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Review Article

Update on the use of cardiac markers in the diagnosis of acute coronary syndrome

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Abstract

Accurate identification of the cause of chest pain is a challenge to the emergency physician because a significant proportion of patients with acute coronary syndrome (ACS) present atypically. Cardiac troponins are the most sensitive and specific biochemical markers of myocardial damage, and are an important diagnostic tool in the evaluation of ACS. High-sensitivity troponins (hsTn) have been introduced in recent years, and have been shown to have increased accuracy in the diagnosis of acute myocardial infarction (AMI), both at presentation and upon early onset of chest pain. A combination of hsTn readings at presentation and at either 2 hours or 3 hours after the onset of symptoms increases the sensitivity of diagnosing AMI as compared to at presentation alone, and this combination may negate the need for other cardiac markers. The absolute change in hsTn 2 hours after presentation was also found to be useful in the diagnosis of AMI, but not the relative change. However, hsTn has lower specificity in comparison with traditional troponin, and its levels may be elevated even in certain non-ACS settings. The interpretation of troponin values in patients with chronic renal failure must also be done with caution, as their baseline may be elevated, even in the absence of an acute event. Given these pitfalls, the assessment of ACS must still be global, comprising clinical history, electrocardiogram changes, troponin increase, and/or a new wall-motion abnormality on echocardiogram or nuclear scan showing new loss of viable myocardium. High-sensitivity troponin also has a potential use in prognosticating atherosclerotic disease in chronic renal patients as well as population screening of cardiovascular risk factors, although these uses have not been well studied. Identification of patients with unstable angina without myocardial infarction also remains a challenge, as the sensitivity of cardiac troponin in this area remains moderate to low. However, new cardiac markers such as copeptin, ischemia-modified albumin, and heart-type acid binding protein, are still being studied and provide a window of hope in the diagnosis of unstable angina.

Keywords: Acute coronary syndrome; Cardiac markers; Chest pain; Diagnosis; Troponin

1. Introduction

Accurate identification of the cause of chest pain is a challenge to the emergency physician because a significant proportion of patients with acute coronary syndrome (ACS) present atypically.[1] The single or serial 12-lead electrocardiogram (ECG) performed at the emergency department (ED) has a sensitivity of only 40–60% for acute myocardial infarction (AMI) or ACS.[2] ST segment elevations, which are classically seen in the setting of a transmural myocardial infarction, can also be observed in non-ACS conditions such as acute pericarditis, left ventricular hypertrophy, left bundle branch block, Brugada syndrome, and early repolarization patterns.

2. Use of cardiac markers in the diagnosis of ACS

In the past 30 years, improved immunochemical techniques have made it possible for rapid measurements of a variety of markers indicating myocardial cell death. Several of these

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serum proteins including myoglobin, creatine kinase muscle–brain type (CK-MB), and troponins, have been found to be more sensitive in detecting AMI than based on history and ECG alone.[3–5]

Myoglobin is a low molecular weight protein (17 kD) found in muscle tissue. In myocardial injury, myoglobin rises in the initial 1–3 hours, then peaks at 5–7 hours, and returns to baseline by 24 hours. In theory, it is attractive as an early indicator of myocardial injury; however, myocardial myoglobins are not currently distinguishable immunologically from skeletal muscle myoglobin. As such, myoglobin levels may be elevated in patients with renal failure because of reduced clearance. It is also elevated in any clinical situation involving the skeletal muscle, such as trauma, significant systemic illness, or even strenuous exercise. Hence, it should be supplemented by a more cardiac specific-marker such as CK-MB or cardiac troponin.[6]

Due to the lack of a better marker, CK-MB was held as gold standard for AMI diagnosis in the late 1980s and 1990s. It is found in serum 3–8 hours after myocardial cell death with levels peaking at 10–24 hours and normalized within 2–3 days. Previous studies have demonstrated that diagnosis of AMI can be effectively established through the detection of rising levels of CK-MB within 6 hours after onset of symptoms.[4] Unfortunately, both false positives and false negatives have also been reported.

In the myocardium, both CK-MB and muscle–muscle type CK are present. Even though muscle–muscle type is the predominant type of CK-isoenzyme, skeletal muscle does contain small amounts of CK-MB (1–3%). Abnormal CK-MB elevation may be seen in trauma, muscular dystrophies, myositis, rhabdomyolysis, and after extremely vigorous exercise.

Later studies have shown that among chest pain patients, elevated conventional cardiac troponin (cTn) is a better predictor of 1-month and 1-year adverse cardiac events. Acute coronary syndrome patients who have normal troponin value and elevated CK-MB have excellent outcomes. However, patients who have elevated cTn levels without an elevated CK-MB have increased risk for developing future events.[7] Moreover, acute coronary syndrome patients with CK-MB negative but with a positive cTn result showed a benefit with aggressive antiplatelet and anticoagulation treatment, whereas patients with both negative CK-MB and cTn did not.[8,9]

Currently, two types of cTn—myocardial troponin T (TnT)[5] and troponin I (TnI)[10]—are used as markers of ACS. These troponins are genetically distinct from troponin forms found in other muscle tissue, and monoclonal antibodies to these troponins have little cross-reactivity with troponins from skeletal muscles. Unlike CK-MB, cTn is not found in serum of healthy individuals as there is very little day-to-day turnover of cardiac myocytes.

Normally, small quantities of troponins are found free in the myocardial cytosol. The majority is entwined in cardiac myofibrils. After myocardial injury, there is a biphasic rise in serum troponins. The initial surge corresponds to an early release of the free cytoplasmic proteins. This is then followed by a delayed and greatly prolonged rise consistent with breakdown of the cardiac muscle fiber over the next 5–7 days. This persistence is an advantage over CK-MB in patients who present late.

The sensitivity of cTn in detecting an AMI is low within the first hours after onset of chest pain, with a sensitivity of approximately 50% within 3–4 hours of an event. At about 6 hours after the onset of symptoms, the test is positive in about 75% of AMI patients, and in almost 100% at about 12 hours postevent.[11] Serial measurements of cardiac markers have been noted to improve the sensitivity of this instrument in diagnosis of AMI. Troponins are more sensitive for the diagnosis of myocardial injury than CK-MB with the potential of a less likelihood for inadvertently discharging patients with acute coronary syndrome from the ED. CK-MB might no longer required for the evaluation of ACS patients.[12]

3. Beginning of cardiac troponins

Since 2000, cTn has taken center stage for the diagnosis of AMI. ACC/ESC recommended the use of cTn level, equivalent to the 99th percentile of a reference population, measured with imprecision ($\leq$ 10% coefficient of variation, CV), as the cut-off value for the diagnosis of cardiac injury.[13] Until recently, 10% of CV values of the various troponin assays were always higher than the 99th percentile value, and were thus commonly used as the cut-off value instead of the 99th percentile value.

To date, only one manufacturer produces TnT assays (Roche Elecsys, Roche Diagnostics, Basel, Switzerland), and its 99th percentile cut-offs and 10% CV are well established. There are more than 10 commercially available TnI assays, each with their own 99th percentile and 10% CV levels.[14]

4. High-sensitivity troponins

A new generation of high sensitive assays for cardiac troponins (I and T) has been introduced, with the 99th percentile value of high-sensitivity troponin (hsTn) lower than the 10% CV. Two landmark studies on hsTn in the diagnosis of AMI have been published.[15,16]

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is a prospective study that enrolled 786 consecutive patients presenting to the ED with chest pain suggestive of ACS or angina equivalent, in which the onset or peak of symptoms had occurred within 12 hours of presentation.[15] Patients with end stage renal failure on dialysis were excluded. Blood was drawn at presentation, 1 hour, 2 hours, 3 hours, and 6 hours after presentation. The study end points were a final diagnosis of AMI or unstable angina within 60 days follow-up. The diagnosis of unstable angina required a positive cardiac exercise test or cardiac angiogram showing stenosis of >70% of one or more coronary arteries. The final diagnosis was adjudicated by two independent cardiologists reviewing all available records.

A summary of the results is shown in Tables 1 and 2. Seventeen percent of patients had a final diagnosis of AMI,

and another 16% had unstable angina. The study shows that diagnostic accuracy for AMI was significantly higher with the four sensitive troponin assays (Abbott-Architect TnI [Abbott Diagnostics, Abbott Park, IL, USA], Roche high sensitive troponin T [Roche Diagnostics, Basel, Switzerland], Roche TnI [Roche Diagnostics], Siemens TnI ultra [Siemens Healthcare Diagnostics, Erlangen, Germany]) than with the cTn assays (Roche Troponin T, Roche Diagnostics) at the time of presentation (Table 1). In this article, units for troponin levels are standardized as pg/mL instead of the conventional ng/mL due to the relatively smaller values of hsTn.

The superiority of hsTn over cTnT in the diagnosis of AMI is more profound in patients presenting to ED within 3 hours of onset of chest pain (Table 2).

However, the area under the curve (AUC) for diagnosis of unstable angina is low to moderate, with substantial difference among the assays: Abbott–Architect TnI, 0.56; 95% confidence interval (CI), 0.59–0.71; for Roche hsTnT, 0.76; 95% CI, 0.71–0.81; for Roche TnI, 0.56; 95% CI, 0.50–0.63; and for Siemens TnI, 0.68; 95% CI, 0.62–0.74.

A follow-up study from APACE showed that early (after both 1 hour and 2 hours) absolute hsTnI (Siemens TnI ultra) or hsTnT Roche changes were superior to relative hsTn changes in diagnosing AMI.[17] The receiver operating characteristic (ROC) curve-derived optimal cut-off values for absolute changes within 2 hours corresponded to approximately half of the 99th percentile value (7 pg/mL for hsTnT and 20 pg/mL for hsTnI). The superiority of absolute over relative change of hsTn levels was independent of underlying baseline hsTn values and time of onset of symptoms, and was also found to be applicable to the elderly and patients with impaired renal function. A combination of baseline hsTn levels with 1-hour or 2-hour absolute changes, but not relative changes, significantly improved the diagnostic accuracy of AMI as compared to when only baseline hsTn levels were used. Diagnostic accuracies for AMI provided by early absolute changes within 1 hour or 2 hours were not inferior compared with changes within 6 hours. However, this finding might be confounded by the fact that patients with AMI had elevated 0-hour, 1-hour, or 2-hour hsTn and were often already transferred to the coronary catheterization laboratory or coronary care units by 6 hours. Only 36% of the study populations had values of hsTn at baseline as well as after 1 hour, 2 hours, and 6 hours. Further confirmatory studies should to be done to determine whether 0-hour, 1-hour, and 2-hour serial hsTn are adequate instead of 0 hours, 2 hours, and 6 hours to exclude an AMI. Unfortunately, the diagnostic accuracy of absolute 2-hour hsTn changes, relative 2-hour changes, and baseline hsTn levels in differentiating unstable angina from noncardiac chest pain were all low.

Another similar study compared high-sensitivity troponin I (hsTnI) with conventional troponin I (cTnI)—both manufactured by Abbott–Architect—in predicting 30 day cardiac events (adjudicated by two independent cardiologists blinded to hsTnI results) enrolled 1818 consecutive patients (aged 18–85 years) who presented to the chest pain unit for chest pain or angina equivalent.[16,18] Blood was drawn at admission (0 hours), and 3 hours and 6 hours after admission to ED for hsTnI (level of detection, LoD, 3.2 pg/mL; 10% CV, 5.2 pg/mL; 99th percentile, 30 pg/mL), cTnI (LoD, 10 pg/mL; 10% CV and 99th percentile, 32 pg/mL) and eight other cardiac markers. A final diagnosis of AMI was made in 22.7% of cases and 13.2% of patients had unstable angina. The hsTnI had the highest AUC of 0.962 followed by cTnI (AUC, 0.921 vs. hsTnI $p < 0.001$) and subsequently heart-type fatty acid binding protein (H-FABP) (Evidence EV180 system, Randox Laboratories Ltd., Crumlin, UK) (AUC, 0.892 vs. hsTnI $p < 0.001$).

Using the LoD of hsTnI as diagnostic value, hsTnI at 0 hours achieved 100% negative predictive value (NPV) for MI with 35% specificity. Only 26% of the study population had hsTnI less than the LoD, and could have MI ruled out at 0 hours. Using 99th percentile as cut-off value, NPV at 0 hours

Table 2
Comparison between high-sensitivity troponins (hsTn) versus conventional troponin T (cTnT) in patients with recent chest pain (within 3 hours of onset) in the diagnosis of acute myocardial infarction.

Troponin	Area under the curve (95% CI)	A *p*-value of comparison of sensitivity with cTnT
Abbott–Architect TnI	0.96 (0.88–0.99)	0.010
Roche hsTnT	0.92 (0.87–0.97)	0.010
Roche troponin I	0.92 (0.86–0.99)	0.020
Siemens TnI ultra	0.94 (0.90–0.98)	0.005
cTnT	0.76 (0.64–0.88)	N/A

CI = confidence interval.
Note. Data from "Early diagnosis of myocardial infarction with sensitive cardiac troponin assays" by T. Reichlin, W. Hochholzer, S. Bassetti, et al. 2009, *N Engl J Med.* 361, p. 858–67.

Table 1
Comparison between high-sensitivity troponins (hsTn) versus conventional troponin T (cTnT) levels at presentation in the diagnosis of acute myocardial infarction.

Troponin	Area under the curve (95% CI)	LoD, pg/mL	10% CV, pg/mL	99th percentile, pg/mL	A *p*-value of comparison of sensitivity with cTnT
Abbott–Architect TnI	0.96 (0.94–0.98)	10	32	28	0.001
Roche hsTnT	0.94 (0.94–0.98)	3	13	14	0.008
Roche TnI	0.94 (0.92–0.97)	100	300	160	0.060
Siemens TnI ultra	0.96 (0.94–0.98)	6	30	40	0.009
cTnT[a]	0.90 (0.86–0.94)	33	54	33	N/A

CI = confidence interval; CV = coefficient of variance; LoD = level of detection.
Note. Data from "Early diagnosis of myocardial infarction with sensitive cardiac troponin assays" by T. Reichlin, W. Hochholzer, S. Bassetti, et al. 2009, *N Engl J Med.* 361, p. 858–67.
[a] 99th percentile of cTnT is 0.01 ng/mL which corresponds to 33 pg/mL of hsTnT, 10% CV = 0.03 ng/mL which corresponds to 54 pg/mL of hsTnT.

was 94.7% with specificity of 92.1%, NPV at 3 hours were 99.4% and specificity 90.4%. However, this study showed that the use of relative change of hsTnI at 0 hours and 3 hours did not further improve the NPV. The addition of early marker copetin or H-FABP only marginally increased the AUC of hsTnI to 0.968 ($p = 0.010$) or 0.967 ($p = 0.020$), respectively, in the diagnosis of AMI. Combining the 99th percentile cut off at 0 hours and 3 hours, the NPV was same for hsTnI (99.4%) as compared to when both hsTnI and cTnI were used together. The 0-hour hsTn allows an earlier prediction of AMI than the less sensitive cTn. Thus, the excellent performance of hsTn at 0 hours combined with a repeat reading at 2 hours or 3 hours could negate the need for other early markers of myocardial necrosis. Using the 99th percentile of hsTn as cutoff value to differentiate unstable angina from noncardiac chest pain, the AUC was 0.62 with a NPV of 84%.

At the Royal Infirmary of Edinburgh, the hospital decided to implement hsTnI (Abbott Architect assays, Abbott Diagnostics: LoD, 10 pg/mL, 99th percentile, 12 pg/mL; 10% CV, 50 pg/mL) to replace the cTnI (10% CV, 200 pg/mL).[19] During the validation phase, doctors would only be informed that the troponin level was raised if plasma troponin I was ≥200 pg/mL. A total of 2092 patients with suspected ACS were enrolled. Patients were followed up for a median of 453 days. Surprisingly, patients with hsTnI value of 50−190 pg/mL were more likely to have died or had an AMI (39%) at 12 months, compared with those hsTnI < 50 pg/mL (7%) or hsTnI ≥ 200 pg/mL (24%). However, after the implementation phase of hsTnI, patients with hsTnI value of 50−190 pg/mL were less likely to have died or have had an AMI at 12 months (21%; odds ratio, 0.42; 95% CI, 0.24−0.84; $p = 0.01$). The results were unchanged in the hsTnI < 50 pg/mL group (5%) and the hsTnI ≥ 200 pg/mL group (24%). Hence, adopting a diagnostic threshold of hsTnI of 50 pg/mL increased the number of patients diagnosed by AMI by 29%. The poorer outcome of patients with hsTnI 50−190 pg/mL during the validation phase may be explained by the fact that these patients did not receive treatment for AMI i.e., coronary revascularization (17% vs. 59%, $p < 0.01$) and dual antiplatelet therapy (27% vs. 80%, $p < 0.01$) due to the lack of diagnostic information. Lowering the diagnostic threshold of TnI and using hsTnI improved clinical outcome of those patients with hsTnI level 50−190 pg/mL.

5. Common causes for elevated troponin levels in the absence of ACS

In an ACS registry consisting of patients referred for early coronary angiography or primary percutaneous intervention for ACS, hsTn has been proven more sensitive in the diagnosis of AMI (78% vs. 66%). However, hsTn has also been shown to have a higher false positive rate in the diagnosis of ACS than cTn (7% vs. 2%).[20] In another prospective observation study on 337 low to intermediate risk chest discomfort patients with clinical suspicion for ACS presenting to the ED, all patients had a CT coronary angiography done. Conventional TnT and hsTnT were taken just prior to the CT angiogram (median 4.2 hours from presentation). Patients were followed up for 6 months. Thirty-seven patients (10.9%) had the diagnosis of ACS (MI and unstable angina) adjudicated by two physicians with all medical records, including CT angiogram findings and cTnT result, but with blinding to hsTnT. High-sensitivity TnT ≥ 13 pg/mL (99th percentile) was more sensitive than cTnT (cut-off point 10% CV, 0.03 ng/mL, equivalent to 53 pg/mL of hsTnT) in diagnosing ACS (62% vs. 35%; $p = 0.002$); however, the specificity was significantly less than cTnT (89% vs. 99%; $p < 0.001$).[21]

Cardiac troponins are the most sensitive and specific biochemical markers of myocardial damage. However, troponin elevations indicate the presence but not the mechanism of myocardial injury and myocardial damage can occur from a variety of mechanisms other than acute ischemia secondary to coronary artery disease.[22,23]

The non-ACS causes of elevated troponin level can be categorized as follows: (1) *demand ischemia* which refers to a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis, e.g., sepsis or septic shock, hypotension or hypovolemia, atrial fibrillation or other tachyarrhythmias; (2) *myocardial ischemia* caused by vasospasm: Prizemetal's angina, stroke symptoms, or subarachnoid hemorrhage, all of which cause damage due to an imbalance of the automatic nervous system, with resulting excess of sympathetic activity and increased catecholamine effect on myocardial cells; (3) *direct myocardial damage*: cardiac contusion, implantable cardioverter defibrillator shocks, amyloidosis, cardiotoxic effects of chemotherapy, acute pericarditis and myocarditis; (4) *myocardial strain* and pressure overload of both the right and left ventricle, as in congestive heart failure, pulmonary embolism or pulmonary hypertension (pulmonary right-heart strain), and strenuous exercise; and (5) *chronic renal deficiency* (see below).

Some of these patients can present with chest pain or angina equivalent, such as breathlessness. It is prudent to order and interpret the troponin test in tandem with the clinical situation. Troponin tests should not be ordered as a routine in patients presenting with shock and sepsis without clinical suspicion, or those with a low pretest probability for ACS. However, ACS patients might present with atypical symptoms including (but are not limited to) breathlessness, epigastric pain, backache, jaw pain, arm pain, mental confusion, weakness, malaise, syncope, apprehension, and nervousness. These symptoms are especially seen in elderly, female, diabetic, and demented patients. This leads to cTn Tests being ordered in many clinical scenarios. A slight elevation in troponin level is common in hospitalized patients within a large spectrum of clinical settings and comorbidities. It is very important for clinicians to develop a systemic approach to cTn elevation.

To classify troponin elevation into ACS and non-ACS is a challenge. A diagnosis of MI requires a combination of clinical history, ECG changes, troponin increase, and/or a new wall-motion abnormality on echocardiogram or nuclear scan showing new loss of viable myocardium. For patients with low pretest probability of coronary artery disease, the main goal is to identify the underlying cause of the troponin elevation.

6. Chronic troponin elevation in patients with chronic renal failure

High prevalence of elevated troponin levels (T more frequently than I) are observed in patients with chronic renal failure.[24] Cardiac TnT released from injured myocardium may have a longer circulating half-life compared with cTnI because of advanced glycation end products known to accumulate in diabetic patients with renal disease. Cardiac TnI decreases after dialysis, either directly attributable to removal by dialysis or indirectly by degradation of the labile cTnI molecule, resulting in lower circulating cTnI levels compared with cTnT. In a population of 733 end-stage renal failure patients treated with intermittent hemodialysis for at least 30 days, a substantially greater proportion of patients had increased predialysis cTnT level relative to cTnI (Dade–Behring, Siemens Healthcare Diagnostics) regardless of cut-off criteria used; e.g., 99th percentile: 82% (10 pg/mL) versus 6% (100 pg/mL); 10% CV: 53% (30 pg/mL) versus 1.0% (400 pg/mL); and ROC: 20% (100 pg/mL) versus 0.4% (600 pg/mL). Median patient follow-up was 1.6 patient–years with a total of 192 deaths (26.2%). This study reported that elevated TnT but not TnI increased the risk of long-term mortality.

A recent study of a 143 asymptomatic dialysis patients (112 on hemodialysis and 31 on peritoneal dialysis) also suggested that the baseline troponin cut-off values should be adjusted for patients with renal failure.[25] The patients were followed-up for a median of 46.7 months or 3.9 years, and 55 of 143 patients died during the course of the study (38.5%). Baseline predialysis hsTnT and TnT were measured. A cut-off point of 24.15 pg/mL for the hsTnT assay was determined using the ROC curve analysis. cTnT assay was categorized as detected or not detected. All individuals with hsTnT levels below 24.15 pg/mL remained alive during follow-up whereas 54 of 114 (47.4%) patients with values above this point died. This cut-off point was more accurate in predicting prognosis than cTnT being present or absent as was used previously. Serum TnT levels that exceed threshold values in chronic hemodialysis patients proved to be valuable for identifying patients at risk for future adverse cardiac events.

A prospective study of 162 asymptomatic individuals with stable chronic kidney disease not requiring renal replacement therapy showed similar results. These patients underwent echocardiography and coronary artery calcification scoring.[26] Blood sample collected at the time of recruitment showed that 38% of individuals had raised hsTnI (Dimension Vista 1500, Siemens Healthcare Diagnostics) and 68% had raised hsTnT above the 99th percentile of the healthy controls. During follow-up, there was found to be a significant increase in mortality in the group of patients with raised hsTnI and hsTnT. However, whether TnT increases the short-term mortality (30 days) is unclear. It has also not been well studied as to whether elevated TnT might be used as a diagnostic tool for coronary disease and the initiation of treatment of atherosclerotic disease in this patient population.

Cardiac disease is a major cause of death in patients with end stage renal disease.[27] However, the magnitude of rise and falls of troponin to diagnose ACS in chronic kidney disease patients with chest pain or angina equivalent has not been well established. A retrospective chart review of patients with chronic kidney disease (defined as serum creatinine $>$ 176.8 mmol/L or 2.0 mg/L) and with suspected acute coronary syndromes presenting to the ED was conducted. Changes between two consecutive serial cTnT measurements within 12 hours showed that in a subgroup of 64 patients with an initial cTnT measurement above 100 pg/mL, an increase in cTnT of 110 pg/mL in a second cTnT measurement within 12 hours had a positive likelihood ratio of 13.3 and 11.9 for in-hospital and 30-day adverse cardiac event, respectively.[28]

7. Detectable hsTn level in the community

Cardiac hsTnT was detectable ($\geq$3 pg/mL) in 80.9% of a healthy population, e.g., workers of a company aged 35–63 years, excluding those with cardiovascular disease (CVD) and on hemodialysis.[29] 2.2% of this population had hsTnT level of more than 10 pg/mL. The odds ratio for a high predicted CVD risk (10 year risk, $\geq$20%) in the highest tertile of hsTnT ($\geq$5 pg/mL) in comparison to the lowest tertile ($\leq$2 pg/mL) was 3.98 (95% CI 1.72–9.24; $p = 0.001$). No participants had a detectable troponin when measured by the cTn (10% CV, 30 pg/mL, corresponding to 53 pg/mL of hsTnT). Similarly, cardiac hsTnT was detectable in 66.2% of a community population ($n = 4421$) aged 65 years or older without prior heart failure and 16.6 % of this population had hsTnT more than the 99th percentile (13 pg/mL).[30] Again, the population with hsTnT $\geq$ 13 pg/mL was associated with an increased incidence rate of cardiovascular death compared to those with undetectable hsTnT (4.8%; 95% CI, 4.3–5.4 vs. 1.6%; 95% CI, 1.4–1.8). These findings may suggest the usefulness of measuring hsTnT to identify high-risk individuals in the primary prevention of CVD. This may also explain why hsTn has a higher false positive rate in the diagnosis of AMI than cTn. It is unclear at present whether we should use a higher cut-off value for making the diagnosis of AMI in chest pain patients aged $\geq$ 65 years.

8. Diagnosis of unstable angina

In our ED population, about 5–10% of patients with chest pain, nondiagnostic ECGs, and low level of serial hsTn ($<$99th percentile) could still have unstable angina, i.e., underlying severe coronary artery disease. Thus, the identification of patients with unstable angina remains a real challenge. Currently, we have to rely on expensive and labor-intensive cardiac investigations such as stress ECG, stress nuclear scan, or CT coronary angiogram.[31,32] By contrast, elevated B-type natriuretic peptide levels in the presence of acute coronary syndrome predict a worse outcome, but B-type natriuretic peptide has not been shown to be a good marker for the diagnosis of acute coronary syndrome or unstable angina.[33] Currently, new cardiac markers such as ischemic-modified albumin, copeptin, and free

fatty acid binding protein[34−36] have shown potential in diagnosing ACS, and are still being extensively studied, with the hopes that one of them may have utility in the diagnosis of unstable angina.

9. Conclusion

In the context of patients presenting to the ED with chest discomfort, hsTn has been proven to be more sensitive than cTn in the diagnosis of AMI, especially in those with small AMI, and in patients who present early to the ED. Cardiac hsTn has provided strong diagnostic information even in cTn-negative patients, and the excellent performance of hsTn at 0 hours combined with 2 hours or 3 hours could negate the need for other early markers of myocardial necrosis. More studies should be done as to whether this combination is adequate, or if 6-hour hsTn will increase the sensitivity in the diagnosis of AMI.

However, hsTn has also been shown to have a higher false positive rate in the diagnosis of ACS than cTn. It is therefore important to appreciate the non-ACS causes of elevated troponins, both cardiac and noncardiac, in its interpretation. Troponin tests should thus not be ordered routinely in patients with clinical presentations that are not consistent with ACS and in whom the pretest probability for a cardiac event is low.

Given its pitfalls, it would be inappropriate to overemphasize the importance of troponins. Cardiac markers are but an isolated portion of a picture: a diagnosis of MI requires a combination of clinical history, ECG changes, new wall-motion abnormality on echocardiogram or nuclear scan showing new loss of viable myocardium, in addition to changes in cTn levels. Moreover, good clinical skill is still required to differentiate illnesses that mimic ACS and also cause elevated troponin, such as pulmonary embolism.

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