CLINICAL RESEARCH STUDY

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Using High-sensitivity Troponin T: The Importance of the Proper Gold Standard

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ABSTRACT

OBJECTIVE: The study objective was to determine how best to use high-sensitivity cardiac troponin T (hscTnT) to diagnose myocardial infarction.

METHODS: A total of 358 patients presenting with acute coronary syndromes sampled at admission and 2, 4, and 6 to 8 hours. Both contemporary cardiac troponin T (cTnT) and hscTnT were measured. Patients were classified with conventional cTnT values by independent investigators. Myocardial infarction required a cTnT value ≥99th reference percentile and a ≥20% change.

RESULTS: Seventy-nine patients had non-ST-segment elevation myocardial infarction, 105 patients had unstable angina, and 174 patients had nonacute coronary syndromes. A cTnT cutoff at the 10% coefficient of variation value missed 14.5% of infarctions. hscTnT had a sensitivity at admission of 89.9%, but specificity was only 75.1% because of elevations in 45.3% and 25.3% of those with unstable angina and nonacute coronary syndromes, respectively. The optimal value for myocardial infarction diagnosis with hscTnT was 25 ng/L at admission and 30 ng/L during serial sampling. All infarctions were diagnosed within 4 hours, with a time saving of 11 and 68 minutes compared with a cTnT value at the 99th reference percentile value and a cTnT value at a coefficient of variation of 10%. By using the 99th percentile of hsTnT plus a ≥20% change, 25 additional infarctions were identified. With these included, the optimal cutoff decreased to 12 ng/L at admission and 13 ng/L over time, but time to diagnosis increased.

CONCLUSIONS: The gold standard used to diagnose myocardial infarction makes a major difference in the results. When myocardial infarction is diagnosed using hscTnT 99th percentile values with a 20% change, more are identified, diagnosis is delayed, and the optimal value for use is reduced.

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KEYWORDS: High-sensitivity troponin T; Non-ST-segment elevation myocardial infarction

Cardiac troponin (cTn) is the preferred biomarker for the diagnosis of myocardial infarction.[1] With more sensitive assays, such as the high-sensitivity cardiac troponin (hscTn) assay, additional patients are detected.[2,3] However, because some assays lack optimal precision at the 99th percentile,[4,5] some centers use the 10% coefficient of variation value instead.[1] This raises the cutoff value further above normal,[6,7] exaggerating differences between hscTn and contemporary assays.[2,3,8] In addition, as assay sensitivity improves, elevations due to nonischemic pathologies are observed.[9,10] These decrease the specificity of solitary elevations for the diagnosis of myocardial infarction.[1,11] For that reason, a changing pattern of values needs to be used to improve specificity for acute events.[1,12,13] However, many

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*ASJ and JO-L co-directed the work.

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studies have used solitary elevations of hscTn as diagnostic, inflating the number of infarctions detected by not excluding elevations due to nonacute ischemic causes,[10,14] previous infarction,[15] or stable angina.[16] This approach and higher cutoff values exaggerate differences between conventional assays and hscTn assays.

The UltraSensitive Troponin in Acute Coronary syndromes (TUSCA) study was a multicenter trial to evaluate how to best use the high-sensitivity cardiac troponin T (hscTnT) assay to diagnose myocardial infarction.[1,17,18] The assay detects values in more normal subjects than do contemporary assays and has a precision of <10% at the 99th percentile upper reference limit.[19,20]

CLINICAL SIGNIFICANCE

- High-sensitivity cardiac troponin assay is in use worldwide and will soon be used in the United States.
- There is confusion over how best to use the values.
- A problem in this area is that less sensitive assays have been used to define acute myocardial infarction in many studies. This distorts the metrics for the use of the high-sensitivity cardiac troponin T assay.

MATERIALS AND METHODS

Patients and Samples

TUSCA was a prospective multicenter trial involving 5 emergency departments. It enrolled 358 patients with acute coronary syndromes. To minimize selection bias, single physicians enrolled patients after discussions concerning inclusion criteria. Consecutive patients were included if they were aged >18 years, gave a history of ≥5 minutes of symptoms, and signed informed consent. Exclusion criteria included ST-segment elevation, new left bundle branch block, preadmission thrombolytic therapy, defibrillation or cardioversion before sampling, pregnancy or renal failure requiring hemodialysis, unstable angina within 2 months, or coronary artery bypass within 3 months.

Samples were drawn into lithium-heparin tubes by 30 minutes after arrival and at 2, 4, and 6 to 8 hours or until discharge. Samples were centrifuged at room temperature, aliquoted, stored at −80° C, and assayed centrally (Hospital Sant Pau) with the fourth-generation (cTnT) and hscTnT assays.

Clinical Management

Patients were managed per guidelines at each center, using local cTn values. Clinical and electrocardiogram (ECG) data were interpreted with standard criteria.

Laboratory Methods

cTnT and hscTnT were measured with a Cobas e401 system (Roche Diagnostics, Basel, Switzerland). Imprecision in 20 replicates of 8 pooled samples with concentrations from 7 to 928 ng/L were made by diluting a sample with elevated cTnT with a pool with undetectable hscTnT (<5 ng/L). The 99th percentile of the cTnT assay (10 ng/L) had a coefficient of variation of 15.2% and a 10% coefficient of variation of 35 ng/L. The 99th percentile value (14 ng/L) for the hscTnT assay had a coefficient of variation of 6.9%; the 10% coefficient of variation value was 9.3 ng/L. None of the lots with difficulties with calibrators were used.[21]

Final Diagnoses

Final diagnoses were made by an adjudication committee. Non-ST-segment elevation myocardial infarction was diagnosed when patients manifested a cTnT value >99th percentile (10 ng/L) and an increase/decrease >20%. This percentage was chosen on the basis of recommendations for diagnosing reinfarction.[5] Unstable angina required rest angina, worsening angina, a positive ischemia test, transient supra/infra−ST-segment changes during chest pain, or a coronary stenosis ≥70% by angiography without a cTnT value >99th percentile. Other patients were assigned nonacute coronary syndrome diagnoses. Patients with compatible clinical findings and elevated hscTnT with evolving changing pattern were reclassified to myocardial infarction to determine the number of additional patients diagnosed with hscTnT.

Statistical Analyses

A 15% difference in the diagnostic sensitivities of cTnT and hscTnT with α and β errors of 0.05 and 0.20, respectively, required 290 patients. Continuous independent and categoric variables were compared by Mann−Whitney and chi-square tests. The diagnostic performance of cTnT and hscTnT was evaluated by the area under the receiver operating curve (AUC ROC) during serial sampling, and cutoff values were calculated. Except for hscTnT criteria found by ROC analyses ($hscTnT_{ROC}$), diagnostic accuracy was analyzed for the admission value and for values plus a change >20%. For $hscTnT_{ROC}$, all cutoffs derived by ROC analysis were compared by the DeLong test. Time to diagnosis was calculated from the onset of symptoms to the time of the sample diagnosing acute myocardial infarction. A P value ≤.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences (v 18; SPSS Inc, Chicago, Ill).

Study Design

Roche Diagnostics Spain (Barcelona) provided reagents for and supported the logistics of the study, but it was not involved in the design, implementation, or analyses.