How to use high-sensitivity cardiac troponin assays most effectively in clinical practice

July 2013

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Recently developed high-sensitivity cardiac troponin (cTn) assays can measure approximately 10 times lower concentrations with high precision (coefficient of variation, <10 % at the 99th percentile of the upper reference limit) than conventional assays, and can measure cTn concentrations in at least 50 % of a reference population.

Because high-sensitivity cTn assays can detect smaller amounts of myocardial injury within a shorter time after the onset of symptoms, they improve the early diagnosis, particularly early rule-out of acute myocardial infarction (AMI); additional testing of other early markers, such as heart-type fatty acid-binding protein, is no longer needed.

Improvements in analytical sensitivity have also increased the number of cTn elevations in various acute and chronic conditions with cardiac involvement other than AMI.

Thus, clinicians need to discriminate between AMI and chronic causes of cTn elevations and between MI type 1 and type 2. A rise and/or fall in cTn values is helpful in distinguishing AMI from chronic causes of cTn elevations associated with structural heart disease for which cTn values tend not to change acutely but may or may not be useful in differentiating MI type 1 from type 2.

Specific biomarkers reflect different pathophysiological aspects of acute coronary syndrome (ACS).

For example, cardiac troponin (cTn) and heart-type fatty acid-binding protein (H-FABP) are biomarkers of myocardial injury; natriuretic peptides reflect neurohormonal activation and hemodynamic stress; and high-sensitivity C-reactive protein (CRP), myeloperoxidase, and pentraxin 3 reflect various inflammatory processes.

Of these biomarkers, cTn has an important role in the diagnosis, prognostic assessment, and selection of the optimal treatment strategy in patients with suspected ACS. In addition, cTn is indicative of myocardial injury, which is closely associated with adverse outcomes in several other clinical situations such as heart failure [1, 2], renal failure [3], and pulmonary embolism.

The diagnostic cutoff value for acute myocardial infarction (AMI) recommended in the universal definition of myocardial infarction is a cTn value that exceeds the 99th percentile of a healthy population (upper reference limit (URL)), as determined by an assay with acceptable precision [4].

Optimal precision is considered CV ≤10 % at the 99th percentile URL, and it has been shown that using assays that do not have optimal precision (CV >10 % at the 99th percentile URL) does not cause false positive results.

Only assays with CV >20 % at the 99th percentile URL should not be used [4]. Whereas most conventional cTn assays do not fulfill the analytical criteria for optimal precision, recently developed high-sensitivity cTn assays possess a >10 times lower limit of detection, meet the analytical precision requirements, and can measure cTn concentrations in at least 50 % of a reference population.

Because high-sensitivity cTn assays can detect a lower degree of myocardial injury within a shorter time after the onset of symptoms, they improve the early diagnosis of AMI, particularly early rule-out of AMI.

Improvements in analytical sensitivity also have increased the number of cTn elevations in various acute and chronic conditions with cardiac involvement other than AMI. This contradiction has led to a shift in the utility of cTn from a specific identifier of AMI to a general indicator of myocardial injury.

Thus, clinicians need to discriminate between AMI and chronic causes of cTn elevation and between spontaneous myocardial infarction (MI type 1) and myocardial infarction secondary to an ischemic imbalance (MI type 2).

Early and reliable diagnosis of ami

The use of high-sensitivity cTn assays in patients with ACS allows earlier detection of AMI, increases the number of cases defined as AMI, and proportionately decreases the number of unstable angina cases.

High-sensitivity cTn assays improve the early and reliable diagnosis of AMI. Recent multicenter trials have demonstrated that the negative predictive value of high-sensitivity cTn assays for AMI with a single test on presentation is >95 % [5, 6].

By including a second sample result within 3 hours of presentation, the diagnostic sensitivity increases to 100 % [6]. Thus, high-sensitivity cTn assays can rule out AMI within 3 hours of presentation.

However, measurement of high-sensitivity cTn should be repeated 6 hours after presentation in patients in whom the 3-hour values are unchanged, but in whom the clinical suspicion of AMI remains high [7].

High-sensitivity cTn versus H-FABP

H-FABP is a low-molecular-mass cytoplasmic protein that, along with myoglobin, is among the earliest markers released into circulation after acute myocardial injury.

The H-FABP content of skeletal muscle is only 10-20 % of that of cardiac muscle, whereas the myoglobin content of skeletal muscle is approximately twice that of cardiac muscle. Along with other groups, we have shown that H-FABP is more useful than myoglobin and cTn for the early diagnosis of AMI [8-10].

Recently, we prospectively investigated the diagnostic and prognostic value of the serum level of high-sensitivity cardiac troponin T (cTnT) relative to H-FABP in 460 consecutive patients (median age 67.5 years) hospitalized in the cardiac emergency department for suspected ACS within 6 hours after onset of chest symptoms.

Cardiac events, which were defined as cardiac death or rehospitalization for ACS or heart failure, were monitored for 12 months after admission. The final diagnosis was adjudicated by two independent cardiologists. A total of 224 (48.7 %) patients were diagnosed as having AMI (ST-segment elevation myocardial infarction, 154 patients; emergent coronary angiography within 24 hours after admission, 195 patients).

The area under the receiver operating characteristic curve (AUROC) was higher for high-sensitivity cTnT than for H-FABP.
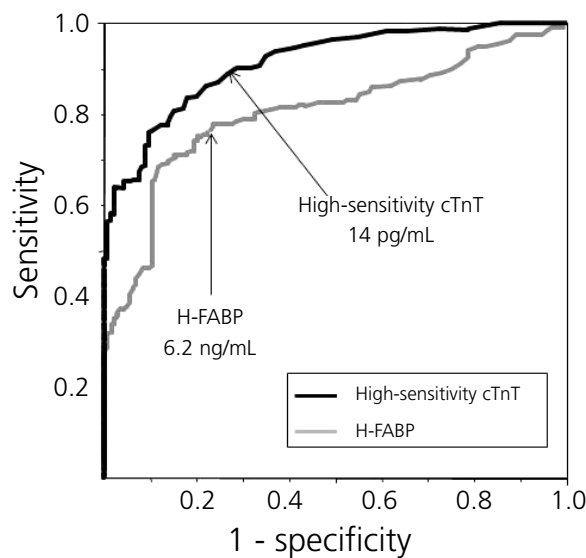

FIG. 1: Receiver operating characteristic (ROC) curves of high-sensitivity cTnT and H-FABP concentration between the AMI group and the non-AMI group. For the detection of AMI within 6 hours of onset of chest pain, the upward and leftward shift in the ROC curve between the AMI group and the non-AMI group was greater for high-sensitivity cTnT than for H-FABP. The area under the ROC curve of high-sensitivity cTnT (0.88, 95 % CI = 0.84-0.92) was significantly (P = 0.01) greater than the area under the H-FABP curve (0.82, 95 % CI = 0.78-0.88).

	High-sensitivity cTnT	H-FABP	P
AUROC	0.88	0.82	0.01
Sensitivity	90 %	77 %	<0.00001
Specificity	75 %	78 %	ns
NPV	87 %	78 %	<0.00001

TABLE I: Clinical performance of high-sensitivity cTnT vs H-FABP

The sensitivity and negative predictive value (NPV) of increased high-sensitivity cTnT (>14 pg/mL of the 99th percentile of a healthy population) were higher than those of increased H-FABP (≥6.2 ng/mL of the upper reference limit).

In addition, there was no significant difference in specificity between high-sensitivity cTnT and H-FABP. During a 12-month follow-up period, there were 38 (8.3 %) cardiac events, including 11 cardiac deaths.

In a stepwise Cox regression analysis, increased high-sensitivity cTnT (relative risk, 14.5; P = 0.009), but not H-FABP, was independently associated with cardiac events.

Patients with increased high-sensitivity cTnT had a higher risk of cardiac events within 12 months than those without (14.1 % vs 0.5 %, respectively; P < 0.0001). These findings indicate that a high-sensitivity cTnT assay may provide diagnostic and prognostic information superior compared with that of the H-FABP assay in the early phase of suspected ACS.

Additional testing of other early makers, such as H-FABP, is no longer required.

Discriminating between ami and chronic causes of cTn elevations

Elevation of cTn indicates myocardial injury regardless of its etiology, and does not necessarily indicate the presence of AMI. Improvements in analytical sensitivity have increased detection of cTn elevations, particularly mild cTn elevation, because of AMI but also because of numerous acute or chronic diseases other than AMI [4].

Accordingly, the specificity and positive predictive value of an elevated high-sensitivity cTn level are reduced if the diagnosis of AMI alone is considered.

With high-sensitivity assays, mild elevation of cTn detected in several patients with stable angina [11] or chronic heart failure [12] as well as in the general population [13, 14] is used to identify patients with

1. Injury related to primary myocardial ischemia
• Plaque rapture
• Intraluminal coronary artery thrombus formation

2. Injury related to supply/demand imbalance of myocardial ischemia
• Tachy/bradyarrhythmias
• Aortic dissection or severe aortic valve disease
• Hypertrophic cardiomyopathy
• Cardiogenic, hypovolemic, or septic shock
• Severe respiratory failure
• Severe anemia
• Hypertension with or without left ventricular hypertrophy
• Coronary spasm
• Coronary embolism or vasculitis
• Coronary endothelial dysfunction without significant coronary artery disease

3. Injury not related to myocardial ischemia
• Cardiac confusion, surgery, ablation, pacing, or defibrillator shocks
• Rhabdomyolysis with cardiac involvement
• Myocarditis
• Cardiotoxic agents, e.g., anthracyclines, trastuzumab (Herceptin)

4. Multifactorial or indeterminate myocardial injury
• Heart failure
• Stress (Takotsubo) cardiomyopathy
• Severe pulmonary embolism or pulmonary hypertension
• Sepsis and critically ill patients
• Renal failure
• Severe acute neurological diseases, e.g., stroke, subarachnoid hemorrhage
• Infiltration diseases, e.g., amyloidosis, sarcoidosis
• Strenuous exercise
• Electroconvulsive therapy

TABLE II: Elevations of cardiac troponin values because of myocardial injury

Modified from Thygesen K, Alpert JS, White HD *et al* [4]

either silent or clinically underestimated disease and, therefore, with a high risk of death.

Several studies have shown that high-sensitivity cTn elevation may be associated with adverse outcomes in patients with diabetes mellitus [15] or chronic kidney disease [16], suggesting that high-sensitivity cTn may be used as biomarkers in primary prevention of cardio-vascular disease, leading to identification of high-risk populations or individuals with silent heart disease.

Recently, we showed that quartiles of high-sensitivity cTnT values were associated with an increased cardiac event rate in 442 ambulatory patients with chronic kidney disease who were not undergoing dialysis (Fig. 2) [16].

Considering the high frequency of mildly elevated high-sensitivity cTn values in the community, particularly in patients with cardiovascular comorbidities, an increased high-sensitivity cTn concentration alone will be inadequate for clinical decision making.
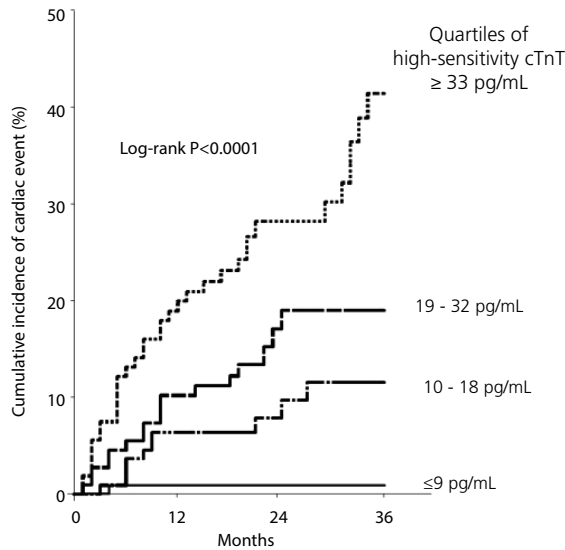
FIG. 2: Kaplan-Meier curves for cardiac events according to quartiles of high-sensitivity cTnT values. During the follow-up period (median 22 months), 63 cardiac events occurred in 442 ambulatory chronic kidney disease patients not on dialysis whose estimated glomerular filtration rate was <60 mL/min/1.73 m2. Kaplan-Meier incidence rates of cardiac events for 3 years were 0.88 %, 11.5 %, 19.0 %, and 41.4% among quartiles 1, 2, 3, and 4 according to high-sensitivity cTnT levels (P <0.0001) A clear difference among quartiles is evident. Modified from Hasegawa M, Ishii J, Kitagawa F et al [16].

The exception may be extremely elevated values, which are most often caused by AMI or myocarditis [17]. In other circumstances, cTn has to be interpreted as a quantitative variable.

It is important to distinguish AMI, which requires a rise and/or fall of cTn values, from chronic elevations that are associated with structural heart disease and tend not to acutely change.

Serial high-sensitivity cTn measurements and detection of early changes could improve specificity and overall diagnostic performance.

Recently, Reichlin *et al* demonstrated that a simple algorithm incorporating high-sensitivity cTnT baseline values and absolute changes within the first hour could be used to safely rule out and accurately identify AMI if performed within 1 hour in 77 % patients with chest pain [18].
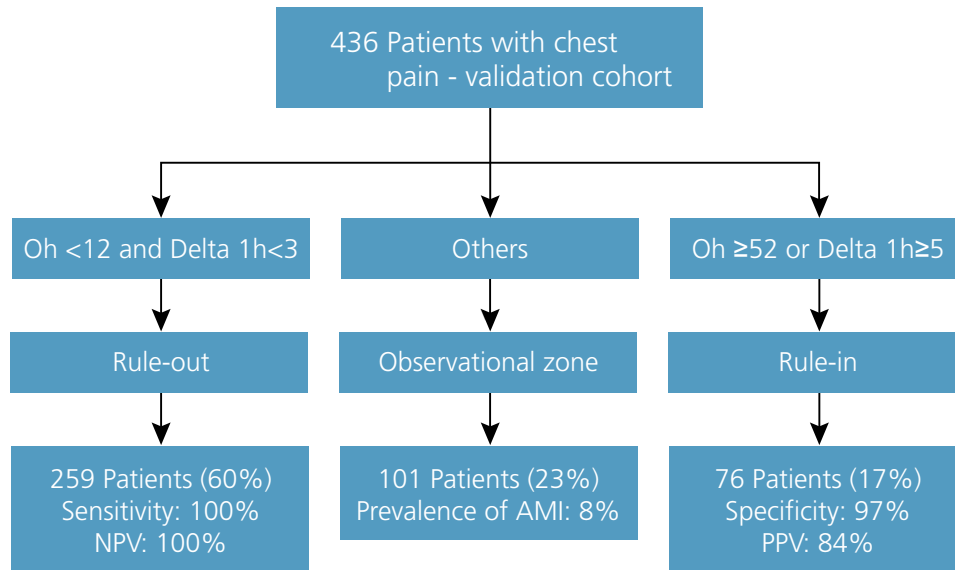

FIG. 3: Algorithm for diagnosis of AMI using high-sensitivity cTnT in patients presenting with chest pain. Results are displayed for the validation cohort (n = 436). High-sensitivity cTnT values are presented in pg/mL. 0 hours indicates high-sensitivity cTnT at presentation to the emergency department; Delta 1 hour, absolute change of high-sensitivity cTnT within the first hour; NPV, negative predictive value; and PPV, positive predictive value. Modified from Reichlin T, Schindler C, Drexler B et al [18].

Discriminating between type 1 and type 2 myocardial infarction

It should be clear that a rise and/or fall of cTn values is not specific for AMI but is rather indicative of acute myocardial injury.

The diagnosis of AMI is no longer restricted to those with a primary coronary event, usually atherosclerotic plaque rupture (MI type 1), but also in those with conditions caused by an imbalance between myocardial oxygen supply and/or demand in the coronary circulation (MI type 2; e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyar-rhythmia, anemia, respiratory failure, hypotension, and hypertension).

With high-sensitivity cTn assays, the frequency of MI type 2 appears to increase. A rise and/or fall of cTn values on serial testing may or may not be useful in differentiating MI type 1 from type 2 [19]. However, the etiology is entirely different. Thus, the clinical features should be considered to differentiate between MI type 1 from MI type 2.

Conclusions

High-sensitivity cTn assays improve the early diagnosis, particularly early rule-out AMI, and additional testing of other early makers, such as H-FABP, is no longer needed.

Improvements in analytical sensitivity also have increased the number of cTn elevations in various acute and chronic conditions with cardiac involvement other than AMI. Thus, clinicians need to understand how to most effectively use high-sensitivity cTn assays in clinical practice.

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