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Original article

"30-minute-delta" of high-sensitivity troponin I improves diagnostic performance in acute myocardial infarction

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ABSTRACT

Background: Rapid and accurate diagnosis of acute myocardial infarction (AMI) are critical for the initiation of effective medical treatment. Recently, a high-sensitivity cardiac troponin I (hs-cTnI) assay was developed as a biochemical marker for the early diagnosis of AMI. Current guidelines recommend that serial measurements of cardiac troponin should be performed in patients who present symptoms suggestive of acute coronary syndrome. The aim of this study was to evaluate the diagnostic performance of 30-minute serial measurements of hs-cTnI for the detection of AMI.
Methods: We prospectively enrolled patients presenting with suspected AMI within 12 h from symptom onset. We measured hs-cTnI levels at presentation and 30 min later to calculate the "30-minute-delta". The diagnostic performance was determined by the area under the receiver operating characteristic curve (AUC).
Results: Among the 71 patients enrolled in this study, 55 (77%) were diagnosed with AMI. The hs-cTnI level at presentation was significantly greater in the patients with AMI than in those without AMI [306.2 (77.3–1809.9) pg/mL versus 22.5 (7.2–115.5) pg/mL, $p < 0.01$]. The "30-minute-delta" was also significantly greater in patients with AMI [54.6 (13.5–288.0) pg/mL versus 1.9 (0.6–6.3) pg/mL, $p < 0.01$]. The AUC of the "30-minute-delta" was significantly greater than that of a single measurement at presentation (0.911 versus 0.829, $p < 0.05$).
Conclusions: The "30-minute-delta" of hs-cTnI presents improved diagnostic performance for AMI compared with a single measurement.

Introduction

Acute myocardial infarction (AMI) is a major cause of mortality and morbidity worldwide. Patients with suspected AMI must be evaluated immediately to identify life-threatening emergencies. The universal definition of MI is based on rise or fall of cardiac biomarkers such as cardiac troponin (cTn) with at least one value above the 99th percentile of the upper reference limit associated with symptoms and/or ST-T changes on electrocardiogram (ECG) suggestive of myocardial ischemia [1]. The American College of Cardiology/American Heart Association non-ST segment elevation acute coronary syndrome (NSTE-ACS) guidelines in 2014 also recommend that cTn should be measured on first assessment and repeatedly 3–6 h later [2]. Such serial or delta measurement is of significant importance, because cTn value may not exceed the 99th percentile value when the time from onset to measurement is within 1–2 h, and also it may frequently exceed the 99th percentile value in patients with chronic cardiac or kidney diseases.

Because high-sensitivity cTn assays provide extremely sensitive detection of AMI at presentation, the time interval from its first measurement to the second one can be significantly shortened [3]. Keller et al. studied delta measurements using high-sensitivity troponin I (hs-cTnI) values recorded at presentation and 3 h later,

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and confirmed improvement in the diagnostic performance [4]. Rubini Gimenez et al. further reported a one-hour rule-in and rule-out algorithm of hs-cTnI values [5], and their findings were adopted in the "2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation" [6]. Delta measurements performed within a time interval shorter than 1 h are expected to provide more efficient AMI diagnoses. Therefore, the aim of this study was to evaluate the diagnostic performance of thirty-minute serial measurements of hs-cTnI for the detection of AMI.

Methods

Study patients

We prospectively enrolled 71 consecutive patients presenting to the Hirosaki University Hospital between May 2015 and January 2016 with symptoms suggestive of AMI within 12 h from onset. Written informed consent was obtained from all patients. This study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee of our institution.

A clinical assessment was performed for all patients including history taking, physical examinations, a 12-lead ECG, laboratory test including cardiac enzyme values, echocardiography, and coronary angiography. Blood samples for routine tests were collected from all patients at presentation. The left ventricular ejection fraction (LVEF) was assessed by echocardiography or left ventriculography.

Final diagnosis of AMI

The final diagnosis of AMI was determined based on all available data by two independent cardiologists. A primary diagnosis of AMI was done according to the current guidelines when there was evidence of myocardial necrosis that was consistent with myocardial ischemia together with clinical symptoms and/or ECG changes suggestive of new ischemia (new ST-T changes or new left bundle branch block) or imaging evidence of a new loss of viable myocardium or a culprit coronary lesion classified according to the Ambrose criteria [7]. All other patients were categorized as "non-AMI" for this study. The treatment of the patients was left to the discretion of the physician.

Measurement of hs-cTnI

The blood samples used to determine the hs-cTnI values were collected in tubes containing potassium ethylenediaminetetraacetic acid at the time of the patient's presentation to our hospital. Additional samples were obtained 30 min after presentation. After centrifugation, the plasma samples were frozen at −80 °C in a blinded fashion in a core laboratory until they were subjected to a cardiac troponin assay (Architect Stat High-Sensitive Troponin I; Abbott Laboratories, Abbot Park, IL, USA). The limit of detection in this assay is 1.9 pg/mL (range, 0–50,000 pg/mL) and the 99th percentile cut-off is 26.2 pg/mL [8].

Statistical analysis

All continuous variables were expressed as the mean ± standard deviation (SD) or the median (interquartile range), and categorical variables were expressed as numbers and percentages. An unpaired *t*-test or chi-square test was used to compare the differences between two groups. Mann–Whitney's *U* test was used for nonparametric variables. Receiver operating characteristic (ROC) curves were constructed to assess the AMI diagnostic performance for absolute values according to the 1st and 2nd hs-cTnI values or the absolute changes in hs-cTnI within 30 min (the "30-minute-delta"). The area under the curve (AUC) values were compared using bootstrap analyses [9]. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated from the optimal cut-off values derived from the ROC curves. Statistical analyses were performed using JMP 11 software (SAS, Cary, NC, USA). A *p*-value of less than 0.05 was considered statistically significant.

Results

Study patients

Among the enrolled 71 patients, 55 (77%) were adjudicated as AMI (AMI group), and the remaining 16 were non-AMI (non-AMI group). The characteristics of the patients are shown in Table 1. The AMI group had more males and a lower LVEF than the non-AMI group. In the AMI group, 46 (84%) were diagnosed with ST-segment elevation AMI. In the non-AMI group, ECG at presentation showed ST-segment elevation in 1 patient, ST-segment depression in 5, T-wave inversion in 8, and pacemaker rhythm in 2. Time from symptom onset to 1st sampling did not differ between the 2 groups. None of the study patients was diagnosed with left bundle branch block.

Hs-cTnI at presentation and 30 min later

The hs-cTnI levels at presentation were significantly higher in the AMI group than in the non-AMI group [306.2 (77.3–1809.9) pg/mL versus 22.5 (7.2–115.5) pg/mL, $p < 0.01$] (Fig. 1A). Furthermore, the hs-cTnI levels at 30 min after presentation were also significantly higher in the AMI group than in the non-AMI group [394.5 (121.2–2136.5) pg/mL versus 24.4 (7.4–117.4) pg/mL, $p < 0.01$] (Fig. 1B). The "30-minute-delta," a difference between 1st and 2nd hs-cTnI values, was significantly higher in the AMI group than in the non-AMI group [54.6 (13.5–288.0) pg/mL versus 1.9 (0.6–6.3) pg/mL, $p < 0.01$) (Fig. 1C).

Comparison of diagnostic performance

The AMI diagnostic accuracy as quantified by the AUC was significantly higher in the "30-minute-delta" than in the 1st hs-cTnI value at presentation [0.911, 95% confidence interval (CI) 0.765–0.970 versus 0.829, 95% CI 0.671–0.920, $p < 0.05$ by bootstrap method] (Fig. 2).

Optimal cut-off value of the "30-minute-delta" of hs-cTnI for the early diagnosis of AMI

The optimal cut-off value of the 1st hs-cTnI value at presentation according to the ROC analysis was 62.9 pg/mL, and the sensitivity, specificity, PPV, and NPV values were 83.6%, 68.7%, 90.2%, and 55%, respectively. Similarly, the optimal cut-off value of the "30-minute-delta" of hs-cTnI was 3.7 pg/mL, and the sensitivity, specificity, PPV, and NPV values were 98.2%, 75.0%, 93.1%, and 92.3%, respectively. We show the schema of the "30-minute-delta" algorithm for the earlier diagnosis of AMI according to our results (Fig. 3). Among the 51 patients with hs-cTnI values ≥ 62.9 pg/mL at 1st sampling, 50 exceeded the cut-off values of "30-minute-delta" (3.7 pg/mL) and 46 were diagnosed as having AMI. The final diagnoses of the remaining 4 patients were congestive heart failure ($n = 3$) and takotsubo cardiomyopathy ($n = 1$). Most notably, among the 20 patients with hs-cTnI values < 62.9 pg/mL at 1st sampling, 8 presented the "30-minute-delta" that exceeded the cut-off values and were all diagnosed as having AMI. The remaining 12 patients

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