Analytical Validation of a High-Sensitivity Cardiac Troponin T Assay
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We report the development of a novel high-sensitivity cardiac troponin T (hs-cTnT) assay, a modification of the Roche fourth-generation cTnT assay, and validation of the analytical performance of this assay.

METHODS: Validation included testing of analytical sensitivity, specificity, interferences, and precision. We established the 99th percentile cutoff from healthy reference populations (n = 616). In addition, we studied differences in time to a positive result when using serial measurements of hs-cTnT vs cTnT in patients with a confirmed diagnosis of non-ST elevation myocardial infarction (non-STEMI).

RESULTS: The hs-cTnT assay had an analytical range from 3 to 10 000 ng/L. At the 99th percentile value of 13.5 ng/L, the CV was 9% using the Elecsys® 2010 analyzer. The assay was specific for cTnT without interferences from human cTnI or cTnC, skeletal muscle TnT, or hemoglobin concentrations up to 1000 mg/L, above which falsely lower values would be expected. When the assay was evaluated clinically, a hs-cTnT higher than the 99th percentile concentration identified a significantly higher number of patients with non-STEMI on presentation (45 vs 20 patients, P = 0.0004) compared with cTnT, and a final diagnosis of non-STEMI was made in 9 additional patients (55 vs 46 patients, P = 0.23) after serial sampling. Time to diagnosis was significantly shorter using hs-cTnT compared with cTnT [mean 71.5 (SD 108.7) min vs 246.9 (82.0) min, respectively; P < 0.01].

CONCLUSIONS: The analytical performance of hs-cTnT complies with the ESC-ACCF-AHA-WHF Global Task Force recommendations for use in the diagnosis of MI.

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The Joint ESC-ACCF-AHA-WHF4 Task Force for the Redefinition of Myocardial Infarction has recommended the use of cardiac troponin (cTn) T or I for the diagnosis of acute myocardial infarction (AMI) (1). However, there are also important analytical requirements to ensure the reasonable comparability in myocardial infarction (MI) diagnosis. The guidelines suggest the need to detect increases of cTn in blood that exceed the 99th percentile of cTn concentrations in a normal reference population. The guidelines also suggest that the CV of the cTn assay used be ≤10% at the 99th percentile concentration. The vast majority of cTn assays lack adequate precision at the 99th percentile value, and most assays cannot truly define this value for a normal reference population. Thus, inconsistency of analytical definition of a positive cTn result and MI diagnosis has been observed between assays when concentrations are near the 99th percentile values (2). Previously, undetectable cTn concentrations have been documented to contain substantial diagnostic and prognostic information (3–8). Minute elevations of cTn are related to cardiovascular risk factors, carotid artery plaque burden, and myocardial dysfunction (9). In this context, we describe the validation of a novel high-sensitivity (hs)-cTnT assay.

Materials and Methods

ASSAY FORMAT AND COMPONENTS OF hs-cTnT ASSAY
We used the Elecsys®/cobas e™ cTnT fourth-generation assay (Roche Diagnostics) on the Elecsys 2010/cobas e 411 and Modular® Analytics E170/cobas e 601 immunoanalyzers (Roche Diagnostics) according to the instructions of the manufacturer. The assay uses fragment antigen-binding (FAB) fragments of 2 cTnT-specific mouse monoclonal antibodies in a sandwich format. The antibodies recognize epitopes located in
the central part of the cTnT molecule (amino acid positions 125–131 and 135–147, respectively). Detection is based on an electrochemiluminescence immunoassay (ECLIA), using a Tris(bipyridyl)-ruthenium(II) complex as label (10).

The new hs-cTnT assay (brand name TnThs) is a modification of the fourth-generation cTnT assay. The biotinylated capture antibody remained unchanged. The detection antibody was genetically reengineered, replacing the constant C1 region in the monoclonal mouse FAB fragment with a human IgG C1 region, leading to a mouse–human chimeric detection antibody. The rationale for this replacement was to further reduce the susceptibility to interferences by heterophilic antibodies (HAMAs). The variable region of the detection antibody is identical to that of the fourth-generation assay. Analytical sensitivity was improved by increasing the sample volume from 15 to 50 μL, increasing the ruthenium concentration of the detection antibody, and lowering the background signal via buffer optimization.

The assay procedure is analogous to that of the fourth-generation assay. First, the biotinylated capture antibody (2.5 μg/mL), the ruthenium-labeled detection antibody (2.5 μg/mL), and sample are incubated in homogenous phase for 4.5 min (Elecsys 2010/cobas e 411; STAT application) or 9 min (Modular E170/cobas e 611; normal application). Streptavidin-coated beads are added, and binding of the formed immune complexes to the microparticles takes place during a second 4.5- or 9-min incubation. After the second incubation, the reaction mixture is transferred into the measuring cell, where beads are captured to the electrode surface by a magnet. The measuring cell is washed to remove unbound label and filled with detection buffer containing Tris-propylamine. After applying voltage to the electrode, the emitted chemiluminescence light is detected by a photomultiplier. Results are determined via a 2-point calibration curve that is instrument specific.

**STANDARDIZATION OF hs-cTnT ASSAY**

We generated a new reference curve by diluting a stock solution of recombinant human cTnT [12 000 ng/L; isolated from cell culture of *E. coli* BL21 containing a plasma endothelin (pET) vector with human cardiac troponin T isoform 3 gene (Roche)] with analyte-free human serum (9 calibration points; 0–19 000 ng/L). We measure the initial concentration of the stock solution with the fourth-generation cTnT assay. We selected 5 newly produced master calibrators describing the standard curve in the range between 0 and 11 000 ng/L. We assigned values to the master calibrators by reading the reference curve on 8 different E170/cobas e 601 instruments, with 1 run per instrument. We used the Rodbard algorithm (11) to calculate the reference and master curves, and we used the median of all 8 values for each single master calibrator as the assigned value. The master curve was integrated into the barcode on the reagent Rack-Pack by including the curve parameters (11). Simultaneously, we selected 2 separately prepared kit-calibrators with target values at 18 and 4200 ng/L and assigned the values from readings on the master curve (median concentrations derived from 1 run on 8 instruments). The actual calibration, which is lot-specific, is contained in the barcode and can be adjusted by measuring the 2 kit calibrators to yield the instrument-specific calibration.

**ANALYTICAL PERFORMANCE**

The limit of blank (LoB) and limit of detection (LoD) were determined in accordance with Clinical and Laboratory Standards Institute (CLSI) EP17-A requirements (12). The LoD represents the 95th percentile value from n = 60 measurements of analyte-free samples over several independent series. We assessed dilution linearity by serial dilution of 3 human serum samples spiked with recombinant cTnT to concentrations covering the whole measuring range. Each sample was diluted up to 1:10 with analyte-free human serum as diluent in 10 consecutive steps. We measured all dilutions in duplicate with the various assay applications (STAT/normal) and calculated linearity separately for each assay application and instrument (E 2010/cobas e 411 or E170/cobas e 601). A mean (SD) recovery of the measured cTnT concentration of 100% (20%), compared with the expected cTnT concentration, was required to demonstrate acceptable linearity. We determined repeatability (within-run precision) and intermediate precision (between-run precision) according to CLSI protocol EP5-A2 using 6 pooled human serum samples and 2 controls (13). Each sample was measured in duplicate in 42 runs on 21 days, with 2 runs per day (n = 84).

**CROSS-REACTIVITY**

To detect cross-reactivity of other myofibrillar proteins with the hs-cTnT assay, human serum pools containing 18 and 38 ng/L native cTnT were spiked with the proteins to be investigated at a concentration of 50 000 ng/L. All samples were measured in duplicate. Cross-reactivity was defined as the ratio (cTnTspiked − cTnTnonspiked)/50 000 ng/L.

**INTERFERENCE TESTING**

Specificity of signal. To differentiate between a cTnT-specific signal and a signal generated by interferences or background noise, we designed competition experiments using free nonconjugated specific cTnT anti-
bodies (IgG of detection antibody M7) as well as non-conjugated unspecific antibodies such as IgG of an anti-thyroid-stimulating hormone (anti-TSH) antibody. Human serum samples with cTnT concentrations at the 99th percentile decision limit value (14 ng/L) and below were spiked with either the specific or unspecific antibody at the highly excessive dose of 1 g/L and incubated for 30 min at 25 °C. We measured the samples in duplicate, using 2 different lots of reagents. Signal reduction is expected only after spiking the samples with cTnT-specific antibody.

**Endogenous interferences.** We investigated possible interferences by endogenous substances following the methods of Glick (14). Human sera containing 18, 40, and 1000 ng/L cTnT (baseline sera) were spiked with the interference substance, and a dilution series of 10 dilution steps was made for each serum with the corresponding baseline serum. We measured the various dilutions in duplicate. For each dilution step, we calculated the percentage cTnT recovery compared to the baseline value. Interference was regarded acceptable if the cTnT recovery was within 100% (20%).

To investigate the influence of hemolysis, we used a freshly prepared hemolysate from purified erythrocytes for spiking and measured the hemoglobin concentration with hemoglobin assay HB500 (Diaglobal).

**METHOD COMPARISON**
We compared the fourth-generation cTnT STAT assay with the hs-cTnT STAT assay on the Elecsys 2010 system using 134 routine specimens from randomly selected patients with cTnT concentrations (fourth generation) between 10 and 10 000 ng/L. All samples were measured as a single determination. We calculated regression data according to the method of Passing and Bablok (11). To compare serum/plasma values, we measured 125 matched serum/Li-heparin sample pairs (range 3–9160 ng/L) and 109 matched serum/K₂EDTA sample pairs (range 3–9430 ng/L) in single determination.

**NORMAL REFERENCE (99TH PERCENTILE VALUE)**
We studied healthy individuals at 2 different centers to determine the upper reference limit for hs-cTnT. The combined study population included 616 apparently healthy volunteers and blood donors between 20 and 71 years old, including 307 women (49.8%).

**CLINICAL PERFORMANCE**
We studied patients with confirmed non-ST elevation acute coronary syndrome (ACS). The diagnosis of non-ST-elevation MI (non-STEMI) was made in the presence of signs or symptoms of myocardial ischemia and a fourth-generation cTnT concentration ≥0.03 μg/L within 24 h after the index event, with a typical rise and/or fall. Blood was collected on presentation and at 60-min intervals during the initial 6 h, and then after 24 h. We excluded patients with an initial negative cTnT result who underwent PCI before a second sample was obtained and demonstrated a postprocedural increase of cTnT and patients with an estimated glomerular filtration rate <60 mL/min/1.73m².

**STATISTICAL ANALYSIS**
We tested differences of categorical variables using the \( \chi^2 \) or Fisher exact test. We used unpaired Student \( t \)-tests or repeated-measures ANOVA with Bonferroni correction for multiple comparisons to compare continuous variables and performed nonparametric correlation analysis and Passing–Bablok linear regression analysis for comparison of assays.

**Results**
The LoB for the hs-cTnT assay was determined to be 3 ng/L, and the LoD 5 ng/L. Linearity was documented by dilution up to 10 000 ng/L. cTnT recovery was 100% (20%) after 1:10 dilution steps of 3 human serum samples spiked with recombinant cTnT to concentrations of approximately 30, 1000, and 10 000 ng/L. Identical values were obtained for all assay applications (STAT/normal) and all instruments (E 2010/cobas e 411 or E170/cobas e 601). Thus, the analytical measurement range was 3–10 000 ng/L.

Supplemental Fig. 1, which accompanies the online version of this article at www.clinchem.org/content/vol56/issue2, displays method comparison data between the fourth-generation cTnT and the hs-cTnT. There was a reasonable concordance over the whole measuring range \((y = 0.962x + 20\ \text{ng/L}; r = 0.9928; n = 605)\) except at the very low end. At 30 ng/L cTnT (fourth generation), hs-cTnT values were approximately 75% higher (Fig. 1). As a consequence, cTnT concentrations could not be directly compared between determinations with the fourth-generation and hs-cTnT assay at concentrations <100 ng/L. Test results with the fourth-generation cTnT assay measured at 30 ng/L were measured at approximately 50 ng/L with the hs-cTnT assay.

The hs-cTnT assay did not show significant cross-reaction with human skeletal muscle troponin T, human cTnI, human skeletal muscle troponin I, or human troponin C. Cross-reactivity with human skeletal muscle troponin T was 0.003%, human cTnI 0.2%, human skeletal muscle troponin I 0.003%, and human troponin C <0.001%.

After addition of a high concentration (1 g/L) of cTnT-specific antibody to samples containing 17, 8, or
4 ng/L, the signal was reduced to background level and hs-cTnT was no longer measurable. Conversely, addition of nonspecific TSH antibody reduced neither the signal nor the measurable concentrations of hs-cTnT significantly (Supplemental Fig. 2). No interference was seen with hemolysed blood for hemoglobin concentrations above 0.016 mmol/L (1000 mg/L), with a hemolysis index <100 as measured on Roche Diagnostics Modular clinical chemistry analyzers. No interference was observed with bilirubin concentrations up to 428 µmol/L, triglyceride concentrations up to 15 000 mg/L (intralipid), and biotin up to 82 nmol/L.

As cTnT is measured in serum, Li-heparin plasma, or EDTA plasma, we tested the recovery of cTnT using matched-pair analysis across the entire measuring range. There was a good correlation between serum and Li-heparin (y = 0.953x – 0.18 ng/L; r = 0.99790, n = 118) and serum and K₂-EDTA (y = 0.962x + 0.42 ng/L; r = 0.9935, n = 104). For lithium-heparin samples, larger maximal deviations of +50% (n = 2), +60% (n = 1), and +78% (n = 1) were observed in only 4 samples. The maximum negative difference was up to −30%. Correlation was excellent between serum and K₂-EDTA plasma, with a maximal difference of 20%.

The interassay precision for the 2010/cobas e 411 STAT and Modular E170/cobas e601 normal applications is shown in Fig. 2 (results determined in 54 and 46 pool samples, respectively). An imprecision (CV) of 9% was found at 13.5 ng/L with the Elecsys 2010/cobas e 411 STAT assay.

hs-cTnT vs cTnT on early and final diagnosis of non-STEMI
Using the hs-cTnT assay and 99th percentile cutoff, the number of patients with a final diagnosis of unstable angina decreased from 31 to 22 with a corresponding increase of the number of non–STEMI (Fig. 4). On admission, the use of the 99th percentile value identified a significantly higher number of patients with non-STEMI (45 vs 20 patients, P = 0.0004) than the fourth-generation assay. After serial sampling, the hs-cTnT assay identified more patients having a non-STEMI than the fourth-generation assay (55 vs 46 patients, P = 0.23). Given the small number of patients studied, this difference was not significant.

Differences between hs-cTnT and cTnT assays in serial monitoring
Two thirds of all patients with cTnT values <0.03 µg/L on admission had hs-cTnT values ≥13.5 ng/L. This percentage was even higher in patients presenting later than 4 h after onset of symptoms than in those admitt-
ted within 4 h (Fig. 5). The baseline hs-cTnT sample at a ROC-optimized cutpoint was associated with a sensitivity of 80.0% (95% CI 59.3–93.1), specificity of 81.0% (95% CI 65.9–91.4), a positive predictive value of 71.48% (95% CI 50.9–87.0), and a negative predictive value of 87.1% (95% CI 72.6–95.7). Additional blood draws within 3–5 h after admission improved the test performance further (Table 1 and Supplemental Fig. 3). Diagnosis of non-STEMI was made a mean of 2.92 h earlier than with cTnT [71.5 (108.7) min vs 246.9 (82.0) min].

Discussion

This hs-cTnT assay allows the detection of cTnT at the 99th percentile of an apparently healthy reference population with <10% variability, and thus complies with the requirements of the ESC-ACCF-AHA-WHF (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, World Heart Federation) (1), ESC/ACC (European Society of Cardiology, American College of Cardiology) (15), and IFCC Task Force (16) on redefinition of AMI. To meet the precision criteria, a 4-fold lowering of the analytical sensitivity was required. This was achieved by significant modification of the assay including increases in sample volume and ruthenium concentration to increase signal and changes in the buffer composition to reduce background signal.

Increases in analytical sensitivity can lead to an unintended rise in interference and background noise; however, hs-cTnT maintained its high cardiospecificity in competition experiments using monoclonal car-
specific and unspecific antibodies. Furthermore, there was no significant cross-reactivity with skeletal troponin T or C. Serum and plasma matrices provide comparable data and can be used without concern of interferences. Interassay imprecision (intermediate precision) was <10% when measured at the 99th percentile value (13.5 ng/L) using the Elecsys 2010 and was in general better for the normal application than the STAT application.

This assay was standardized against the fourth-generation assay and demonstrated an excellent correlation from 100 to 10 000 ng/L. As a consequence of the higher precision at low concentrations, there were significant differences in hs-cTnT and cTnT results below a value of 100 ng/L. As shown in Fig. 2, the 0.03 g/L (30 ng/L) 10% CV concentration of the fourth-generation assay is equivalent to a concentration of approximately 0.05 μg/L (50 ng/L) with the hs-cTnT assay. The 0.03 μg/L (30 ng/L) concentration with the hs-cTnT assay corresponds to a concentration of 0.01 μg/L (10 ng/L) with the fourth-generation assay. Thus, concentrations with the hs-cTnT assay should not be admixed with those obtained with the fourth-generation assay.

The hs-cTnT assay identified nearly 20% more patients with a final diagnosis of non-STEMI. This observation is in line with previous studies demonstrating that the use of the 99th percentile value as cutoff will increase the number of non-STEMI diagnoses (17). Moreover, hs-cTnT enabled an earlier diagnosis of non-STEMI. Two thirds of all patients with negative fourth-generation cTnT values already had increased

![Table 1. ROC analysis: performance of serial measurements for prediction or exclusion of non-STEMI using hs-cTnT.](image)

*Table 1. ROC analysis: performance of serial measurements for prediction or exclusion of non-STEMI using hs-cTnT.*

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Within 3 h</th>
<th>Within 5 h</th>
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<tr>
<td><strong>Area under the curve</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
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<td>0.883</td>
<td>0.945</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.703-0.900</td>
<td>0.786-0.946</td>
<td>0.865-0.985</td>
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<tr>
<td><strong>Optimal cutpoint, ng/L</strong></td>
<td>&gt;9.49</td>
<td>&gt;17.15</td>
<td>&gt;17.41</td>
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<tr>
<td><strong>Sensitivity, %</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>80.0</td>
<td>84.6</td>
<td>96.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>59.3-93.1</td>
<td>65.1-95.5</td>
<td>80.3-99.4</td>
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<tr>
<td><strong>Specificity, %</strong></td>
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<tr>
<td>Mean</td>
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<td>83.0</td>
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<tr>
<td>95% CI</td>
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<td>69.2-92.3</td>
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<td>Mean</td>
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<td>57.4-89.0</td>
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<tr>
<td><strong>Negative predictive value, %</strong></td>
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<tr>
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<td>77.9-97.4</td>
<td>86.8-99.6</td>
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*Fig. 5. Plot showing cumulative percentage of patients with a cTnT value above decision cutpoint and subdivided by time from onset of symptoms to admission <4 h versus ≥4 h.*

By definition, fourth-generation cTnT concentration was <0.03 μg/L. ULN, upper limit of normal.
hs-cTnT values (≥13.5 ng/L) on admission. This percentage was even higher in patients presenting later than 4 h after onset of symptoms than in those admitted within 4 h. Use of the admission hs-cTnT value to predict or exclude a non-STEMI on subsequent measurements was superior to use of the fourth-generation assay, and a second blood draw within the next 3–5 h improved the performance of hs-cTnT considerably.

Time to a positive result was significantly shorter using a 99th percentile threshold with the hs-cTnT assay than with the fourth-generation assay (71.5 (108.7) min vs 246.9 (82.0) min, respectively; P < 0.01). Thus, our results are in line with previous findings from Melanson et al. (18) showing that lowering the decision cutoff from the 10% CV to the 99th percentile threshold and using a more sensitive assay facilitates earlier detection of non-STEMI. More recently, the superior performance of high-sensitivity troponin T and troponin I assays for earlier detection of myocardial infarction compared to the less sensitive fourth-generation cTnT assay was confirmed in 2 larger trials (19, 20).

In a multicenter trial on 1818 consecutive patients with suspected AMI, Keller et al. (19) studied the performance of the high-sensitivity cTnI assay compared to the standard cTnT assay on admission, as well as after 3 and 6 h. In line with our results, the authors reported that a single sensitive troponin I value ≥0.04 μg/L had a negative predictive value of 84.1% and a positive predictive value of 86.7% in patients presenting within 3 h after chest-pain onset. Reichlin et al. (20) studied 718 consecutive patients who presented with symptoms suggestive of AMI and found superior performance of all 4 of the high-sensitivity cTn assays studied for earlier detection of MI compared with the standard assay, particularly among patients who presented within 3 h after onset of symptoms. However, these increases of assay sensitivity have been associated with decreases in specificity.

In a recent editorial, Morrow (21) pointed out that there is an urgent need to differentiate between tissue specificity of troponin and clinical specificity for myocardial infarction. As a lower decision cutoff will likely decrease diagnostic specificity, close adherence to the Universal MI definition is mandatory to discriminate ischemic from nonischemic causes of cTn elevation (1). This definition requires the presence of a typical rise and fall of cTn and at least 1 additional feature suggesting myocardial ischemia. The magnitude of rise or fall needed to define a substantial change is still unknown. After exclusion of AMI, the reason for the observed cTn elevation should be pursued actively to identify the possible causes of myocardial injury (21). Among others (22), these causes can include acute pulmonary embolism (23), chronic pulmonary arterial hypertension (24), end-stage renal disease (25), and acute (26) and chronic (27) heart failure.

Because there are no data on the risk associated with low hs-cTnT concentrations in patients with ACS, future prospective trials are needed to evaluate the benefits of specific interventions. However, higher sensitivity along with improved precision should allow better determination of the underlying etiologies and the clinical significance of these low concentration elevations. Unfortunately, we cannot provide any data on a broader spectrum of patients than those admitted to our chest pain unit.

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References


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