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High-sensitive cardiac troponin T

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Abstract

Cardiac troponin is the preferred biomarker for the diagnosis of acute myocardial infarction (AMI). The recent development of a high-sensitive cardiac troponin T (hs-cTnT) assay permits detection of very low levels of cTnT. Using the hs-cTnT assay improves the overall diagnostic accuracy in patients with suspected AMI, while a negative result also has a high negative predictive value. The gain in sensitivity may be particularly important in patients with a short duration from symptom onset to admission. Measurement of cardiac troponin T with the hs-cTnT assay may provide strong prognostic information in patients with acute coronary syndromes, stable coronary artery disease, heart failure and even in the general population; however, increased sensitivity comes at a cost of decreased specificity. Serial testing, as well as clinical context and co-existing diseases, are likely to become increasingly important for the interpretation of hs-cTnT assay results.

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1 Introduction

The troponin complex regulates the contraction of striated muscles and consists of three subunits (troponin C, troponin T, and troponin I). Troponin C is a 18 ku protein that binds to calcium ions. Troponin T is a 37 ku protein that binds to tropomyosin, thereby attaching the troponin complex to the thin filament. Troponin I is a 24 ku protein that binds to actin and decreases troponin C affinity for calcium, thus inhibiting actin–myosin interactions.[1]

Troponin T and troponin I are present in cardiac and skeletal muscles, but are encoded by different genes in the two types of muscle, yielding proteins that are immunologically distinct.[1] Assays that are based on high-affinity antibodies and are specific for cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are available. Because the amino acid sequence of cardiac troponin C and skeletal troponin C is identical, no such assays have been developed for the troponin C component.

The majority of cardiac troponin (cTn) is bound to myofilaments, and the remainder is free in the cytosol which accounts for 3%–8% of the total amount.[2] After disruption of the sarcolemmal membrane of the cardiomyocyte, troponin from the cytoplasmic pool is initially released, followed by a more protracted release from quantities bound to deteriorating myofilaments.[1] In peripheral blood, cTnT begins to rise within three to four hours after the onset of myocardial injury and remains increased for 10–14 days.[3]

2 Cardiac troponin assays

There are a number of cTnI assays on the market. These cTnI assays are not standardized at this time and studies have documented substantial differences across methods.[4] Apart from the lack of commutable reference material, other factors contributing to quantitative differences between the cTnI methods include the variable antibody immunoreactivity to different circulating cTnI forms and varying calibrators used in different cTnI assays.[4] The proper way to achieve complete standardization for cTnI assays would be to use antibodies with similar epitope specificities and a serum-based common reference material for calibration.[4] However, that is a complicated process and the progress has been slow.[5]

In contrast to cTnI, there is only one manufacturer for the cTnT assay and the above shortcomings could be avoided. The first-generation assay for cTnT used bovine cTnT as the reference material and exhibited non-specific binding to human skeletal muscle troponin,[6] but this problem was

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overcome by refinement of the detection antibody in the second-generation assay and the use of recombinant human cTnT for standardization in the third-generation assay.[7,8] The fourth-generation cTnT assay uses fragment antigen-binding (FAB) of two 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). Detection of cTnT is based on an electrochemiluminescence immunoassay using a Tris(bipyridyl)-ruthenium(II) complex as a label.[9] The fourth-generation cTnT assay has a limit of detection (LoD) of 0.01 ng/mL, a 99th percentile cut-off point of 0.01 ng/mL, and a 10% coefficient of variation (CV) of 0.03 ng/mL.[10] For the diagnosis of acute myocardial infarction (AMI), the fourth-generation cTnT assay is considered the standard assay. In addition, samples in which there is an increases of cTn in the blood exceeding the 99th percentile of the normal reference population, the guidelines suggest that the CV of the ideal cTn assay used is ≤ 10% at the 99th percentile concentration.[11,12] Clearly, the fourth-generation cTnT assay lacks adequate precision.

The new high-sensitive cTnT (hs-cTnT) assay is a modification of the fourth-generation cTnT assay.[9] The biotinylated capture antibody was not changed. The detection antibody was genetically re-engineered, 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.[9] The rationale for this replacement was to further reduce the susceptibility to interference by heterophilic antibodies. The variable region of the detection antibody is identical to that of the fourth-generation assay. The analytical sensitivity was improved by increasing the sample volume from 15 μL to 50 μL, increasing the ruthenium concentration of the detection antibody, and lowering the background signal via buffer optimization. As a result of these modifications, the analytic performance of the hs-cTnT assay was significantly improved; specifically, the LoD was 0.003 ng/mL (3 ng/L), the 99th percentile cut-off point was 0.014 ng/mL (14 ng/L), and the CV was 10% at 0.013 ng/mL (13 ng/L).[9] Due to a lower LoD and a increased precision, the hs-cTnT assay is able to detect more subtle elevations indicative of cardiac injury

3 Early diagnosis of myocardial infarction

The early identification of individuals at high or intermediate risk for myocardial ischemia is crucial because patients benefit the most from early and aggressive treatment.[13] The rapid and reliable diagnosis of AMI is a major unmet clinical need.[14] Myocardial necrosis is accompanied by the release of structural proteins and other intracellular macromolecules into the cardiac interstitium, such as cTn, creatine kinase, and myoglobin.[3] The preferred biomarker for myocardial necrosis is cTn, which has nearly absolute myocardial tissue specificity as well as high clinical sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[15] According to international consensus and task force definitions of myocardial infarction (MI), the diagnosis of MI is based mainly on evidence of myocardial ischemia, together with an elevated cTn level exceeding the 99th percentile and demonstrating an increase or decrease over time.[11] The universal definition recommends the use of a more sensitive troponin assay with a CV of 10% at the diagnostic cut-off concentration representing the 99th percentile of a reference population.[12] The recently developed hs-cTnT assay which has a lower CV satisfies this criterion,[9] together with a lower LoD.

In unselected emergency department (ED) patients with symptoms suggestive of an AMI, the hs-cTnT assay significantly improved the early diagnosis of AMI compared with the standard troponin T assay (fourth-generation cTnT).[16] According to the diagnostic criterion for an AMI, a hs-cTnT level > the 99th percentile (0.014 ng/mL), had a sensitivity, specificity, negative predictive value, and positive predictive value (95% confidence interval [CI]) of 95% (90%–98%), 80% (77%–83%), 99% (97%–100%), and 50% (43%–56%), respectively.[16] Based on a standard troponin T assay > 10% CV (0.035 ng/mL), the sensitivity, specificity, negative predictive value, and positive predictive value (95% CI) for diagnosis of AMI was 72% (64%–80%), 97% (96%–98%), 94% (92%–96%), and 85% (76%–91%), respectively. The diagnostic accuracy for AMI, as quantified by the area under the receiver-operating-characteristic curve (AUC), was significantly higher with the hs-cTnT assay than the standard assay (AUC for hs-cTnT, 0.96, 95% CI, 0.94–0.98 *vs*. AUC for the standard assay, 0.90; 95% CI, 0.86–0.94).[16] The superiority of the hs-cTnT assay was most pronounced among patients with a recent onset of chest pain. Among patients who presented within three hours after the onset of chest pain, the AUC was significantly higher with the hs-cTnT assay than the standard assay (AUC for hs-cTnT, 0.92, 95% CI, 0.87–0.97 *vs*. AUC for the standard assay, 0.76, 95% CI, 0.64–0.88).[16] The diagnostic performance of the hs-cTnT assay was similar in patients with non-ST segment elevation MI (NSTEMI) and ST segment elevation MI.[16] The hs-cTnI assay also improved the diagnostic ability in patients with AMIs.[16] Aldous *et al*.[17] reported that in patients with chest pain who did not have ST segment elevation, the hs-cTn assay at a

cut-off point of 99th percentile (0.014 ng/mL) was highly sensitive for the diagnosis of MI two hours after presentation compared with the standard assay. Improvement in the early diagnosis of AMIs in such patients is of paramount importance, because of the opportunity to extend early treatment options to all patients with AMIs.[16] More rapid diagnosis of AMI may reduce more complications by facilitating an earlier revascularization, earlier transfer to the coronary care unit, and earlier initiation of evidence-based treatment for AMIs.[14,16]

In patients with symptoms suggestive of acute coronary syndrome (ACS) and an initially negative cTnT concentration (< 0.03 ng/mL with the standard cTnT assay),[18] the criterion for the hs-cTnT assay (hs-cTnT ≥ 0.014 ng/mL) enables earlier detection of evolving NSTEMI compared to the criterion of the standard cTnT assay (cTnT ≥ 0.03 ng/mL).[18] On admission, 61.5% of the patients with ACS had hs-cTnT concentrations ≥ 0.014 ng/mL, and increased gradually to 100% of patients within six hours, and the overall number of MI diagnoses increased by 34.6%.[18]

In elderly patients (> 70 years of age) presenting with symptoms suggestive of AMI, the AUC was significantly greater for the hs-cTnT assay compared to the standard cTnT assay (AUC for the hs-cTnT assay, 0.94 *vs*. AUC for the standard cTnT assay, 0.90).[19] Because 51% of the elderly patients with a final diagnosis other than an AMI had elevated baseline hs-cTnT levels (≥ 0.014 ng/mL), the best cut-off value to detect an AMI for the hs-cTnT assay based on the AUC in elderly patients differed clearly from those in younger patients (0.054 ng/mL for elderly patients *vs*. 0.017 ng/mL for younger patients).[19]

In patients with pre-existing coronary artery disease (CAD) presenting with symptoms suggestive of an AMI, the diagnostic accuracy at presentation was significantly greater for the hs-cTn assay compared with the standard assay (AUC for the hs-cTnT assay, 0.92 *vs*. AUC for the standard cTnT assay, 0.87).[20] The optimal cut-off levels tend to be higher in patients with pre-existing CAD than in patients without a history of CAD (0.030 ng/mL for patients with pre-existing CAD *vs*. 0.020 ng/mL for patients without a history of CAD).[20]

For serial changes in the hs-cTnT assay within two hours after presenting with symptoms of a MI in patients with suspected ACS, Aldous *et al*.[21] reported that the diagnostic specificity of hs-cTnT improved with the use of relative change (δ) ≥ 20% in patients with concentrations ≥ 99th percentile at a cost of a reduction in sensitivity, while the diagnostic sensitivity improved with the use of a $\delta \geq 20\%$ in patients within 0–2 hours at concentrations < 99th percentile. However, Reichlin *et al*.[22] showed that the absolute changes in hs-cTnT levels have a significantly higher diagnostic accuracy for AMI than relative changes, and the optimal criterion of absolute change was 0.007 ng/mL for two hours.

In addition to diagnosing a MI, precisely and promptly ruling out a MI is important in an overcrowded ED.[23] With the previous cTn assay in most patients, blood should be obtained for testing upon presentation to the hospital and at 6–9 h after presentation to provide adequate clinical sensitivity for detecting a MI.[3] The diagnostic performance of the hs-cTnT assay was excellent, even in patients within two hours after the onset of chest pain.[16] The sensitivity for MI approaches 100% by including a second sample within three hours of presentation.[18,24] With the hs-cTnT assay, the negative predictive value for MI with a single test on admission is 95%, and thereby at least as high as achieved with previous assays using serial measurements.[25] Body *et al*.[26] reported that undetectable hs-cTnT (< 0.003 ng/mL) at presentation had a high negative predictive value for patients with chest pain at ED. An initially undetectable hs-cTnT has a sensitivity of 99.8% (95% CI, 99.1%–100.0%) and a negative predictive value of 99.4% (95% CI, 96.6%–100.0%) for ruling out an AMI.[26] Pending further validation, this strategy may reduce the need for serial testing and empirical treatment, enabling earlier reassurance for patients with chest pain and fewer unnecessary evaluations and hospital admissions.[26]

4 The prognostic value of hs-cTnT

4.1 In patients with CAD or diabetes mellitus

The cTn level is an important marker for risk stratification in patients with ACS. In patients with a suspected AMI, compared with the standard cTnT assay, the prognostic accuracy of hs-cTnT for death was significantly higher (AUC, 0.79; 95% CI, 0.74–0.84) than cTnT (AUC, 0.69; 95% CI, 0.62–0.76). After adjustment for the Thrombolysis in Myocardial Infarction (TIMI) risk score that included the standard cTnT assay result, hs-cTnT > the 99th percentile (0.014 ng/mL) was associated with a hazard ratio (HR) for death of 2.60 (95% CI, 1.42–4.74). Addition of hs-cTnT to the TIMI risk score improved the reclassification of patients (net reclassification improvement, 0.91; 95% CI, 0.67–1.14). Subgroup analyses showed that this effect resulted from the better classification of patients without an AMI at the time of testing.[27] In patients with pre-existing CAD and symptoms suggestive of an AMI, elevated levels of hs-cTnT predicted mortality independent of pre-existing CAD, age, gender, and cardiovascular risk factors.[20] In patients with chest pain who did not have ST segment elevation, the hs-cTnT assay was superior to the standard assay in pre-

dicting death (HR, 5.4; 95% CI, 2.7–10.7) and heart failure ([HF]; HR, 27.8; 95% CI, 6.6–116.4) at one year.[17] The hs-cTnT levels (≥ 0.001 ng/mL) were detected in 97.7% of patients with a mean age of 63.6 years, stable CAD, and preserved left ventricular function; ≥ 99th percentile of apparently healthy subjects (0.0133 ng/mL) represented 11.1% among this population.[28] During a median follow-up period of 5.2 years, after adjustment for other independent prognostic indicators, the hs-cTnT levels were significantly associated with the incidence of cardiovascular death (adjusted hazard ratio [aHR] per unit increase in the natural logarithm of the troponin T level, 2.09; 95% CI, 1.60–2.74) and HF (Ahr, 2.20, 95% CI, 1.66–2.90) but not with MI.[28] An increased risk associated with higher levels of hs-cTnT was evident well below the LoD (0.01 ng/mL) of standard cTnT assays and below the 99th percentile of values in a healthy population.[28] In the convalescence phase after an ACS, the levels of hs-cTnT continued to have prognostic value. A high seven week hs-cTnT (> 0.014 ng/mL) predicted adverse clinical outcomes independent of conventional risk factors, left ventricular dysfunction and left ventricular hypertrophy on echocardiography (aHR, 2.69, 95% CI, 1.45–5.00). Patients with persistent hs-cTnT elevation at seven weeks were also at an increased risk of cardiovascular events compared with patients who had an initial high hs-TnT which then normalized.[29] In female patients with diabetes mellitus (DM), the hs-cTnT levels were detectable in 45.5% of participants.[30] After adjustment for traditional risk factors and hemoglobin A1c, detectable hs-cTnT was associated with subsequent total cardiovascular disease and cardiovascular disease-related deaths.[30]

4.2 In patients with HF

Among patients with chronic HF, the cTnT was detectable in 92.0% of the patients using the hs-cTnT assay (LoD ≥0.001 ng/mL) compared to 10.4% using the standard cTnT assay (LoD ≥ 0.01 ng/mL).[31] After a median follow-up of 24 months, mortality was 7.8% in the lowest quartile of hs-cTnT levels and 35.6% in the highest quartile of hs-cTnT levels. The risk of death and hospitalization for HF increased significantly with an increase in the hs-cTnT level. Levels of hs-cTnT > median (0.012 ng/mL) were associated with more severe HF and worse outcomes.[31] Levels of hs-cTnT < the LoD using the standard cTnT assay retained prognostic value.[31] In patients with chronic HF recruited in multicenter clinical trials, the prevalence of elevated hs-cTnT (≥ 0.0135 ng/mL) at baseline was 64.0% in GISSI-HF and 47.1% in Val-HeFT.[32] Increases in the hs-cTnT levels over time were associated with age, DM, worsening of renal function, and increases in N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations.[32] Changes in hs-cTnT concentrations were associated with all-cause mortality and worsening HF. Serial measurement of hs-cTnT levels had robust prognostic value beyond that of a single measurement.[32] In patients with acute decompensated HF, a positive cTn test is associated with higher in-hospital mortality independent of other predictive variables.[33]

4.3 In patients with acute pulmonary embolism

Acute pulmonary embolism (PE) is a relatively common cardiovascular emergency, but it can lead to acute life-threatening, and potentially reversible right ventricular failure. An acute PE should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative obvious cause.[34] Early risk stratification of patients with acute PE is also important. In normo-tensive patients with confirmed PEs, the median value of hs-cTnT was 0.0272 ng/mL and 64% of patients had a hs-cTnT level ≥ 0.014 ng/mL.[35] The baseline hs-cTnT levels were higher in patients with adverse 30-day outcomes. A hs-cTnT cut-off value of 0.014 ng/mL showed excellent prognostic sensitivity and negative predictive value (both 100%).[35] In comparison, as many as 50% of patients with adverse early outcome would have been misclassified as low risk if a standard cTnT assay (cut-off 0.03 ng/mL) was used. Logistic regression indicated a two-fold increase in the risk of an adverse outcome for each increase in hs-cTnT by one standard deviation of the natural logarithm. Patients with elevated hs-cTnT levels had a reduced probability of long term survival.[35] Lankeit *et al*.[36] showed that the hs-cTnT assay can improve risk stratification in patients with acute PEs. In 526 normo-tensive patients with acute PEs, a hs-cTnT level > 0.014 ng/mL predicted early death and a decreased probability of 6-month survival.[36] Like the simplified Pulmonary Embolism Severity Index (sPESI) score, the hs-cTnT predicts risk for short-term adverse outcomes in normo-tensive patients with acute PEs. A hs-cTnT level of 0.014 ng/mL and a sPESI score of one had similar sensitivity (94% *vs*. 87%), specificity (40% *vs*. 42%), and an AUC (0.67 *vs*. 0.73) in predicting 30-day adverse outcomes.[37]

4.4 In patients with pulmonary arterial hypertension

Right ventricular failure is a leading cause of death in patients with pulmonary arterial hypertension (PAH). In PAH patients with a mean pulmonary artery pressure of 45 ± 18 mmHg, the levels of cTnT were detectable in 90.9% of the participants using the hs-cTnT assay compared to 30.9% using the standard assay.[38] Concentrations > the 99th per-

centile were observed in 27.3% of the participants using the hs-cTnT assay compared to 10.9% using the standard assay.[38] The levels of hs-cTnT were related to systolic right ventricular dysfunction and an impaired 6-min walk distance, and predicted death at least as effectively as heart-type fatty-acid-binding protein (hFABP) or NT-proBNP. Moreover, the levels of hs-cTnT above predicted the World Health Organization functional II class better than NT-proBNP or hFABP.[38]

4.5 In the general population

In community-dwelling adults ≥ 65 years of age without prior HF, a cTnT level was detectable (≥ 0.003 ng/mL) by hs-cTnT in the majority of participants (66.2%).[39] In this cohort of older adults without known HF, the baseline hs-cTnT levels and the changes in hs-cTnT levels were significantly associated with a risk of new-onset HF and cardiovascular death.[39] For participants with the highest hs-cTnT concentrations (> 0.0129 ng/mL), there was an incidence of 6.4 per 100 person-years for HF (aHR, 2.48; 95% CI, 2.04–3.00) and 4.8 per 100 person-years for cardiovascular death (aHR, 2.91; 95% CI, 2.37–3.58) compared to participants with undetectable hs-cTnT levels (incidence, 1.6 per 100 person-years for HF and 1.1 per 100 person-years for cardiovascular death).[39] For individuals with an initially detectable hs-cTnT, a subsequent increase of > 50% was associated with a greater risk for HF (aHR, 1.61; 95% CI, 1.32–1.97) and cardiovascular death (aHR, 1.65; 95% CI, 1.35–2.03) and a decrease of > 50% was associated with a lower risk for HF (aHR, 0.73; 95% CI, 0.54–0.97) and cardiovascular death (aHR, 0.71; 95% CI, 0.52–0.97) compared to participants with a ≤ 50% change.[39]

In the general population aged 30–65 years, the hs-cTnT levels were associated with structural heart disease and subsequent risk for all-cause mortality.[40] The prevalence of detectable cTnT (≥ 0.003 ng/mL) was 25.0% using the hs-cTnT assay compared to 0.7% using the standard assay.[40] The prevalence of left ventricular hypertrophy increased from 7.5% in the lowest hs-cTnT category (< 0.003 ng/mL) to 48.1% in the highest hs-cTnT category (≥ 0.014 ng/mL); the prevalence of left ventricular systolic dysfunction and chronic kidney disease (CKD) also increased across categories.[40] During a median follow-up of 6.4 years, all-cause mortality increased from 1.9% to 28.4% across higher hs-cTnT categories.[40] After adjustment for traditional risk factors, C-reactive protein level, CKD, and NT-proBNP level, the hs-cTnT category remained independently associated with all-cause mortality.[40]

In the general population aged 54–74 years of age free from CAD and stroke at baseline, the hs-cTnT levels (≥ 0.003 ng/mL) were detected in 66.5% of the participants.[41] The prevalence of detectable hs-cTnT in this population was similar to another study (66.2%), including participants ≥ 65 years of age without prior HF.[39] At the 10-year follow-up in fully adjusted models, compared to participants with undetectable levels of hs-cTnT (< 0.003 ng/mL), those participants with hs-cTnT levels in the highest category (≥ 0.014 ng/mL) had a significantly increased risk for CAD (HR, 2.29; 95%CI, 1.81–2.89), fatal CAD (HR, 7.59; 95% CI, 3.78–5.25), total mortality (HR, 3.96; 95% CI, 3.21–4.88), and new-onset HF (HR, 5.95; 95% CI, 4.47–7.92). Even a minimally elevated hs-cTnT level (≥ 0.003 ng/mL) was associated with an increased risk for mortality and new-onset HF. For patients with stable CAD and individuals free from CAD and stroke at baseline, the hs-cTnT levels has stronger prognostic value for new-onset HF and total mortality, with the exception of MI.[28,41]

5 The mechanism of hs-cTnT elevation in patients not having an AMI

Despite the nearly absolute specificity of cTn for myocardial tissue, the greater sensitivity of the cTnT assay was confusing.[42] For the standard cTnT assay, the prevalence of detectable cTnT (≥ 0.01 ng/mL) is rare (0.7%) in the general population.[43] For the hs-cTnT assay, in the general population 54–74 years of age free from CAD, stroke and HF at baseline, a hs-cTnT concentrations > 0.014 ng/mL was detected in 7.4% of individuals.[41] A similar prevalence was reported in another study.[39] In adults ≥ 65 years of age without prior HF, a hs-cTnT concentrations ≥ 12.94 ng/L was detected in 16.6% of individuals.[39]

In patients with stable CAD, a stronger correlation existed between the hs-TnT level and the total non-calcified plaque burden (r = 0.79).[44] Moreover, patients with remodeled non-calcified plaque had even higher hs-TnT values than all other groups, suggesting that the chronic, clinically silent rupture of non-calcified plaque with subsequent microembolisation may be a potential source of hs-cTnT elevation.[44]

In patients with HF, the prevalence of detectable troponin is high. Using the hs-TnT assay (LoD < 0.001 ng/mL, 92% of patients had a detectable value.[31] In addition to CAD, others mechanisms of cardiomyocyte damage could contribute to the cTn release in patients with HF, such as inflammatory cytokines, oxidative stress, hibernating myocardium, and apoptosis.[45,46] In patients with end-stage renal disease (ESRD), the prevalence of elevated hs-cTnT concentrations is 100%, and the elevated hs-cTnT concentrations are highly

prognostic of adverse events.[47] CAD is common in patients with CKD.[48] In addition to small areas of clinically silent myocardial necrosis, decreased clearance is another important factor for the elevated cTnT level in patients with CKD.[49] Because cardiovascular disease begins early in the course of CKD, differentiation of sources of elevated hs-cTnT levels in CKD patients is difficult. Nevertheless, the hs-cTnT elevation is still an independent predictor for adverse events.[47]

In patients with essential hypertension, hs-cTnT was detectable in 78% of participants.[50] The hs-cTnT levels were independently correlated with age, renal function, and electrocardiographic evidence of left ventricular hypertrophy. Apoptosis of cardiomyocytes may play an important role in compensatory hypertrophy due to hypertension.[50] In patients with DM, the alterations in glucose metabolism which shift to fatty acid metabolism may lead to increased oxidative stress, and may be an important mechanism underlying myocardial cell injury and cTnT release.[30]

In addition to the above-mentioned diseases, cTn elevation is common in many diseases, such as stroke, pulmonary embolism, sepsis, acute aortic dissection, acute perimyocarditis, hypovolemia, myocardial contusion, Tako-tsubo, and tachycardia.[42,51,52] Although cardiomyocytes can be renewable,[53] approximately one gram of myocardial mass, corresponding to 64 million cells, is lost per year in the human heart.[42,54] Everett *et al*.[30] speculated that the very low, but detectable hs-cTnT levels, may reflect a normal biological process of myocyte turnover. The detectable hs-cTnT in patients without AMIs may reflect a more malignant process of accelerated cell turnover caused by exaggerated catecholamine release, increased ventricular load, increased oxygen demand or decreased supply, inflammatory processes, hypoxia, and subendocardial ischemia.[42] Even though the regeneration of myocytes may contribute to an increase in muscle mass of the myocardium, a gradual decrease (from 1% turning over annually at 20 years of age to 0.3% at 75 years of age), < 50% of cardiomyocytes are exchanged during a normal lifespan.[53] Thus, it is not surprising that higher hs-cTnT levels predicted a worse prognosis regardless of conditions in cardiac or non-cardiac diseases. For exercise-induced cTnT release in a healthy population, the value of hs-cTnT is still uncertain.[55] Recent studies have demonstrated that in the case of reversible injury to the myocyte without necrosis, the cTn within the cytosol can be released as an intact protein via increased membrane permeability.[56]

Due to the high prevalence of elevated cTnT concentrations in patients with ESRD, a change in cTn concentration > 20% at 6–9 h after presentation has been recommended for the diagnosis of MI.[57] In patients with pre-existing CAD with a final diagnosis other than AMI, the high incidence (40%) of elevated hs-cTnT levels challenges the criterion of > 99th percentile for the diagnosis of AMI,[20] as suggested by current guidelines.[11] Careful clinical assessment, serial testing and thoughtful differentiation are required to separate AMI from other acute and chronic disorders also associated with low-level myocardial injury.[42] In these situations with minor elevation of cTn, observation of kinetic changes in cTn play an important role in distinguishing CAD from non-coronary diseases, especially with use of the hs-cTnT assay.[42]

6 Conclusions

The introduction of the hs-cTnT assay with lower cut-off levels for diagnosing AMI in patients with acute chest pain is associated with enhanced overall diagnostic accuracy. For different ages and in a different clinical context, the optimal criterion for diagnosing AMI varies. The gain in sensitivity may be particularly important in patients with a short duration from symptom onset to admission. A negative hs-cTnT test has a high negative predictive value, and may thus serve as an exclusionary test early in the diagnostic process.

In addition to risk stratification for ACS, the levels of hs-TnT can serve as a risk stratification in patients with stable CAD, HF, and non-cardiac disease conditions, even at levels below the LoD of the previous generation of assays. As multiple cardiac and non-cardiac conditions are associated with mild-to-moderate hs-cTnT elevations, the pretest likelihood of CAD, clinical presentation, and serial testing will become increasingly important for identifying those patients with true ACS.

References

1 Antman EM. Decision making with cardiac troponin tests. *N Engl J Med* 2002; 346: 2079–2082.
2 Katus HA, Remppis A, Scheffold T, *et al*. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol* 1991; 67: 1360–1367.
3 Morrow DA, Cannon CP, Jesse RL, *et al*. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 2007; 115: e356–e375.
4 Thygesen K, Mair J, Katus H, *et al*. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010; 31: 2197–2204.
5 Apple FS. Counterpoint: Standardization of cardiac troponin I assays will not occur in my lifetime. *Clin Chem* 2012; 58:

169–171.
6 Wu AH, Valdes R Jr., Apple FS, *et al*. Cardiac troponin-T immunoassay for diagnosis of acute myocardial infarction. *Clin Chem* 1994; 40: 900–907.
7 Muller-Bardorff M, Hallermayer K, Schroder A, *et al*. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. *Clin Chem* 1997; 43: 458–466.
8 Hallermayer K, Klenner D, Vogel R. Use of recombinant human cardiac Troponin T for standardization of third generation Troponin T methods. *Scand J Clin Lab Invest Suppl* 1999; 230: 128–131.
9 Giannitsis E, Kurz K, Hallermayer K, *et al*. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010; 56: 254–261.
10 Hermsen D, Apple F, Garcia-Beltran L, *et al*. Results from a multicenter evaluation of the 4th generation Elecsys Troponin T assay. *Clin Lab* 2007; 53: 1–9.
11 Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 60: 1581–198.
12 Thygesen K, Alpert JS, White HD, *et al*. Universal definition of myocardial infarction. *Circulation* 2007; 116: 2634–2653.
13 Mehta SR, Granger CB, Boden WE, *et al*. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; 360: 2165–2175.
14 Wright RS, Anderson JL, Adams CD, *et al*. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011; 57: e215–e367.
15 Jaffe AS, Ravkilde J, Roberts R, *et al*. It's time for a change to a troponin standard. *Circulation* 2000; 102: 1216–1220.
16 Reichlin T, Hochholzer W, Bassetti S, *et al*. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009; 361: 858–867.
17 Aldous SJ, Richards M, Cullen L, *et al*. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. *CMAJ* 2012; 184: E260–E268.
18 Giannitsis E, Becker M, Kurz K, *et al*. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem* 2010; 56: 642–650.
19 Reiter M, Twerenbold R, Reichlin T, *et al*. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. *Eur Heart J* 2011; 32: 1379–1389.
20 Reiter M, Twerenbold R, Reichlin T, *et al*. Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays. *Eur Heart J* 2012; 33: 988–997.
21 Aldous SJ, Richards AM, Cullen L, *et al*. Early dynamic change in high-sensitivity cardiac troponin T in the investigation of acute myocardial infarction. *Clin Chem* 2011; 57: 1154–1160.
22 Reichlin T, Irfan A, Twerenbold R, *et al*. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation* 2011; 124: 136–145.
23 Goodacre S, Cross E, Arnold J, *et al*. The health care burden of acute chest pain. *Heart* 2005; 91: 229–230.
24 Weber M, Bazzino O, Navarro Estrada JL, *et al*. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. *Am Heart J* 2011; 162: 81–88.
25 Hamm CW, Bassand JP, Agewall S, *et al*. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32: 2999–3054.
26 Body R, Carley S, McDowell G, *et al*. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011; 58: 1332–1339.
27 Hochholzer W, Reichlin T, Twerenbold R, *et al*. Incremental value of high-sensitivity cardiac troponin T for risk prediction in patients with suspected acute myocardial infarction. *Clin Chem* 2011; 57: 1318–1326.
28 Omland T, de Lemos JA, Sabatine MS, *et al*. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009; 361: 2538–2547.
29 Ang DS, Kao MP, Dow E, *et al*. The prognostic value of a 7-week high sensitivity troponin T level after an acute coronary syndrome. *Heart* 2012; 98: 1160–1165.
30 Everett BM, Cook NR, Magnone MC, *et al*. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: the Women's Health Study. *Circulation* 2011; 123: 2811–2818.
31 Latini R, Masson S, Anand IS, *et al*. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007; 116: 1242–1249.
32 Masson S, Anand I, Favero C, *et al*. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation* 2012; 125: 280–288.
33 Peacock WFt, De Marco T, Fonarow GC, *et al*. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008; 358: 2117–2126.
34 Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med* 2010; 363: 266–267.

35 Lankeit M, Friesen D, Aschoff J, *et al*. Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism. *Eur Heart J* 2010; 31: 1836–1844.
36 Lankeit M, Jimenez D, Kostrubiec M, *et al*. Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. *Circulation* 2011; 124: 2716–2724.
37 Dunn AS. ACP Journal Club. The simplified Pulmonary Embolism Severity Index and high-sensitivity troponin T predicted prognosis in PE. *Ann Intern Med* 2012; 156: JC4–JC12.
38 Filusch A, Giannitsis E, Katus HA, *et al*. High-sensitive troponin T: a novel biomarker for prognosis and disease severity in patients with pulmonary arterial hypertension. *Clin Sci* (Lond) 2010; 119: 207–213.
39 deFilippi CR, de Lemos JA, Christenson RH, *et al*. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010; 304: 2494–2502.
40 de Lemos JA, Drazner MH, Omland T, *et al*. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010; 304: 2503–2512.
41 Saunders JT, Nambi V, de Lemos JA, *et al*. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011; 123: 1367–1376.
42 Agewall S, Giannitsis E, Jernberg T, *et al*. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011; 32: 404–411.
43 Wallace TW, Abdullah SM, Drazner MH, *et al*. Prevalence and determinants of troponin T elevation in the general population. *Circulation* 2006; 113: 1958–1965.
44 Korosoglou G, Lehrke S, Mueller D, *et al*. Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. *Heart* 2011; 97: 823–831.
45 Kociol RD, Pang PS, Gheorghiade M, *et al*. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol* 2010; 56: 1071–1078.
46 Olivetti G, Abbi R, Quaini F, *et al*. Apoptosis in the failing human heart. *N Engl J Med* 1997; 336: 1131–1141.
47 Jacobs LH, van de Kerkhof J, Mingels AM, *et al*. Haemodialysis patients longitudinally assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and cardiac troponin I assays. *Ann Clin Biochem* 2009; 46: 283–290.
48 Hage FG, Venkataraman R, Zoghbi GJ, *et al*. The scope of coronary heart disease in patients with chronic kidney disease. *J Am Coll Cardiol* 2009; 53: 2129–2140.
49 Tsutamoto T, Kawahara C, Yamaji M, *et al*. Relationship between renal function and serum cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail* 2009; 11: 653–658.
50 Sato Y, Yamamoto E, Sawa T, *et al*. High-sensitivity cardiac troponin T in essential hypertension. *J Cardiol* 2011; 58: 226–231.
51 Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med* 2005; 142: 786–791.
52 Kelley WE, Januzzi JL, Christenson RH. Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. *Clin Chem* 2009; 55: 2098–2112.
53 Bergmann O, Bhardwaj RD, Bernard S, *et al*. Evidence for cardiomyocyte renewal in humans. *Science* 2009; 324: 98–102.
54 Olivetti G, Giordano G, Corradi D, *et al*. Gender differences and aging: effects on the human heart. *J Am Coll Cardiol* 1995; 26: 1068–1079.
55 Shave R, Baggish A, George K, *et al*. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol* 2010; 56: 169–176.
56 Sabatine MS, Morrow DA, de Lemos JA, *et al*. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. *Eur Heart J* 2009; 30: 162–169.
57 Wu AH, Jaffe AS, Apple FS, *et al*. National Academy of Clinical Biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin Chem* 2007; 53: 2086–2096.