Specific biomarkers reflect different pathophysiological aspects of acute coronary syndrome (ACS). Of these biomarkers, cardiac troponin (cTn) plays an important role in the diagnosis, prognostic assessment, and management of patients with suspected ACS. 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), as determined by an assay with acceptable precision (coefficient of variation ≤10%) at the upper reference limit. Although most conventional cTn assays do not fulfill the analytical criteria, recently developed high-sensitivity cTn assays possess a more than 10-fold lower limit of detection and meet the analytical precision requirements. The improved analytical sensitivity of the cTn assay facilitates the precise quantification of myocardial injury, irrespective of its etiology.

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With the advent of high-sensitivity assays, cTn has become an early marker 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 more than 95%. By including a second sample result within 3 h of presentation, the diagnostic sensitivity increases to 100%. Thus, high-sensitivity cTn assays can rule out AMI within 3 h of presentation. The new European Society of Cardiology (ESC) guidelines, which were presented at the ESC 2011 Congress in Paris, propose a fast-track rule-out protocol (3 h) if high-sensitivity cTn assays are available.

The use of high-sensitivity cTn assays results in a higher percentage of non-ACS patients with elevated cTn levels. Thus, cTn assay specificity lowered if the diagnosis of AMI alone is considered. Low elevation of cTn is particularly detected in many patients with stable angina or chronic heart failure, as well as in the general population, to identify patients with either silent or clinically underestimated disease and, therefore, with a high risk of death. Thus, additional clinical studies are needed to distinguish chronic cTn elevation from acute cTn elevation. It is likely that both the cTn level at presentation and the change (Δ) in the cTn level within 1–3 h are critical elements in ruling out AMI in patients with elevated cTn levels.

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-mass cytoplasmic protein that, along with myocardial, is among the earliest markers released into the circulation after 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 for the early diagnosis of AMI.

The value of H-FABP in the early diagnosis of AMI was highlighted by a prospective multicenter trial in Japan that utilized a qualitative whole blood rapid panel test for H-FABP, which positively detected serum H-FABP ≥6.2 ng/ml. The sensitivity of the H-FABP test was significantly (P<0.001) higher than that of the cTnT (cTnT) test in patients who presented within 2 h (89% vs. 22%), between 2 and 4 h (96% vs. 57%), and between 4 and 6 h (100% vs. 67%). Among patients who presented more than 6 h after the onset of symptoms, the sensitivity of the H-FABP and cTnT tests was excellent. Conversely, the specificity of the H-FABP test was significantly lower than that of the cTnT test within 2 h of the onset of symptom (52% vs. 94%, P=0.002). These findings indicate that if patients present within 6 h of the onset of chest pain, H-FABP provides a more appropriate platform for diagnosis and prognosis than cTnT. Conversely, if patients present more than 6 h after the onset of chest pain, cTnT is appropriate. Because accurate prediction of the ischemic interval in ACS is difficult, a combination of H-FABP and cTnT measurements would provide a better early risk assessment for patients with ACS than would the measurement of either of these markers alone. However, the diagnostic performance of high-sensitivity cTn assays relative to H-FABP assays has not been fully evaluated in patients with suspected ACS.

In this issue of the Journal, Inoue et al investigate the diagnostic ability of a high-sensitivity cTnT assay relative to that of H-FABP, high-sensitivity C-reactive protein, myeloperoxidase, and pentraxin 3 assays for the early diagnosis of ACS at the time of patient presentation in the emergency department. Of the 432 patients enrolled, 85 presented within 2 h of the onset of chest pain; furthermore, 252 patients presented within 6 h of the onset of chest pain, and 302 (69%) had a final diagnosis of ACS.

The major finding of this study is that the diagnostic performance of the high-sensitivity cTnT assay is similar to that of the H-FABP assay for the early diagnosis of ACS. The area under the receiver-operating characteristic curve of both the high-sensitivity cTnT and H-FABP assays exceeded 0.80. In the present study, the use of the high-sensitivity cTnT improved the sensitivity for early diagnosis of ACS to 87.9%. Thus, high-sensitivity cTnT assays can diagnose ACS as early as H-FABP and can reliably rule out ACS in the early hours.
after the onset of symptoms. Considering the excellent sensitivity of high-sensitivity cTnT measurement for the early diagnosis of ACS, combining it with H-FABP measurement may not provide a clear advantage over the measurement of high-sensitivity cTnT alone.

In the study by Inoue et al the specificity of the high-sensitivity cTnT assays was low compared with that of the H-FABP assay (61.2% vs. 78.2%). High-sensitivity cTnT levels were elevated in 21% of the patients with atypical chest pain, 9% of those with effort angina pectoris, 88% of those with takotsubo myocarditis, and 62% of those with vasospastic angina. Because elevation of high-sensitivity cTnT levels indicates myocardial injury irrespective of the cause, the high rate of elevation of cTnT in non-ACS patients reflects its high sensitivity for myocardial injury. Thus, it is necessary for clinicians to rely on other techniques to more precisely classify patients in the clinical setting.

Reliable diagnosis of the very early phase of ACS is challenging. Inoue et al suggest that the combination of myeloperoxidase and H-FABP measurements may improve the diagnosis of ACS for patients presenting within 2 h of the onset of symptoms. Although these findings are interesting, the sensitivity of the combined myeloperoxidase and H-FABP measurements was low (69.2%). Thus, the effectiveness of this combination for the diagnosis of the very early phase of ACS should be investigated in future large studies.

Finally, the improved analytical sensitivity of the cTn assay facilitates the early diagnosis of AMI. High-sensitivity cTn assays can rule out AMI within 3 h after presentation. However, a substantial increase in the detection of non-ACS patients with slightly elevated cTn levels because of non-ischemic causes of myocardial injury occurs. This contradiction has led to a shift in how cTn is viewed, from a specific identifier of AMI to a general indicator of myocardial injury, requiring clinicians to understand the application of high-sensitivity cTn values.

References