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Diagnostic sensitivity of high-sensitivity troponin T in acute myocardial infarction in patients with chest pain

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ABSTRACT

Introduction: The diagnosis of acute myocardial infarction (AMI) is based on an increase in plasma troponin levels above the 99th percentile of a healthy reference population values. On admission, over 30% of patients with AMI do not have specific symptoms and up to 70% of them may have normal or non-diagnostic ECG recordings. In these patient subgroups cardiac troponin assays may play a critical role in diagnosing AMI. Several diagnostic kits with enhanced analytic sensitivity (high-sensitivity kits) have been developed recently.
Aim of study: To compare diagnostic sensitivity of troponin I (cTnI) and high-sensitivity troponin T (hs-cTnT) in the diagnosis of acute myocardial infarction in patients with chest pain.
Type of study: Prospective, observational.
Patients and methods: We evaluated prospectively 107 consecutive patients [median (inter-quartile range) age: 64 (55–75) years; 29 women] admitted to intensive cardiac care unit for chest pain, with admission cTnI levels < 0.1 μg/l. In all patients, the parameters determined on admission included their levels of cTnI (chemiluminiscence immunoassay with microparticles, Abbott, Architect i2000 analyzer), hs-cTnT (electrochemiluminiscence immunoassay; Roche Cobas e411 analyzer), and myoglobin (immunoturbidimetry). The diagnosis of AMI was established by the attending cardiologist (using the "universal" definition of acute myocardial infarction). The cTnI and hs-cTnT cut-off values for AMI were 0.033 μg/l and 14 ng/l, respectively. Troponin I levels were again determined at 6 and 12 hours after admission.
Results: A total of 50 patients (46.7%) were diagnosed to have AMI with ST-segment elevation (STEMI), 35 patients (32.7%) developed AMI without STE (non-STEMI), 10 patients (9.3%) experienced a Type 2 AMI, four patients (3.7%) had unstable angina, and eight patients (7.5%) chest pain of non-coronary etiology (most often vertebrogenic pain). The diagnostic sensitivity of admission cTnI and hs-cTnT levels for AMI was 72% and 78%, respectively ($p = 0.1814$). The correlation between cTnI and hs-cTnT was 0.67 ($p < 0.001$; Spearman rank correlation coefficient). The diagnostic sensitivity of admission hs-cTnT and cTnI in STEMI patients was 82% vs. 70%, respectively ($p = 0.0771$). In non-STEMI patients, similar baseline cTnI and hs-cTnT diagnostic sensitivity was found, 74.3% and 71.4%, respectively ($p = 0.91$).
Conclusion: Patients with STEMI showed a trend toward a baseline diagnostic sensitivity of hs-cTnT superior to that of cTnI. In non-STEMI patients, the sensitivity of admission cTnI and hs-cTnT was similar.

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SOUHRN

Úvod: Pro diagnózu akutního infarktu myokardu (AIM) je nezbytný nález vzestupu plazmatické koncentrace troponinu nad 99. percentil hodnot referenčního zdravého souboru. Více než 30 % pacientů s AIM nemá při přijetí specifické klinické známky a až 70 % může mít normální nebo nediagnostické EKG. U těchto pacientů je stanovení kardiálních troponinů pro diagnózu AIM zásadní. V poslední době byly vyvinuty diagnostické soupravy se zvýšenou analytickou senzitivitou (vysoce senzitivní soupravy).
Cíl studie: Porovnání diagnostické senzitivity troponinu I (cTnI) a vysoce senzitivního troponinu T (hs-cTnT) v diagnostice akutního infarktu myokardu u nemocných s bolestí na hrudi.
Typ studie: Prospektivní, observační.
Materiál a metody: Do studie jsme postupně zařadili 107 pacientů (medián [interkvartilové rozpětí] věku 64 [55–75] let; z toho 29 žen), kteří byli přijímáni na kardiologickou jednotku intenzivní péče pro bolest na hrudi a cTnI při přijetí byl < 0,1 μg/l. U všech pacientů jsme při přijetí měřili cTnI (chemiluminiscenční imunoanalýza na mikročásticích, Abbott, přístroj Architect 2000), hs-cTnT (elektrochemiluminiscenční imunoanalýza; Roche, přístroj Cobas e411) a myoglobin (imunoturbidimetricky; Beckman-Coulter, přístroj AU 5400). Diagnózu akutního infarktu myokardu určil ošetřující kardiolog (podle „univerzální" definice AIM). Hraniční hodnoty pro AIM u cTnI a hs-cTnT byly 0,033 μg/l a 14 ng/l, resp. hodnota troponinu I byla dále stanovena za 6 a 12 hodin od přijetí.
Výsledky: U 50 (46,7 %) nemocných byl nález uzavřen jako AIM s elevacemi úseku ST (STEMI), u 35 (32,7 %) nemocných byl zjištěn AIM bez elevací úseku ST (non-STEMI), u 10 (9,3 %) nemocných AIM 2. typu, u 4 (3,7 %) pacientů nestabilní angina pectoris, 8 (7,5 %) nemocných mělo bolesti na hrudi nekoronární etiologie, nejčastěji vertebrogenní. Diagnostické citlivosti příjmového cTnI a hs-cTnT pro AIM byly 72 % a 78 % (p = 0,1814), korelace mezi cTnI a hs-cTnT byla 0,67 (p < 0,001; Spearmanův korelační koeficient). Diagnostická senzitivita příjmového hs-cTnT a cTnI byla u nemocných se STEMI 82 % versus 70 % (p = 0,0771). U pacientů s non-STEMI byla senzitivita příjmového cTnI a hs-cTnT obdobná, 74,3 % a 71,4 % (p = 0,91).
Závěr: U nemocných se STEMI jsme zjistili trend k vyšší senzitivitě hs-cTnT oproti cTnI. U nemocných s non-STEMI byla senzitivita příjmového cTnI a hs-cTnT obdobná.

Klíčová slova:
Akutní infarkt myokardu
Bolest na hrudi
Diagnostická citlivost
Troponin I
Vysoce senzitivní troponin T

Introduction and aim

Troponins are proteins of a tropomyosin complex of striate muscle myocytes involved in muscle contractility. The troponin complex consists of three specific proteins, troponin C (calcium-binding unit), troponin T (tropomyosin-binding subunit), and troponin I (subunit binding actin, thereby inhibiting contraction). The troponin C in cardiomyocytes and skeletal muscle is identical. As troponins T and I in the above tissues show different antigenic properties, those present in the myocardium are referred as "cardiac" (cTn); these troponins are currently the most important laboratory markers in the diagnosis of acute myocardial infarction (AMI) [1–3]. Novel highly sensitive troponin assays have refuted the assumption that troponins are released into blood only in pathological situations. Measurable levels can be found even in absolutely healthy individuals, a finding reflecting the physiological regeneration of cardiomyocytes (approx. 1% of cardiomyocytes succumb to apoptosis each year). As a result, any cTn detected in blood originates in the myocardium (100% organ specificity); but the boundaries discriminating reversible from irreversible alterations (necrosis) in the myocardium have not been clearly identified yet [4,5]. Advances in the analytical potential of assays determining cTn levels are progressively shifting the clinical perception of cTn measurement results from qualitative scales of simply "positive/negative" toward fully quantitative determination allowing for earlier diagnosis of AMI and opening space for a potential role of cTn in establishing prognosis in a variety of diseases. From the perspective of clinical practice, a diagnostic dilemma is particularly obvious in patients with chest pain and unspecific ECG changes (30–40% of AMI patients do not have symptoms on admission, and normal or non-diagnostic ECG recordings may be present in up to 70% of patients) [6]. In these patients, we often have to wait until results of cardiospecific laboratory investigations become available. The analytical sensitivity of standard cTn kits does allow to detect a demonstrable increase in cTn levels after 3–4 hours since the onset of coronary ischemia [7]. This may lead to later initiation of treatment of acute coronary syndrome in the decision-making algorithm. High-sensitivity cTn assays eliminate this drawback due to earlier evidence of myocardial necrosis and identification of even minor lesions [7]. Another important consideration is their ability to distinguish between unstable angina and AMI without ST-segment elevation (non-STEMI), an area where a high degree of sensitivity may be important in establishing the correct diagnosis.

The aim of our pilot study was to compare the diagnostic sensitivity and specificity of troponin I (cTnI) and high-sensitivity troponin T (hs-cTnT) in the differential diagnosis of chest pain in patients admitted to an intensive cardiac care unit.

Patients and methods

A total of 107 consecutive patients (for more detailed characteristics of patients – see Table 1), admitted to our intensive cardiac care unit between 8/2010 and 8/2011 for chest pain and with cTnI levels < 0.1 μg/l on admission, were included into our study. The limit was based

Table 1 – Basic characteristics of the study population.

	n (%)
Men	78 (73%)
DM	31 (29%)
Arterial hypertension	88 (82%)
Smoking status	63 (59%)
Dyslipidemia	90 (84%)
Previous CHD	26 (24%)
eGFR < 1 ml/s	32 (30%)
Age (yrs)	64.0 [54.5–75.0]
eGFR (ml/s)	1.15 [0.93–1.39]

CHD – coronary heart disease; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate according to the four parameter MDRD equation (Modification of Diet in Renal Disease).

on the assumption that high-sensitivity assays should best demonstrate their superiority at low cTn levels. The time between onset of chest pain and admission sampling was ≤ 4 h in 71 (66%) patients, > 4 h and ≤ 8 h in 17 (16%) patients, > 8 h and ≤ 12 in 8 (7%) patients and > 12 h in 11 (10%) patients. The parameters measured on admission in all patients included cTnI (chemiluminiscence immunoassay on microparticles, Abbott Architect i2000 analyzer) and myoglobin (immunoturbidimetry; Beckman-Coulter, AU 5400 analyzer). Hs-cTnT (electrochemiluminiscent immunoassay; Roche Cobas e411 analyzer) has determined retrospectively. After < 1 h following the collection, the sample was stored at 2–8 °C for < 8 h and then frozen at –80 °C until analysis. Analysis was performed batch-wise < 10 months after collection. The stability of sample suggested by manufacturer is 24 hours at 2–8 °C and 12 months at –20 °C. The time course of troponin I levels were determined from blood samples collected on 3 occasions (on admission, and 6 and 12 hours later). High-sensitivity cTnT was measured only in blood samples obtained on admission. The cut-off values of cardiac troponins for AMI were set at the 99th percentile of the reference population (using data of kit manufacturers), with both manufacturers declaring a < 10% coefficient of variation. As a result, the cut-off values for cTnI and hs-cTnT were 0.033 µg/l and 14 ng/l, respectively. The myoglobin cut-off value for AMI in our study was the upper reference limit (using data of the kit manufacturer) of 92 µg/l (men) and 76 µg/l (women).

Statistical analysis

Statistical analysis was performed using MS Excell 2010 and R 2.1.2.0 software (http://r-project.org). Descriptive statistics is presented as a median (inter-quartile range), unless otherwise stated. Correlation was calculated using a non-parametric method (Spearman coefficient of correlation); differences between 2 groups were determined using the Wilcoxon sign rank test and effects on cardiac troponins by various factors were tested using multiple regression analysis. Statistical significance of differences between the diagnostic sensitivity of cardiac troponins was calculated using the McNemar's chi-square test according to a published procedure [8].

The diagnosis of AMI was established by the attending cardiologist. To diagnose AMI in patients with chest pain, the physician used the modified universal definition of MI [1] according to the following algorithm:

- Detection of an increase in troponin I with at least one value above the 99th percentile of the reference population within 24 hours of the complaints onset.
- At the same time, evidence of ischemia by at least one of the following findings: new changes in the ST segment, newly developed LBBB, development of pathological Q waves, or new wall motion abnormality as assessed by an imaging technique.

In patients with evidence of AMI, ECG curves were used to distinguish AMI with and without STE from Type 2 AMI, with the latter due to increased oxygen consumption or decreased oxygen supply in the presence of a coronary spasm, embolization into a coronary artery, in anemia, hypotension, or hypertension.

Results

Acute myocardial infarction was diagnosed in a total of 95 patients (89%). Details specifying causes of chest pain and diagnostic sensitivity of the respective markers are shown in Table 2. All patients with STEMI had a revascularization procedure, 49 patients underwent primary

Table 2 – Diagnostic sensitivity of cTnI and hs-cTnT with individual diagnoses (blood sampling on admission). Figures in parentheses show numbers of positive results (above the cut-off values).

Diagnosis [n]	cTnI	hs-cTnT	*p* (hs-cTnT vs. cTnI)	Myoglobin
non-STEMI [35]	74.3% (26)	71.4% (25)	0.92	71.4% (25)
STEMI [50]	70% (35)	82% (41)	0.0771	72% (36)
Type 2 AMI [10]	70% (7)	80% (8)	–	80% (8)
Total AMI [95]	71.6% (68)	77.9% (74)	0.1814	72.6% (69)
Unstable angina [4]	25% (1)	50% (2)	–	0% (0)

AMI – acute myocardial infarction; cTnI – troponin I; hs-cTnT – high-sensitivity troponin T; non-STEMI – AMI without STE; STEMI – AMI with STE.

Table 3 – Diagnostic specificity of individual tests (blood sampling on admission). Figures in brackets with individual specificities show numbers of negative results (below the cut-off value).

	cTnI	hs-cTnT	*p* (hs-cTnT vs. cTnI)	Myoglobin
No AMI (n = 12)	75 % (9)	50 % (6)	0.2482	50 % (6)

AMI – acute myocardial infarction; cTnI – troponin I; hs-cTnT – high-sensitivity troponin T.

percutaneous coronary intervention (PCI: the proportion of interventions on right coronary artery [RCA], ramus circumflexus [RC] and left coronary artery [LAD] were 45%, 8%, and 47% resp.) and one patient was scheduled for coronary artery bypass grafting (CABG). In the group of non-STEMI patients, a revascularization procedure was performed in 32 individuals (30 had PCI: the proportion of interventions on RCA, RC, and LAD were 35%, 24%, and 41% resp., 2 patients were scheduled for CABG, 2 patients were treated conservatively, 1 patient was not scheduled for coronary angiography). On admission, hs-cTnT and cTnI levels were 24.2 (14.1–34.2) ng/l and 0.05 (0.02–0.08) µg/l, respectively.

Admission hs-cTnT in patients with non-STEMI had a diagnostic sensitivity similar to that of cTnI. A statistically and clinically significant correlation of 0.67 was found between the measured values of both cardiac troponins ($p < 0.001$; Spearman rank correlation coefficient). Using a multiple regression model (hs-cTnT levels as a dependent variable; diabetes mellitus, dyslipidemia, hypertension, smoking status, history of CAD [coronary artery disease], sex, interval between the onset of complaints and admission to hospital, and estimated glomerular filtration rate using the MDRD equation as independent variables), we found that the admission levels of hs-cTnT are significantly determined by the presence of dyslipidemia ($p = 0.019$; 95% CI for beta = 2.7–26.8) and a history of CHD at the limit of statistical significance ($p = 0.05$). Using an analogical model, cTnI levels were significantly affected also by a history of CHD ($p = 0.033$) and smoking status at the limit of statistical significance ($p = 0.091$).

Our group of patients included 4 individuals whose chest pain was due to unstable angina, and 8 individuals with chest pain of non-ischemic etiology. While aware of the low informative value of our findings, we used our data to derive the specificities of individual tests (Table 3).

Further, we compared the discrepancies in baseline positivity and negativity of hs-cTnT and cTnI. High-sensitivity troponin T was positive, in contrast with admission negative value of troponin I, in 12% of patients (n = 13), of whom 10 had AMI, the finding in 1 patient was assessed as unstable angina, and chest pain in 2 patients was assessed as of non-coronary etiology. In 4% of baseline TnI positive patients (n = 4), admission value of hs-cTnT was negative (3 non-STEMI patients and 1 STEMI patient).

Discussion

Diagnostic sensitivity of high-sensitivity troponins for the diagnosis of AMI might be superior to that of myoglobin and "standard" troponins as early as on admission [9,10]. In our study, we found that the sensitivity of hs-cTnT in STEMI patients was higher by 12% as compared with cTnI. However, in patients where cTn assay is critical for the diagnosis, (i.e., in non-STEMI patients), the sensitivity of admission cTnI and hs-cTnT levels was similar. This might be due to the usually longer interval between the onset of chest pain and baseline laboratory investigations in our non-STEMI patients, when the sensitivity of cTnI and hs-cTnT may be already comparable.

It should be noted that the terms "standard", "sensitive", and "highly sensitive" have been used inconsistently and reflect the advances in analytical sensitivity and accuracy of assays. This could possibly also explain the comparable sensitivity of both assays observed in our non-STEMI patients. The cTnI assay (chemiluminiscence assay on microparticles, Abbott Architect i2000 analyzer, Abbott) belongs to the "sensitive" generation and the diagnostic efficacy of this assay has been reported by some authors to be comparable with the "highly sensitive" ones [11,12].

A limitation of our study is its highly selected study population with a very low proportion of diagnoses other than AMI. As a result, our data were not large enough to reliably calculate the diagnostic specificity, which was lower for hs-cTnT as compared with cTnI. On the other hand, it is most desirable for the prevalence (pretest probability) of AMI in the study population to be as high as possible [13], a requirement met in our study. It can be assumed that a decreasing prevalence of AMI in a study population is associated with a decrease in diagnostic specificity, i.e., an increasing proportion of false positive results. At the same time, there is growing evidence that any increase in cTn levels (even below the cut-off value for AMI) is associated with a worsening of prognosis [14]. The question thus arises whether the higher numbers of false positive results (using current criteria) in hs-cTnT are due to an inherent error of the assay or, rather, contributes to improving care of the patient. The recent guidelines of the European Society of Cardiology (ESC) for the management of non-STEMI patients [15] have incorporated hypersensitive cTn assays into the diagnostic algorithm because of their ability of earlier detection in AMI patients. In the case of an ambiguous clinical picture, it is recommended to perform a control assay 3 hours later, when its sensitivity for AMI diagnosis is close to 100%. The Czech guidelines for myocardial revascularization procedures [16] have not included high-sensitivity troponin assays into the diagnostic algorithm yet. In our retrospective study, we focused on diagnostic properties of hs-cTnT at patient admission. That is why we could not (unfortunately) determine concentrations of hs-cTnT after 3 to 6 h after admission due to missing samples at these times. Specific universal algorithms (timing and frequency of blood sampling for cTn) adjusted to the needs of high-sensitivity troponin assays beyond a stage of local experience have not been established. Decreasing the

cut-off value for AMI, a process necessarily associated with the increasingly widespread use of high-sensitivity troponins thus – quite paradoxically – places higher demands on the evidence-based decision-making of the physician, whether or not they will indicate a cTn assay and the way they will interpret its results. The ultimate consideration in diagnosing AMI continues to be clinical suspicion only then followed by confirmation using cTn (and not in reverse order) [17].

Conclusion

The baseline diagnostic sensitivity for acute myocardial infarction of hs-cTnT is superior to that of cTnI, particularly in STEMI patients. In patients with non-STEMI, the baseline sensitivity of cTnI and hs-cTnT was similar. Further studies are needed to better evaluate the role of hs-cTnT in patients with acute chest pain.

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