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Original Contribution

The meaning of elevated troponin I levels: not always acute coronary syndromes☆

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ABSTRACT

Background: Troponin elevation can be caused by etiologies other than acute coronary syndromes (ACS). Our hypothesis was that elevated troponins occur more frequently in non-ACS cases but that ACS cases (type 1 ST-elevation myocardial infarction [STEMI] and type 1 non-STEMI [NSTEMI]) have significantly higher troponin elevations.
Methods: This was a cross-sectional cohort analysis of a random subset of all patients with elevated troponins (defined as ≥0.06 ng/mL) over a 1-year period from July 2013 to June 2014. The first positive troponin I and the peak were used in this study. All included patients had medical record reviews looking for whether our cardiologists or hospitalists attributed the elevated troponin to an ACS (NSTEMI or STEMI) or non-ACS cause. Non-ACS causes were categorized as infection, cancer, renal diseases, cardiovascular disease, pulmonary disease, trauma, cardiac arrest, neurologic disease, hypertension, or other. Data were extracted by 2 investigators on the cause of the elevated troponin. Three sessions to educate data extractors were arranged and methods of data extraction discussed, then a 5% sample was reevaluated by the other extractor to determine interrater agreement measures. Parametric data were evaluated with *t* test and analysis of variance. Dichotomous variables were compared using χ^2 test. Troponin data were evaluated using nonparametric Kruskal-Wallis or Mann-Whitney *U*. A logistic regression model was created with variables selected a priori to evaluate the predictive ability of these variables in differentiating ACS vs non-ACS causes of elevated troponin.
Results: We evaluated 458 randomly selected patients from 1317 unique cases of all patients with initial elevated troponins at least 0.06 mg/mL during the study period. There was 84% interrater agreement in the 5% sampling. Seventy-nine percent had a non-ACS cause of elevated troponin, and the average initial positive troponin I level was significantly lower in the non-ACS cases (0.14; 95% confidence interval [CI], 0.08-0.37) than those with documented STEMI (10.2; 95% CI, 0.75-20.1) or NSTEMIs (0.4; 95% CI, 0.13-1.7). In the non-ACS group, the median initial troponin was 0.14 ng/mL (0.08-0.37 ng/mL). Peak troponin levels were highest in STEMI, next NSTEMI, and lowest in non ACS causes. The most frequent subgroups in the non-ACS group were non-ACS cardiovascular, infectious, renal, or hypertensive causes. In a linear regression model adjusting for age and sex, higher troponin levels had higher odds of being related to ACS causes (adjusted odds ratio, 1.4; 95% CI, 1.2-1.6) than non-ACS causes.
Conclusion: The etiology for most initial elevated troponin I levels in a randomly selected population is the result of non-ACS causes. As initial + troponin levels increased, they were more likely associated with ACS causes than with non-ACS causes. Average initial + and peak troponin values were highest in STEMIs, next highest in NSTEMIs, and lowest overall in non-ACS causes.

1. Introduction

Myocardial infarction (MI) is an important entity to diagnose in the emergency department (ED). Troponin tests have classically been used to diagnose MI, and current assays are more sensitive such that troponin may be elevated from several etiologies including those that are primarily noncardiac [1,2].

The most recent definition of MI was updated in 2012 and categorizes MIs into 5 different types. The first 2 types are most relevant to this article and will be briefly defined here. *Type 1 MI* is defined as a spontaneous MI related to atherosclerotic plaque rupture, ulcerations, fissuring, erosion, or dissection. It includes type 1 ST-elevation myocardial infarction (STEMI) and type 1 non-STEMI (NSTEMI). *Type 2 MI* is defined as secondary to an ischemic imbalance and involves a condition other than coronary artery disease such as spasm, hypotension, tachyarrhythmias, and several other causes [3] including atrial fibrillation [4].

Although elevated troponin levels are highly sensitive diagnostic indicators of myocardial injury, there are other causes of elevated levels.

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Previous studies have evaluated the etiologies of elevated troponins with normal cardiac catheterizations and found tachycardia, myocarditis, and congestive heart failure to be the most frequent causes. These studies identified the patient population through searching in the catheterization database for patients with normal angiograms and positive troponins [1,2]. Previous studies have found that some patients with elevated troponins did not have an acute coronary syndrome (ACS) cause. A previous study by Khan et al [5] showed that of 102 patients with elevated troponin I values, 35 patients did not have a final diagnosis of ACS. A previous study by Ilva et al [6] noted that only 83% of patients diagnosed as ACS by ED physicians actually had a diagnosis of ACS at discharge. Another study looked at all elevated troponins in their hospital system and found only 53% to have a diagnosis of ACS [7].

Our present study looked to evaluate the significance of an elevated initial and peak troponin I level at least 0.06 ng/mL in the undifferentiated hospital population, looking for the differences in rates of type 1 STEMI, type 1 NSTEMI, vs type 2 MIs present among this population.

Our hypothesis was that elevated troponins occur more frequently in non-ACS cases but that ACS cases (type 1 STEMI and NSTEMI) have significantly higher troponin elevations. In addition, we sought to describe the group of undefined non-ACS causes of elevated troponins. We also looked at troponin peaks and compared the groups for these values.

2. Methods

This was a cross-sectional cohort analysis of a random subset of all patients with elevated troponins (defined as ≥0.06 ng/mL) over a 1-year period from July 2013 to June 2014 in those 18 years or older. The original set had 1317 unique patients with an elevated troponin I. Medical record reviews were done on a randomized subset of those with elevated troponin I (n = 458/1317; 35%) looking for whether the cardiologists or admitting hospitalist at our institution attributed the elevated troponin to an ACS (type 1 STEMI or NSTEMI) vs a non-ACS cause.

In our institution, the troponin I is measured on serum specimens. The cutoff for a positive is 0.06 mg/mL. The first positive ≥0.06-mg/mL level drawn and the peak were used for our study purpose; therefore, our levels are not necessarily the first troponin if it were negative. Inclusion criteria were patients 18 years or older with elevated troponins during the period July 2013 to July 2014 (13-month period). Non-ACS causes were categorized as infection, cancer-related, renal diseases, cardiovascular disease (including heart failure), pulmonary disease, trauma, cardiac arrest, neurologic disease, or hypertension/hypertensive emergency. The etiology was determined by reviewing the discharge summary and seeking the admitting team's final diagnosis. The initial positive and peak troponin level were compared in STEMI vs NSTEMI vs non-ACS causes as well.

Data were extracted by 2 investigators on the cause of the elevated troponin I. Three sessions to educate data extractors were arranged and methods of data extraction discussed, then a 5% sample was reevaluated by the other extractor as an agreement measure. Agreement was determined on this 5% sample.

Demographic data were obtained including age and sex, and comparisons were made between types of ACS (STEMI, NSTEMI) or non-ACS causes of elevated troponins.

Data collected included whether the initial troponin I elevation was due to NSTEMI, STEMI, or a non-ACS cause and, if a non-ACS cause, the specific reason for the elevated troponin. In addition age, sex, initial troponin I level, and peak levels were collected and comparisons were made for NSTEMI and STEMI vs non-ACS causes. Peak troponins were compared as well.

Institutional review approval was obtained for the study as exempt.

3. Statistical analysis

Dichotomous variables were compared with χ^2 tests. Parametric data were compared using t test and analysis of variance. Nonparametric data were compared using Mann-Whitney U (2 groups) and Kruskal-Wallis (>2 groups) tests. A logistic linear regression model was created on variables selected a priori to evaluate the predictive ability of these variables to differentiate ACS vs non-ACS causes of elevated troponin. Variables included were age, sex, troponin I level, and ACS/non-ACS cause. Hosmer-Lemeshow statistic was used to determine the fit of the model.

Assuming mean percentile ranks of the medians had an SD of 20 and a difference between values of 20, our study was powered at 80% with 26 patients per group. To ensure study group compliance, we made sure that the smallest group met this requirement.

4. Results

There were 1317 unique cases of patients 18 years or older with elevated troponin I at least 0.06 ng/mL over the 1-year study period, July 2013 to June 2014. Of the 1317, 458 were randomly selected to be evaluated for cause of elevated troponin. Interrater measures showed 84% agreement in the 5% sampling.

Mean age for STEMI was 55 ± 12 years; NSTEMI, 60 ± 13 years; and non-ACS, 61 ± 16 years. A total of 68% of STEMI and NSTEMIs were in men and 58% of non-ACS causes were in men. There were more men in the ACS group vs non-ACS group. Table 1 shows demographics for our data. At final diagnosis, 362 (79%) were determined to be from a non-ACS cause. The median initial troponin I levels were significantly higher in those with STEMI (median, 10.2) vs NSTEMI (median, 0.4) vs non-ACS causes (median, 0.14). The mean rank differences of the medians between groups for initial troponins indicated that there were significant differences between STEMIs and NSTEMIs (mean rank difference, 20; 95% confidence interval [CI], 9-32), between STEMIs and non-ACS cases (mean rank difference, 40; 95% CI, 30-50) and between NSTEMIs and non-ACS cases (mean rank difference, 20; 95% CI, 13-27). The peaks were significantly different from each other as well with highest peaks in STEMI, next in NSTEMI, and lowest in non ACS causes (see Table 1). The first + troponin was the peak level in 196 (43%) of 459 overall in 9 (32%) of 28 STEMIs, in 26 (38%) of 68 NSTEMIs, and in 161 (44%) of 362 non-ACS category.

In the non-ACS group, the largest cause-subgroups were non-ACS cardiovascular, infection, renal, or hypertensive causes. The subgroup of non-ACS cardiovascular causes was significantly older, and the subgroup with cardiac arrest was significantly younger than the other groups. Of note, the subgroups of cardiac arrest and hypertension related had higher median initial positive troponin levels. These data are shown in Table 2.

In a multivariable logistic regression model shown in Table 3, age, sex, and initial + troponin I level were all entered as predictors and the outcome was ACS vs non-ACS. Neither age nor sex was significantly predictive of type of troponin elevation in this model. However, a change of one in initial troponin I level was associated with an increased adjusted odds ratio (aOR) of having an ACS cause of the initial elevated troponin I (aOR, 1.4; 95% CI, 1.2-1.6). Hosmer-Lemeshow statistic suggested a good fit of the data ($P = .35$).

5. Discussion

In the present study, we randomly selected 458 patients with elevated troponin I to determine ACS vs non-ACS causes based on final diagnoses. We compared all first elevated troponin I in our study. We found that initial elevated troponin levels were highest in those with STEMI, next highest in NSTEMI patients, and lowest in those with non-ACS causes. Troponin levels for STEMI and NSTEMI were significantly different both from non-ACS causes and from each other. The peaks were significantly different in the groups as well with highest in the STEMI group.

In the non-ACS group of elevated initial troponins, cardiac arrest and hypertension/hypertensive emergency patients had significantly higher

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Table 1
Comparison of type of elevated troponin I levels (≥0.06 ng/mL)

	All elevated troponin I cases	STEMI	NSTEMI	All non-ACS cases
n	458	28 (6%)	68 (15%)	362 (79%)
Age (y)	60 ± 16	55 ± 12	60 ± 13	61 ± 16
Sex (male)	58%	68%	68%	56%
First + troponin I level (ng/mL), median (IQR)	0.18 (0.09-0.60)	10.2 (0.75-20.1)	0.4 (0.13-1.7)	0.14 (0.08-0.37)
Mean percentile rank of the median first + troponin I	50 ± 29	85 ± 20	65 ± 28	45 ± 27
Peak troponin I level (ng/mL), median (IQR)	0.33 (0.12-1.46)	34.7 (13.98-40)	1.34 (0.42-10.6)	0.21 (0.11-0.80)
Increase in troponin from first + to peak, median (IQR)	0.021 (0-0.37)	2.80 (0-34.13)	0.31 (0-2.39)	0.01 (0-0.11)

Abbreviation: IQR, interquartile range.

initial troponin I levels than did the other groups. As in other studies, causes included non-ACS cardiovascular (most frequent), infection, renal failure, and hypertension [2,6]. In addition, we found those who had a primary diagnosis of cancer had elevated initial troponins as well.

In our study, there were significantly more patients with a non-ACS etiology of elevated troponins, more than in previous studies. We speculate that this could be due to a more sensitive troponin I assay, an institutional or population variability in our hospital or city, and perhaps due to obtaining troponins for workup of different etiologies for the elevations in mind. These may include pulmonary embolism, heart failure, atrial fibrillation, sepsis, trauma, and others, with the intent to determine prognostic implications in these diagnoses. Trending elevated troponins may help for these diagnoses as well.

The first positive troponin was most often *not* the peak in our study. This reiterates the need to look further for causes of *any* elevated troponin.

The 2000 American College of Cardiology/European Society of Cardiology definition of MI emphasizes the use of cardiac markers in diagnosing MI; subsequently, the number of patients diagnosed with NSTEMI was increased [8]. Other factors may lead to ischemic myonecrosis that are not acute MIs [8]. In this article, troponin is noted to have a nearly absolute specificity with a high sensitivity as well. It is stated that biomarkers reflect myocardial damage but do not indicate a mechanism. It is recommended that an elevated value without clinical evidence of ischemia requires a search for other causes of cardiac damage [8]. Two successive blood samples are also recommended.

Causes of myocardial injury with necrosis due to nonischemic myocardial injury include such conditions as heart failure, renal failure, myocarditis, arrhythmia, pulmonary embolism, and cardiac procedures [3]. Also included are injury causes that affect the supply/demand imbalance of myocardial ischemia including hypertension, severe anemia, respiratory failure, aortic dissection, and tachyarrhythmias [3]. Some causes may be multifactorial or indeterminate and include sepsis, trauma, acute neurologic disease, strenuous exercise, infiltrative diseases (amyloidosis/sarcoidosis), and trauma [3].

In a study by Mahajan et al [2], causes of elevated troponin without MI included gastrointestinal bleeding, DKA, chronic obstructive pulmonary disease exacerbation, collagen vascular disease, coronary spasm, and a category unknown (7%). Perhaps there are other causes as of yet unknown.

In a study by Khan et al [5], of 102 consecutive patients with troponin I at least 0.6 ng/mL, 35 did not have a final diagnosis of ACS. The causes in this study included cardiomyopathy, muscular disorders, central nervous system disorders, HIV disease, chronic renal disease, sepsis, lung disease, and endocrine disorders. Other causes may be in play as well. The mean troponin levels were lower in the non-ACS group, as was the case in our study. The study recommended that those with lower troponin levels should be interpreted with caution.

In a study by Ilva et al [6], 991 consecutive ED patients believed to have ACS had troponins drawn. In this study, 83% had ACS as a cause with 17% determined to be non-ACS causes. In this study, the non-ACS causes included cardiac, pulmonary embolism, renal failure, and sepsis. Many of our patients with non-ACS causes had these etiologies as well.

Another study by Alcalai et al [7] looked at all patients admitted with positive troponins during their hospital stay. An ACS cause was found in 326 of 615 patients. Non-ACS causes included cardiac, sepsis, and pulmonary embolism.

We were surprised in our study of the number of those with elevated troponin I without ACS, higher than that reported in other studies, at a rate of 79%. Our study is unique in including *only* those with positive troponins in our hospital system and includes many of the same etiologies. However, we found that more patients had a non-ACS cause than previous studies. The first positive troponin was compared in our analysis as well as the peaks.

Although those with elevated troponin I and non-ACS had generally significantly lower troponin levels than those ACS with STEMI or NSTEMI, some did not have such low levels, indicating that it may be difficult to exclude ACS simply based on a troponin I level or a low level of suspicion. In our study, the non-ACS causes were mostly cardiovascular, infection, renal, and hypertension related.

6. Conclusion

There are many causes of an elevated troponin I. A patient who does not appear to be having ACS should have other causes ruled out. Initial elevated troponin I levels were highest in STEMIs, next highest in NSTEMIs, and lowest overall in the non-ACS group, and the peak levels were significantly different in the same direction as well. Elevated troponin I levels were more likely to be from non-ACS causes than ACS causes. Non-ACS causes were most often due to non-ACS cardiovascular, sepsis, renal, and hypertension.

Table 2
Differences in types of non-ACS troponin I elevation (significant differences in bold)

	% of cases	Age (y)	Male sex	Troponin I initial + level, median (IQR)
All non-ACS cases	362 (79%)	61 ± 16	56%	0.14 (0.08-0.37)*
Infection	65 (14%)	60 ± 15	46%	0.18 (0.09-0.42)
Cancer	15 (3%)	58 ± 14	53%	0.20 (0.08-2.0)
Renal	35 (8%)	59 ± 14	53%	0.13 (0.09-0.36)
Cardiovascular	98 (22%)	66 ± 16*	57%	0.13 (0.08-0.25)
Pulmonary	25 (5%)	57 ± 17	60%	0.13 (0.08-0.30)
Trauma	23 (5%)	60 ± 22	57%	0.13 (0.10-0.70)
Cardiac arrest	20 (4%)	49 ± 19*	75%	0.20 (0.15-0.66)
Neurologic	25 (5%)	64 ± 17	60%	0.10 (0.08-0.42)
Hypertension	34 (8%)	59 ± 14	35%*	0.10 (0.07-0.21)

Abbreviation: IQR, interquartile range.
* Denotes statistical significance ($P < .05$).

Table 3
Multivariable logistic regression aORs of association of the outcome of ACS vs non-ACS causes of elevated troponin I with the predictor variables of age, sex, and troponin levels

	β	SE	aOR	95% CI on aOR
Age	0.00	0.01	1.0	0.98-1.02
Sex	−0.5	0.3	0.6	0.4-1.1
Troponin I initial + level	0.3	0.06	1.4	1.2-1.6

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7. Limitations

The ultimate etiology of the elevation in troponin relied on the discharge summary diagnoses. Some of the patients did not have a catheterization to definitively exclude ACS. Some patients also did not have a cardiology consult and relied on a hospitalist diagnosis.

The study was retrospective in nature and may not have had data available or reliable as prospective data collection.

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