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High sensitive cardiac troponin T: Testing the test

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ABSTRACT

Background: High sensitive cardiac troponin T (hs-TnT) found its way into everyday clinical routine to diagnose acute myocardial infarction (AMI). However, its levels vary considerably based on the underlying pathophysiology of the patients. Hence we sought to test the applicability of the currently only available hs-TnT assay (Roche Diagnostics, Switzerland) to diagnose acute myocardial infarction.

Methods and patients: Retrospectively, we analyzed the hs-TnT results of 1573 patients admitted to a level A university hospital emergency department. Overall 323 patients had an acute cardiac event defined as Non-ST Elevated Myocardial Infarction (NSTEMI) and 286 patients had a ST-Elevated Myocardial Infarction (STEMI). 964 patients served as controls, consisting of patients with other cardiac and non-cardiac morbidity.

Results: The sensitivity of hs-TnT for detecting an acute cardiac event was more than 92% overall. The specificity varied around 35% depending on the respective patient cohort. ROC curve analysis of the initial hs-TnT results showed that the AUC in total cardiac events (STEMI and NSTEMI) was 0.81. Detailed analysis resulted in an AUC of 0.79 in NSTEMI and 0.84 in STEMI patients detected via the initial hs-TnT. We further tested the ESC algorithm for detecting NSTEMI and obtained a sensitivity of about 83%, while 43% of all non-NSTEMIs are classified as NSTEMIs.

Conclusion: We show that the specificity of hs-TnT for AMI is very low and conclude that the current assay including its delta values represents myocardial damage of any origin. This damage alone does not substantiate an AMI diagnosis even when international algorithms are applied.

1. Introduction

Serum cardiac troponin I and T are sensitive and specific biomarkers for myocardial damage, and their measurement is recommended for the diagnosis of acute myocardial infarction [1]. Elevated levels of serum cardiac troponin measured by conventional cardiac troponin assays correlate with adverse outcomes in patients with both acute and chronic heart failure (HF) [2–4]. However, in the majority of patients with HF, serum cardiac troponin levels are lower than the assay detection limits. Recently, a novel and highly sensitive cardiac TnT (hs-TnT) assay has been developed to detect low-grade circulating cTnT levels below the detection levels of conventional assays. This assay improves the diagnostic sensitivity for myocardial infarction [5], prognostic discrimination, compared with conventional assays in patients with HF [6], and risk stratification for cardiovascular events and mortality in both patients with stable coronary artery disease (CAD) and the general population [7–10].

The concentrations of circulating cardiac troponin detected with the hs-TnT assay are modestly and persistently elevated in patients with stable HF, regardless of overt CAD [11]. Various reasons have been proposed for the elevated cTnT levels in patients with HF, including increased wall stress, myocyte damage from inflammatory cytokines or oxidative stress, altered calcium handling, and coronary microvascular dysfunction (CMVD) [11–13]. However, not only cellular factors influence systemic cTnT levels. Further, morbidities such as stroke, cancer, or renal dysfunction alter hs-TnT levels [14–16]. Therefore, these and other factors strongly influence the systemic concentrations detected in those individuals [15,16]. Although the 99th percentile of healthy individuals is the defined reference value to diagnose acute myocardial infarction (AMI) according to the universal definition of AMI, optimal clinical decision levels or cut off levels for patients at presentation to the ED may differ from the 99th percentile of healthy individuals [17].

Delays in excluding AMI ("rule out") interfere with evaluation of alternative diagnoses and contribute to medical errors and costs associated with crowding in the emergency department (ED). The measurement of hs-TnT is despite its limitation an essential and integral part

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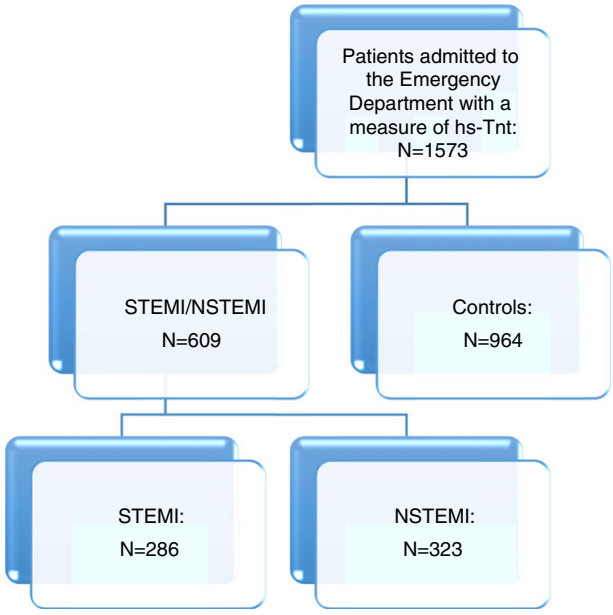

Fig. 1. Patient flow chart.

of the current diagnostic routine for AMI. Because of its known limitations we aimed to examine the diagnostic performance of the high sensitive cardiac troponin T assay (Roche Diagnostics, Switzerland) for the early diagnosis in patients with and without AMI.

2. Methods

2.1. Study and patient collective

For the retrospective part starting from January 1st 2012, 1573 consecutive patients > 18 years of age presenting to the Emergency Department of Bern, Switzerland with symptoms suggestive of AMI with an onset of chest pain or history of cardiologic medical records, who had a hs-TnT measurement during their routine medical treatment (flow chart, Fig. 1) were enrolled. The controls consisted of patients with cardiac and non-cardiac morbidity. Overall 5120 medical record entries were included into this retrospective analysis (See Fig. 2).

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

2.2. Routine clinical assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. The hs-TnT (Roche Diagnostics, Switzerland) was measured at presentation and serially thereafter as long as clinically indicated. The cut off was defined by the manufacturer with >14 ng/L. Timing and treatment of patients were left to discretion of the attending physician.

Table 1
Baseline levels of hs-TnT in different subgroups. Data is given in means ± SD (range/max).

Hs-troponin T STEMI (ng/l) (n = 286)	2323 ± 5456 (76,680)
Hs-troponin T NSTEMI (ng/l) (n = 323)	459 ± 926 (6750)
Hs-troponin T controls (ng/l) (n = 964)	84 ± 342 (7980)

At event: for patients with STEMI and NSTEMI.
STEMI: ST-elevated myocardial infarction.
NSTEMI: non-ST-elevated myocardial infarction.

2.3. Adjudicated final diagnosis

Adjudication of the final diagnosis was performed at the emergency medicine department (University Hospital of Bern) and included Roche hs-TnT to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by this assay. Independent cardiologists reviewed all available medical records – patient history, physical examination, results of laboratory testing (including hs-TnT levels), radiological testing, ECG, echocardiography, cardiac exercise stress test, lesion severity, and morphology in coronary angiography – pertaining to the patient from the time of ED presentation to the 90-day follow up. Specifically, the patients' description of pain (typical, atypical, nonspecific), time since onset and peak of symptoms, and new ECG findings were taken into account for the adjudication of the final diagnosis. Furthermore, hs-TnT levels of prior admissions were considered to assess whether the hs-TnT levels were elevated previously. It also was recorded if the patient was taken to the catheterization laboratory, whether there was an event and the number of vessels diseased. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a second cardiologist.

In the retrospective study part, myocardial necrosis was diagnosed by at least one hs-TnT value above the 99th percentile of healthy individuals, together with a significant rise or fall [18,19].

2.4. Statistical analysis

Descriptive statistics were calculated for the description of troponin distributions. ROC analysis was employed for the assessment of the diagnostic/prognostic accuracy of troponin relative to event, STEMI, NSTEMI etc. The area under the ROC curve (AUC) was used as an index of diagnostic performance. Pairs of sensitivity and specificity were used via the Youden index for the estimation of an optimal cutoff point or for the assessment of cutoff points widely used in clinical practice. p-Values less than 0.05 were considered statistically significant. Multiple logistic regression analysis was carried out to assess associations between AMI and its different forms and hs-TnT, estimated glomerular filtration rate, age and sex in an attempt to establish a score. For this analysis each subject was only assessed once. The hs-TnT and estimated glomerular filtration rate measures were used at the age at that point of time. Stata 13.1 (Stata Corp., College Station, TX) was used for data analysis. For illustrative purposes, ROC surface analysis was employed to assess troponin as a diagnostic marker of controls, nstemi, stemi, that is, in a 3-class diagnostic setting, where the clinician wants to classify a patient to one of the ordinally scaled three classes given

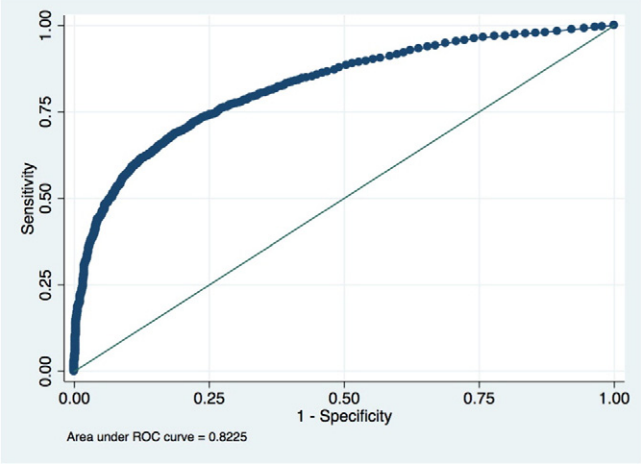

Fig. 2. The hs-TnT assay (Roche Diagnostics, Switzerland) detecting overall cardiac events. All measures of patients included (n = 1573).

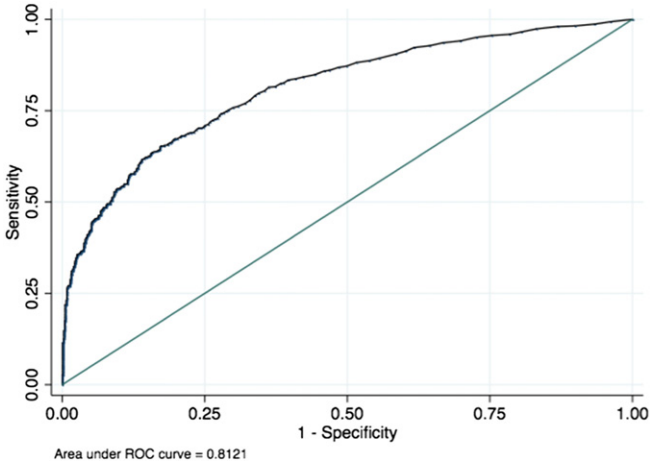

Fig. 3. ROC-curve analysis based on all events detected only via initial hs-TnT measurement (n = 609 STEMI and NSTEMI, n = 964 controls).

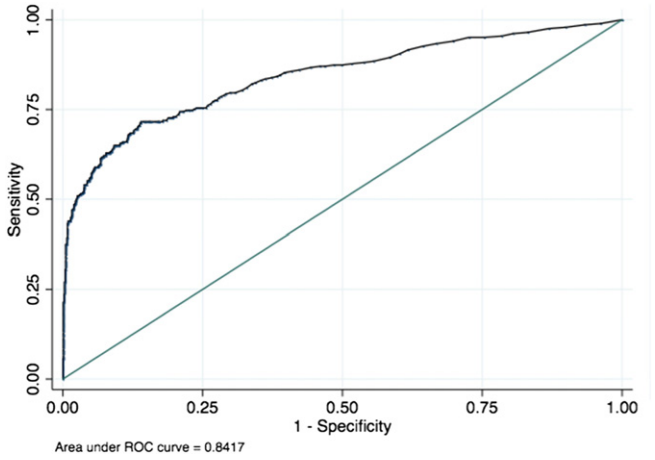

Fig. 4. ROC-curve analysis based on STEMI detected via initial hs-TnT measurement (n = 286, n = 964 controls).

their troponin levels [20]. ROC surface analysis was implemented using Matlab 2013a (Mathworks Inc., Natick, MA) [20].

3. Results

The study population consisted of 1098 (69.8%) male and 475 (30.2%) female subjects. The mean age was 67.99 (±13.72) years. The different hs-troponin values of each group are shown in Table 1.

When testing whether hs-TnT can detect any STEMI or NSTEMI event, hs-TnT has a sensitivity of about 93% considering values equal to or higher than 15 ng/L as an event in a pooled analysis (Fig. 3). This cut-off results in 64% of false positives (PPV and NPV are around 48% and 89% respectively for this cohort). When optimising the Youden index (near 150 ng/l), sensitivity goes down to around 53% (with specificity close to 91%), a choice that would result in PPV and NPV equal to 27% and 23% respectively.

When groups were separated according to STEMI (AUC 0.84; 95% CI: 0.81, 0.87) or NSTEMI (AUC 0.79; 95% CI: 0.76, 0.82), we obtained similar results for detecting the respective event (Figs. 4 and 5).

When we tested whether hs-TnT can detect if there are vessels affected the test was clearly ineffective (results not shown).

We tried finding a score in order to adjust for known confounding factors such as age, sex and estimated glomerular filtration rate. Therefore, multivariate binary logistic regression analysis was applied. Patients with one missing parameter of the aforementioned were excluded from the analysis and new ROC analysis. The event itself showed association with hs-TnT and estimated glomerular filtration rate (both $p < 0.01$;Table 2). The AUC in ROC analysis for hs-TnT and event detection was 0.83 (95% CI: 0.80, 0.85). STEMI patients (n = 265) showed independent associations with hs-TnT, estimated glomerular filtration rate, and age, NSTEMI patients (n = 265) with hs-TnT and estimated glomerular filtration rate (Table 3 a and b). ROC analysis for STEMI patients resulted in an AUC of 0.83 (95% CI: 0.80, 0.87) in NSTEMI patients an AUC of 0.78 (95% CI: 0.75, 0.81) with hs-TnT.

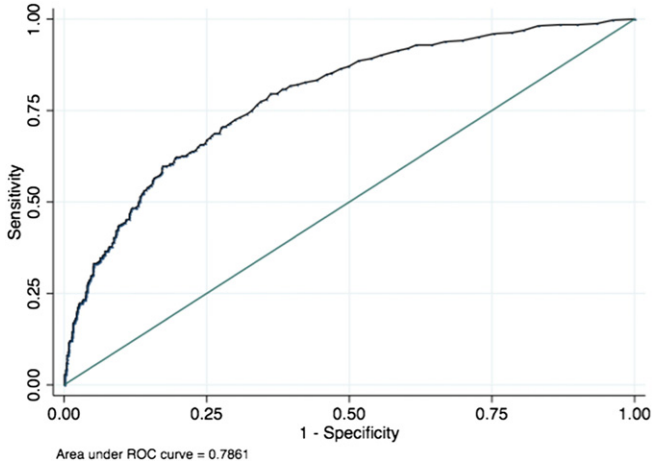

Fig. 5. ROC-curve analysis based on NSTEMI detected via initial hs-TnT measurement (n = 323, n = 964 controls).

Table 2
Multivariable logistic regression analysis of acute myocardial injury detection with different parameters (overall n = 1125 events and controls). Patients with missing data of the 4 applied parameters were excluded from the analysis.

	OR	CI	p-Value
hs-TnT	13.73	6.82, 27.39	<0.001
eGFR	1.02	1.01, 1.03	<0.001
Age	0.99	0.98, 1.002	0.107
Female sex	0.90	0.68, 1.19	0.446

To verify our results we tested the ESC algorithm [21]. We further did not only implement the 1-hour delta but also up to a 6-hour delta. We found a sensitivity of 83.2% (95% CI: 75.0%, 89.6%) for detecting an NSTEMI. 42.9% (95% CI: 35.9%, 50.1%) were false positive results. The results were comparable among all delta groups (1 h, 3 h and 6 h).

4. Discussion

Our results demonstrate a very low specificity of hs-TnT, the only currently available test, for the discrimination of NSTEMI/STEMI, combined or separately. However, this test and its consecutive results are at present an integral part for diagnosing AMI.

Other studies already demonstrated that cut off levels for hs-Tn are assay specific [15]. Still the finding that hs-Tn levels are higher in patients with AMI than in patients with other co-morbidities remains dominant [15]. Further studies demonstrated it as a risk factor for outcome of patients with other cardiovascular risk factors and diseases [8–10,22]. However, the specificity was already known to be less among the studies [15,16,22,23]. One study even pointed at misdiagnosis of AMI because of the interpretation of the current available assays [23]. This study incorporated extended guidelines and recommendations of task forces for the diagnosis of myocardial infarction [24]. The investigators stressed a lack of consensus on how to define healthy individuals because possible effects of age and sex on levels of hs-TnT, that had recently been identified, so that the current regulatory process has come under scrutiny [25–27].

In the current regulatory process, the manufacturer defines the 99th percentile in a separate cohort of healthy individuals. Apparently, differences in these cohorts of healthy individuals are substantial and lead to

Table 3
Multivariable logistic regression analysis of STEMI (A) (overall n = 865 events and controls) and NSTEMI (B) (overall n = 865 events and controls) patients with different parameters. Patients with missing data of the 4 applied parameters were excluded from the analysis.

A)	OR	CI	p-Value
hs-TnT	11.82	5.81, 24.05	<0.001
eGFR	1.02	1.01, 1.03	<0.001
Age	0.98	0.97, 0.99	0.002
Female sex	0.72	0.49, 1.05	0.090
B)	**OR**	**CI**	**p-Value**
hs-TnT	7.61	3.86, 15.03	<0.001
eGFR	1.01	1.004, 1.02	0.001
Age	1.002	0.99, 1.01	0.742
Female sex	0.99	0.71, 1.40	0.968

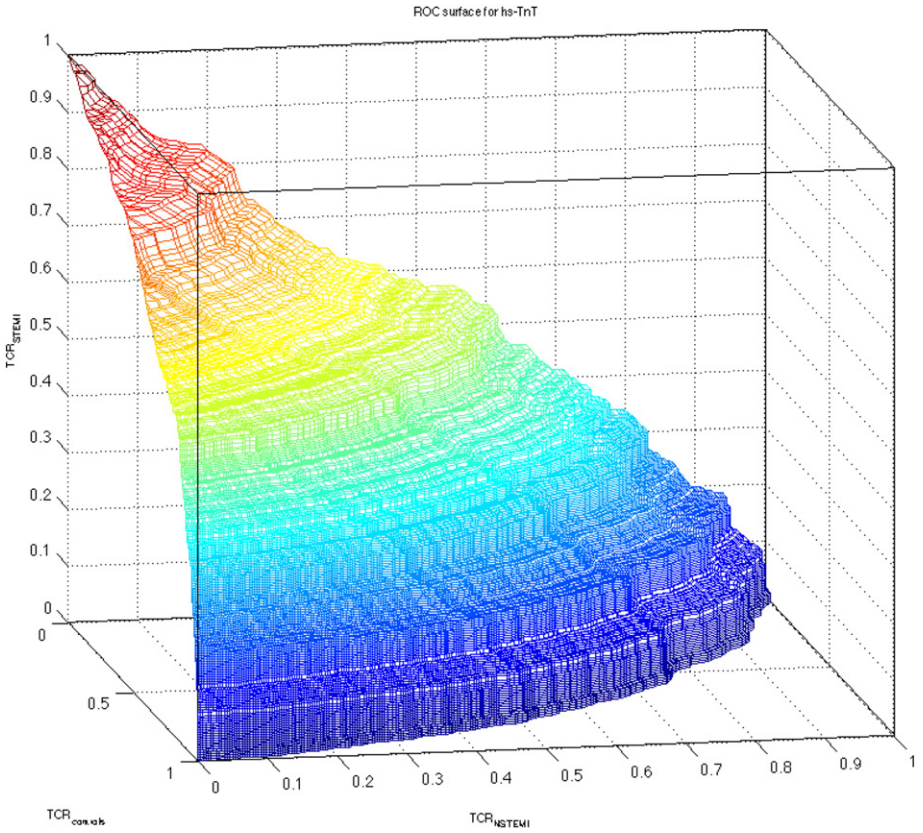

Fig. 6. 3-dimensional ROC surface analysis of hs-TnT including all 3 groups (controls n = 964, NSTEMI n = 323 and STEMI n = 286). Volume under the surface = 34% (95% CI: 30–38%).

major differences in the resulting 99th percentiles regarding not only sensitivity but also specificity. The younger the reference population is and the more stringent the criteria to define cardiac health are, the lower the resulting 99th percentile is [25,28–30]. We therefore refer our results to the fact that first our control group included patients with cardiac morbidity without an acute event. Second, due to this, the sensitivity drops by the measurement of hs-TnT to diagnose AMI in these patients further.

Two important questions are raised. First, the patients admitted to a level A university hospital represent a collective with a broad spectrum of diseases known to increase hs-TnT levels [14–16]. How should the 99th percentile for diagnosing AMI in case of this test be defined? Second, if hs-TnT is only a marker valuable within a specific time course and multiple measurements, is it suitable to diagnose AMI?

Our results are in line with those of other research groups [23]. However, a limitation of our study might be the retrospective design. On the other hand, this demonstrates how the hs-TnT results were handled or interpreted in everyday clinical practice in accordance with the available guidelines. Further, as illustrated by the 3-dimensional ROC analysis, the probability that their ordering is the anticipated one (control < NSTEMI < STEMI) is just 33.6% which is significantly better than chance alone but clearly inadequate for clinical purposes and could not be used as a surrogate to admission ECG (see Fig. 6).

Overall the current available hs-TnT assay has a low specificity for AMI. It does detect any myocardial damage which does not have to be related to AMI. Even an algorithm intended to erase interindividual difference of interpreting the results does not improve the specificity.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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