-risk features for invasively managed NSTEMI-ACS patients related to their vascular anatomy, lesion complexity, and the eventual success of percutaneous intervention, and 3) regardless of the mechanism of troponin release, a high level of troponin I was an independent predictor of LVSD in de novo NSTEMI-ACS patient population.

Troponin I and the presence of hemodynamically significant (flow-limiting) coronary artery disease

Troponin I is independently associated with in-hospital mortality in NSTEMI-ACS patients. Antman et al. reported that short-term mortality increases with rising levels of cardiac troponin I, and the highest increment in mortality was observed when levels are > 5 ng/ml (4). Additionally, Kleiman *et al.* (5) demonstrated that invasive management could improve mortality risk in a NSTEMI-ACS subset of patients with positive cardiac biomarkers.

Interestingly, analyses from the ACTION Registry (NCDR published data) indicate that single vessel flow-limiting coronary artery disease was the most common finding identified by cardiac angiography, and that percutaneous coronary artery intervention was the most common mode of treatment in invasively managed NSTEMI-ACS patients (6,7). We previously reported that the likelihood of hemodynamically significant coronary artery disease in invasively managed NSTEMI-ACS patients when the troponin level is more than 5 ng/ml was significantly higher than that in individuals with a lower troponin level (8).

Concern about elevated troponin was reflected in the guidelines that recommend incorporating risk stratification models (TIMI risk score, Grace risk score, or PURSUIT risk model) to the management strategy for NSTEMI-ACS patients (9). However, none of these models has integrated the additive value of the degree of troponin elevation in their risk-score calculation (10-12).

Being closely associated with mortality and the presence of flow-limiting coronary artery disease, the degree of cardiac troponin elevation should be scored properly in risk stratification modules and contemplated in the timing for invasive management of those presenting with NSTEMI-ACS.

Troponin I and percutaneous coronary artery interventions in NSTEMI-ACS

In the setting of ACS, elevated troponin is associated with impaired myocardial tissue perfusion and lower rate of coronary recanalization after percutaneous coronary intervention (13-18). Troponin elevation also signifies adverse short and long-term prognosis in this patient population (19-22). Similarly, in our study, we observed that elevated troponin was associated with increased thrombus burden, worse systolic function, higher complexity of the lesions, and worse post intervention TIMI flow.

Subgroup analysis of ACS clinical trials showed that elevated troponin identified a subset of NSTEMI-ACS patients who would derive benefit from the addition of antithrombotic therapy and intravenous anti-platelet therapy to a conventional regimen. This is gained via reduction of thrombus formation at the culprit lesion and facilitation of distal micro-thrombi resolution (23-26).

The current guidelines identify the value of elevated troponin when choosing anti-thrombotic therapy, with or without invasive strategy. However, there is no consensus

regarding a clinically relevant level of troponin that will provide the most benefit to invasively managed NSTEMI-ACS patients.

Predictors of left ventricular systolic dysfunction (LVSD) in NSTEMI-ACS:

Ischemic cardiomyopathy is the main etiology for LVSD in the United States and North America. The development of LVSD following ACS significantly worsens short- and long-term prognosis (17,27,28).

We targeted patients with no prior history of coronary artery disease, heart failure or cardiac surgery who were referred for coronary angiograms for a new diagnosis of NSTEMI-ACS to assess the predictors of LVSD. Cardiac troponin I levels >5 ng/ml were the most important predictor of LVSD following a new onset NSTEMI-ACS in patients with no prior history of coronary artery disease (Table 2).

The previous ACC/AHA (2012-2013) guidelines recommended early invasive strategy in NSTEMI-ACS patients with a systolic ejection fraction of less than 40% (9). The timing of this recommendation was revised in the most recent guidelines (29).

Using clinical characteristics and risk factors at admission to identify risk of heart failure influences therapeutic decisions and permits an individualized approach to each patient. LVSD is a major concern among invasively managed ACS patients and imposes a large economic burden on the health care system. Troponin level could be used as a cost-effective tool to stratify patients who are at risk of LVSD, allowing appropriate early measures to improve their outcome.

Troponin I and Early versus Delayed Intervention in NSTEMI-ACS

The optimal timing of angiography has not been conclusively established in NSTEMI-ACS (29). In earlier randomized trials, better outcomes were obtained with an early invasive strategy in patient with troponin I elevation when compared to those with normal troponin levels (30). In other reports, investigators found that early invasive intervention was not superior to a delayed invasive approach in NSTEMI-ACS patients for the prevention of death or myocardial infarction, even in those with positive cardiac biomarkers (31, 32).

The most notable beneficial effect of an invasive versus a conservative strategy in the management of NSTEMI-ACS patients was demonstrated in the reduction of recurrent MI, although the effect on mortality was seen in high-risk patients only (29,33). Prospective trials to determine a clinically relevant troponin level that will determine the timing of an invasive strategy and its impact on patients' outcomes are yet to be conducted (1).

Study Limitations

Our cohort study is subject to the standard bias associated with retrospective observations including selection bias, incomplete records, and loss of patients' long-term follow-up.

The results of our study were derived from a single-center using a particular assay kit for serum troponin testing; thus, generalizability is a concern. Follow-up of cardiac

events, recurrent hospitalizations, and long-term adverse events was beyond the scope of our study.

Conclusion

The degree of cardiac troponin I elevation should be incorporated into the risk stratification models of NSTEMI-ACS to promptly triage high-risk patients to early invasive strategies and tailored anticoagulant therapy to reduce troponin elevation and improve myocardial perfusion.

Acknowledgement

The authors of the study would like to thank Melissa Hodges (Cardiac Clinical Nurse Specialist) for her help with data abstraction.

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