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Minor elevations in troponin T values enhance risk assessment in emergency department patients with suspected myocardial ischemia: analysis of novel troponin T cut-off values

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Abstract

Background: A consensus document developed by a joint committee of the European Society of Cardiology and the American College of Cardiology redefines myocardial infarction (MI) using an increase of troponin I or T as compared to a reference control population (i.e., troponin T (TnT) of 0.01 μg/l). A clinical problem arises when an arbitrary cut-off point is selected for determination of MI (i.e., TnT ≥ 0.1 μg/l), as minor elevations of troponin are associated with increased cardiovascular risk in selected patients with acute coronary syndromes. *Methods*: We prospectively studied 420 unselected patients being evaluated for suspected myocardial ischemia in the emergency department (ED). We compared a 99th percentile MI cut-off limit for TnT, determined by constructing a standard receiver operator curve from our ED population in whom an acute coronary syndrome was excluded, to a standard MI cut-off limit of 0.1 μg/l in assessing cardiovascular risk. We also assessed the prognostic value of detectable TnT concentrations below this 99th percentile MI cut-off, but above the upper reference limit of healthy controls. *Results*: The diagnosis of acute coronary syndromes (ACS) was more frequent in groups with higher TnT concentrations: 16.8% with a normal TnT (< 0.03 μg/l), 29.5% with detectable TnT below the 99th percentile MI limit (0.03–0.066 μg/l), 64.3% with detectable TnT between the 99th percentile and standard MI cut-offs (0.067–0.099 μg/l), and 85.4% with TnT ≥ 0.1 μg/l ($p < 0.001$ for the trend). Thirty-day cardiovascular event rates increased for any detectable concentration of troponin: 1.3% with normal TnT, 4.8% with detectable TnT below the 99th percentile MI limit, 15.4% with TnT between the 99th percentile and standard MI cut-off limits, and 12.5% with TnT ≥ 0.1 μg/l ($p < 0.01$ for the trend). *Conclusion*: Using an MI cut-off concentration for TnT from a "non-ACS reference" population would fail to detect a positive TnT in 11.7% of subjects with an acute coronary syndrome.

Keywords: Troponin T; Mrocardial ischemia; Risk assessment

1. Introduction

Cardiac troponins are now the preferred biomarker for myocardial necrosis [1–3] given the near absolute sensitivity and specificity of troponins as compared to

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CK-MB. A consensus document [1] was developed by the Joint Committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) to revise the definition of myocardial infarction (MI) using more accurate criteria than the World Health Organization (WHO) criteria [2]. The WHO classification relies on two of three criteria consisting of ischemic symptoms, cardiac enzyme rise and a typical ECG pattern with evolution of Q waves. The revised definition of MI requires an elevation of either cardiac troponins (I or T) or the MB fraction of creatine kinase (CK-MB), and one of the two remaining criteria. The ESC/ACC suggested that an abnormal troponin measurement should be defined as that exceeding the 99th percentile of a reference population with a coefficient of variation (CV) of $\leq 10\%$.

Detection of MI is only a partial goal, however, as recent emphasis has switched from the diagnosis of MI to risk stratification to identify patients prone to in-hospital and recurrent cardiac events [4]. The superiority of cardiac troponins for the diagnosis of MI was extended to risk stratification in the recent guidelines for the management of unstable angina and non-ST segment MI [5]. An elevated troponin identifies a high-risk patient with an $\sim$ nine-fold increased risk for MI or death in the next 30 days [6] who may benefit from aggressive medical therapies or an early invasive strategy [7,8].

As small degrees of myocardial necrosis can be reliably detected with a highly sensitive and specific marker such as troponin T (TnT) or I (TnI), the National Academy of Clinical Biochemistry (NACB) had previously recommended two decision limits: a lower cut-off value at the detection limit to establish the presence of true myocardial injury and a higher value to qualify as MI [9]. Similarly, recent acute coronary syndrome guidelines suggest different cut-off values for TnT representing a slightly elevated value (>0.01 μg/l but <0.1 μg/l) or a markedly increased value (≥ 0.1 μg/l) to identify intermediate and high risk patients, respectively [5]. Depending on the cut-off value chosen, the timing of the blood draws, and the duration of follow up, a positive troponin has a wide range of sensitivity (38–63%) and specificity (77–95%) for future adverse cardiac event rates [10].

Ideally, the TnT cut-off should be calculated using logistic analysis to determine the value associated with the highest odds ratios for predicting MI and near term events for a particular assay. However, this is impractical for most hospital laboratories and due to psychological and socioeconomic concerns it may be inappropriate to label all ischemic episodes associated with slightly elevated troponin values as an acute MI. Although the detection limit for TnT is 0.01 μg/l, a single MI cut-off limit of ≥ 0.1 μg/l is typically recommended. Recent multicenter trials have examined multiple TnT cut-off values in assessing risk in large cohorts of patients with acute coronary syndromes and found that adverse outcomes increased with increasing TnT concentrations, even at values below the accepted 0.1 μg/l MI cut-off limit [11,12]. However, as the positive predictive value of minor troponin elevations was examined only in a high-risk cohort with unstable angina or non-ST elevation MI, caution should be exercised in generalizing these results to a heterogenous population. As chest pain is frequently absent at the time of presentation in acute MI patients [13], cardiac biomarkers are routinely obtained in a more diverse patient population.

We prospectively evaluated serial TnT values, as well as clinical and electrocardiographic (ECG) variables, in 420 patients with suspected myocardial ischemia in whom serial CK-MB and TnT determinations were drawn in the ED, irrespective of the presence of chest pain. We constructed a standardized receiver operator curve (ROC) curve to establish a TnT MI cut-off at the 99th percentile of TnT from our ED population patients with suspected myocardial ischemia in whom an acute coronary event was excluded. Given the excellent specificity of TnT, we hypothesized that increases in TnT values above this 99th percentile cut-off of a candidate reference population, but below the standard MI cut-off value, would be predictive of near term cardiac risk in a heterogeneous population with suspected myocardial ischemia.

2. Methods

2.1. Study population

We prospectively evaluated serial TnT determinations in 420 serial patients presenting to the ED with chest pain or other symptoms suggestive of myocar-

dial ischemia for >30 min in duration in the absence of ST elevation in whom serial TnT and CK-MB determinations were obtained. Patients ≥21 years were eligible if they were without the following exclusion criteria: ST elevation at presentation, recent trauma, renal disease (creatinine ≥2 mg/dl), pregnancy, resuscitation, defibrillation or cardioversion in the ED. The median time from onset of symptoms to presentation in the ED was 5.4 h (range 0.5–56 h).

2.2. Laboratory protocol

TnT and CK-MB activity were assayed on specimens collected at 0, 3 and 12 h after presentation. Over 90% of patients had both the 0- and 3-h assay collected and approximately 50% had a 12-h sample collected (as low risk patients were frequently sent home after two negative TnT samples). The TnT assay (Elecsys Troponin T STAT) was a third generation chemiluminescent immunoassay performed on the Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN). The manufacturer's suggested cut-off limit is ≥0.1 μg/l for an abnormal result. The CK-MB was measured on the Vitros analyzer (Ortho Ektachem 950, Ortho Clinical Diagnostics, Raritan, NJ). A CK-MB value of ≥17 U/l, in the setting of an elevated total CK, was used as the cut-off value for an abnormal result based on prior prospective validation at our institution using the aforementioned CK-MB activity assay [14].

2.3. Clinical data

The clinical data collected for this study included history, physical examination, presence or absence of and characteristics of chest pain (atypical or typical based on the Goldman [15] criteria), ECG findings and final diagnosis. The ECG at presentation was interpreted in a blinded fashion as normal, non-diagnostic (paced rhythm or left bundle branch block), ST segment depression (>1.0 mm in ≥2 or more contiguous leads not known to be old or associated with left ventricular hypertrophy) or as non-specific ST-T wave changes. Patients were followed until discharge for the development of acute coronary syndromes or MI and for 30 days for non-fatal MI or death. Follow up data was collected in 399/420 (95%) patients by phone contact and hospital record review.

2.4. Final diagnosis

The diagnosis of acute non-ST elevation MI was determined independently by a blinded observer (SZ) based on serially measured CK-MB or TnT determinations, clinical history and ECG findings as defined by the manufacturer's MI cut-off concentration (≥0.1 μg/l) [1]. Unstable angina was defined as type IIIB according to the Braunwald classification [16]. All other diagnoses were classified as either cardiovascular (stable angina, congestive heart failure, syncope, stroke or dysrhythmia) or non-cardiac (musculoskeletal, pulmonary or gastrointestinal) in nature.

2.5. Statistical analysis

A receiver operator characteristic (ROC) curve for the decision limit for MI was constructed from our ED cohort with suspected myocardial ischemia in whom serial biomarker determinations were performed. The 99th percentile for TnT in patients in whom an acute coronary syndrome was excluded was determined to be 0.067 μg/l with a CV of 8%. This TnT value was used as our MI cut-off limit. A TnT value of <0.03 μg/l was considered normal based on a 99th percentile value of 0.01 μg/l in reference controls and a 10% CV limit of <0.03 μg/l as suggested by the manufacturer and recent studies [11]. We compared cardiac outcomes in four groups based on the peak troponin T values: group 1: TnT <0.03 μg/l (normal TnT), group 2: TnT 0.03–0.066 μg/l (TnT detectable below the 99th percentile MI cut-off), group3: TnT 0.67–0.099 μg/l (TnT detectable above the 99th percentile MI cut-off, but below the standard MI cut-off limit) and group 4: TnT ≥0.1 μg/l (TnT above the standard cut-off limit). We examined if there was any difference between groups with and without low concentrations of detectable troponin in the serum (groups 1 and 2, respectively) or between groups 3 and 4 with elevated TnT values at differing cut-off values.

Descriptive statistics, analysis of variance, *t*-test and cross-tabulation analysis with chi square test were performed using SPSS software (Chicago, IL). We used Magidson's GOLDminer (SPSS) method [17] to predict an ordered response of a dependent variable. The model fit is measured by the chi-square for the regression.

3. Results

The mean age of the patients studied was 64.6 ± 15.6 years. Fifty-one percent of patients were males. Chest pain was the presenting complaint in 319 (76%) and was typical for myocardial ischemia in 58%. Thus, only 44% of the cohort presented with typical chest discomfort, while 24% presented without chest discomfort. Dyspnea was the most common presenting symptom after chest pain followed in order by pain in the epigastrium, back or arms and palpitations or syncope. Diagnostic ST segment depression was present in only 12% of the entire cohort and 29% and 25%, respectively, of unstable angina and MI patients. The ECG was normal in 26%, non-diagnostic in 8% (LBBB or paced) and showed non-specific ST-T changes in 54%. Only 31 patients (7.3%) had both typical chest pain and diagnostic ST segment depression. For the entire cohort, the final diagnosis was an acute coronary syndrome (unstable angina or MI) in 111/420 (26.4%). The final diagnosis was MI in 35 (8.3%) and unstable angina in 76 (18.1%). Seventy-four percent of patients without an acute coronary syndrome had a cardiovascular diagnosis or non-cardiac diagnosis established.

The peak TnT concentrations were normal (< 0.03 μg/l) in 321 patients (76.2%), detectable below the 99th percentile MI cut-off (0.03–0.066 μg/l) in 44 (10.5%), detectable above the 99th percentile MI cut-off, but below the standard MI cut-off (0.067–0.099 μg/l) in 14 (3.3%) and ≥ 0.1 μg/l (above the standard cut-off) in 41 (9.8%). The diagnosis of an acute coronary syndrome was associated with increasing TnT values (16.8% in patients with normal TnT, 29.5% in patients with TnT values below the 99th percentile MI cut-off value, 64.3% in patients with TnT values between the 99th percentile and standard MI cut-offs, and 85.4% in patients with a TnT ≥ 0.1 μg/l) ($p < 0.001$ for the trend) (Table 1). Of the remaining 14.6% of patients with a TnT ≥ 0.1 μg/l without a diagnosis of MI, two thirds (4/6) had cardiovascular diagnoses known to be associated with elevated TnT concentrations (congestive heart failure, pulmonary embolism and tachyarrhythmia) in association with documented coronary artery disease. MI was diagnosed in only 1 (0.3%) patient with a TnT concentration below the 99th percentile (< 0.067 μg/l). By using a MI cut-off concentration determined from a "non-ACS" patient population, TnT would fail to detect as positive 11.7% of ACS subjects. The sensitivity, specificity, and positive and negative predictive values for MI for TnT at 0.03 and 0.067 μg/l are shown in Table 2 as compared to the manufacturer's cut-off of 0.1 μg/l.

The 30-day post hospital clinical event rate (death or non-fatal MI) was 3.3% (13/399) for the entire cohort. Clinical events rates were increased with every concentration of detectable TnT (1.3% with normal TnT, 4.8% with detectable TnT concentrations below the 99th percentile MI cut-off, 15.4% for detectable TnT above the 99th percentile but below the standard MI cut-off, and 12.5% for TnT ≥ 0.1 μg/l; $p < 0.01$ for all groups). Clinical events at follow-up were significantly increased in patients with any TnT concentration above the 99th percentile MI cut-off as compared to patients with lower values (13.2% vs. 1.7%; $p < 0.01$). Clinical events were similarly increased in

Table 1
Troponin T levels and associated acute coronary events and 30-day cardiac event rates

Troponin T level number (%)	Acute coronary syndrome* % (#)	30-day cardiac events** % (#)
Normal (< 0.03 μg/l), 321 (76.2%)	16.8% (54)	1.3% (4)
Detectable below 99th percentile MI cut-off (0.03–0.066 μg/l), 44 (10.5%)	29.5% (13)	4.8% (2)
Detectable between 99th percentile and standard MI cut-off (0.067–0.099 μg/l), 14 (3.3%)	64.3% (9)	15.4% (2)
Above standard cut-off (≥ 0.1 μg/l), 41 (9.8%)	85.4% (35)	12.5% (5)

*$p < 0.001$ for trend.
**$p < 0.01$ for trend.

Table 2
Sensitivity, specificity, positive predictive value and negative predictive value of TnT at different cut-off values

TnT cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.03 μg/l	98.3	88.4	57.6	99.7
0.067 μg/l	75.9	96.7	80	96.2
0.1 μg/l	60.3	98.3	85.4	93.9

PPV = positive predictive value, NPV = negative predictive value.

patients with increases in TnT below the 99th percentile MI cut-off as compared to those with normal TnT concentrations (4.8% vs. 1.3%; $p = 0.01$). Outcomes were similar in patients with TnT concentrations between the 99th percentile MI cut-off and 0.1 μg/l as compared to those above 0.1 μg/l (15.4% vs. 12.5%; $p = 0.71$). Utilizing the GOLDminer method, TnT determinations accounted for 45% of the variability in predicted MI rates and 53% of the variability in clinical event rates. Chest pain and ECG changes did not add significantly to either predictive model when TnT values were known.

4. Discussion

Minor elevations in TnT values are associated with increased near term cardiovascular event rates in an unselected group of patients with suspected myocardial ischemia. TnT determinations above the 99th percentile MI cut-off, based on ED patients without acute coronary syndromes, have a similar prognostic value to TnT concentrations above the traditional cut-off limit. The presence of any detectable troponin T added to risk, but the positive predictive value was low. Our findings are consistent with prior studies of the prognostic value of minor elevations in TnT values in acute coronary syndromes [11,12]. Our study is unique in that it enrolled a broad spectrum of ED patients with suspected myocardial ischemia and examined TnT values based on a reference ED cohort (and not a healthy reference population). TnT increases above the 99th percentile reference group value had a similar prognostic value as TnT above the standard cut-off limit. Both high and low risk patients were enrolled in our study and a significant number of patients presented without chest discomfort. As chest pain is absent in up to one third of MI patients in the National Registry of Myocardial Infarction database [13], cardiac biomarkers are routinely employed in a diverse ED population with a variety of cardiopulmonary complaints. Minor increases in TnT, in the absence of other conditions associated with increased troponins, have prognostic significance and may identify patients who benefit from an early invasive strategy [12].

The presence of ST segment depression and chest pain at presentation added little to our predictive model. However, in this diverse population diagnostic ST depression was present in only 12% and was frequently found in conjunction with an abnormal TnT determination. Of note, strict ECG criteria were employed and non-specific ST depression was common in acute coronary patients given a high prevalence of resting baseline ST changes, ventricular hypertrophy and conduction delays. Typical chest pain in conjunction with diagnostic ST changes was also infrequent (7.3%). Thus, minor increases of TnT, even in the absence of diagnostic ECG changes or characteristic chest pain, are of prognostic importance. In contrast, ST depression is more common in selected patients with acute coronary syndromes and is associated with increased cardiac event rates in this population, both in the presence and absence of increased troponin concentrations [18].

As suggested by the NACB and ESC/ACC committees [1,9], minor increases of TnT likely represent true myocardial injury and have now been shown to have prognostic significance in both low and high risk groups with suspected myocardial ischemia in the absence of ST segment elevation. Caution must be used as precise troponin assays have been developed that enable the detection of baseline concentrations of TnT in healthy individuals. Residual troponin concentrations in healthy subjects likely represents apoptotic turnover of myocardial tissue and not injury [19] and may impair the specificity of TnT determinations if lower cut-off values are used. Additionally, there may be significant differences in the normal reference ranges for troponins between males and females and between Caucasians and African–Americans [20]. There can be up to a 13-fold variation between the lowest and highest measured 99th percentile troponin values [20]. We agree, however, with the NACB and AHA conclusions that elevations of troponins between the upper limit of healthy controls and MI limits reflect "myocardial injury" and should prompt admission and aggressive treatment to reduce cardiovascular risk in appropriate patients with suspected myocardial ischemia.

The optimal troponin cut-off limit for therapeutic decision making and prognostication remains elusive at this time. The ESC/ACC joint committee recently supported a single detection limit at the 99th percentile of troponin concentrations among apparently healthy controls at an appropriate concentration

(CV ≤ 10%) of assay precision which is 0.01 μg/l for TnT [1]. In patients with a clinical history consistent with myocardial ischemia, minor troponin increases add important prognostic information, but the positive predictive value is low. Utilizing a 99th percentile cut-off for a reference ED population with suspected myocardial ischemia improves the predictive value of minor TnT increases, but confirmation awaits further study. Caution is also advised as increases of cardiac troponins occur in other cardiopulmonary settings and will clearly complicate the interpretation of abnormal TnT values, especially in patients with a low clinical suspicion for myocardial ischemia [21]. If confirmed, the results from the current study will help in generalizing the predictive value of minor troponin increases in lower risk individuals. This approach may fail to identify some ACS patients with minor TnT elevations between the 99th percentile of an apparently healthy reference group and the 99th percentile of a "non-ACS" group. This approach is a trade-off between decreased diagnostic sensitivity and reduced specificity.

This study has several important limitations. Our 99th percentile MI detection limit for TnT differs markedly from that of a normal reference population (0.067 vs. 0.01 μg/l) and may not reflect the reference population at other institutions. A typical population of patients with suspected myocardial ischemia in whom a MI is "ruled out" contains many patients with conditions associated with TnT increases in the absence of acute coronary syndromes (congestive heart failure, pulmonary emboli, dysrhythmias, etc.). Additionally, many of these patients have established coronary artery disease and microvascular disease (left ventricular hypertrophy and diabetes) and may have silent ischemia, which can impact TnT concentrations [22–24]. In hemodialysis patients, an elevated TnT concentration is predictive of death and is a marker for extensive coronary artery disease in the absence of ischemic symptoms [22]. Similarly, microvascular disease from ventricular hypertophy secondary to hypertension and diabetes has been proposed as a mechanism of elevated troponins in chronic renal failure patients [23,24]. Thus, it is not surprising that minor elevations of TnT are frequently found in patients with suspected myocardial ischemia, even in the absence of clinically apparent acute coronary syndromes.

Another major limitation of our study is the relatively small number of patients ($n = 58$) with minor TnT increases below the standard 0.1 μg/l cut-off limit. However, there appears to be a significant, albeit small, increment in risk even in patients with any detectable concentration of TnT below the 99th percentile MI cut-off as compared to patients with normal troponin concentrations (4.8% vs. 1.3%; $p = 0.001$). Diagnostic ST segment depression added little to TnT determinations in the prediction of future cardiac events in our model, but there were relatively few patients with diagnostic ST depression in our study. As we employed strict ECG criteria in a diverse patient population, of which only one-quarter had acute coronary events, non-diagnostic ECG changes were fourfold as common as diagnostic ECG changes in our study population. The absence of diagnostic ECG changes is quite reflective of an unselected ED population of patients routinely 'ruled out' for MI and again calls attention to the utility of cardiac biomarkers in conjunction with clinical and electrocardiographic evaluation in clinical practice [25].

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