PART I

Biomarkers for the Evaluation of Patients with Ischemic Heart Disease

Chapter 1

Protocols for diagnosing myocardial infarction

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Introduction

In 2005 cardiac markers of necrosis were ordered for over 13 million patients in Emergency Departments (EDs) in the United States [1]. The use and interpretation of cardiac markers are fundamental for the diagnosis of myocardial infarction (MI). Cardiac marker protocols for diagnosing MI must be viewed in the context of the consensus document published in 2007 concerning the redefinition of MI. This consensus document states the rise and fall of a specific cardiac marker, preferably cardiac troponin I or T (cTnI, cTnT) is essential to the diagnosis of MI, in the context of either ischemic cardiac symptoms, electrocardiographic changes, or a new wall motion abnormality on cardiac imaging [2]. This chapter will discuss the candidate markers for diagnosing MI. In addition, different strategies for "ruling-in" and "ruling-out" MI will be reviewed, including multimarker approaches, analysis of change over time in marker levels, and point-of-care testing.

Candidate markers and kinetics

CK-MB

Prior to the introduction of cTnI and cTnT, creatine kinase (CK)-MB was the most common marker of myocardial necrosis used in the evaluation for MI. CK-MB is an 86,000 Dalton isoenzyme that is predominantly located in myocardial cells and is released into the circulation in the setting of MI. However, CK-MB constitutes 1–3% of the total CK found in skeletal muscle, and is also present in smaller quantities in other tissues such as intestine, diaphragm, uterus, and

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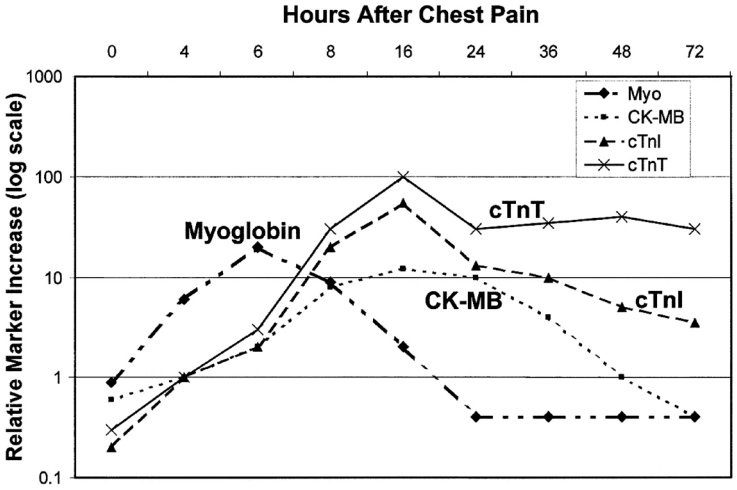

Fig. 1.1 Temporal release patterns of myoglobin, CK-MB, cTnI, and cTnT following myocardial infarction. *Clin Chem* 2007; **53**: 552–574.

prostate [3]. The specificity of CK-MB for diagnosing MI is limited by the fact that it is not unique to the myocardium and is elevated in the setting of muscle trauma. The use of a relative index, which is a function of the level of CK-MB mass relative to total CK activity, improves specificity, but may limit sensitivity [4]. Moreover, CK-MB may be elevated due to clearance abnormalities in renal failure or hypothyroidism. CK-MB becomes elevated in the circulation 3–6 hours after symptom onset in MI, and remains elevated for 24–36 hours (Fig. 1.1).

Cardiac troponin I and T

The troponins (I, C, and T) are a complex of proteins that modulate the calcium-mediated interaction between actin and myosin in myocardial tissue [5]. cTnI and cTnT are 23,500 and 37,000 Dalton molecules, respectively; they have isoforms that are unique to cardiac myocytes, enabling very specific assays using monoclonal antibodies to select epitopes of the cardiac form [6,7]. Most troponin is bound to the contractile apparatus of the cardiomyocyte, but 3% of cTnI and 6% of cTnT exist free in the cytoplasm [8,9]. The initial elevation of cTnI or cTnT detected in the circulation after myocardial necrosis is thought to be a function of the free cytolsolic form, whereas the prolonged elevation is caused by degradation of the contractile pool. The early release kinetics of cTnI and cTnT are similar to CK-MB, allowing detection at 3–6 hours after symptom onset during MI. However, cTnI and cTnT may remain elevated for 4–7 and 10–14 days, respectively.

The cardiac troponins offer numerous advantages over CK-MB for evaluating patients with possible MI. Because cTnT and cTnI do not circulate in

measurable levels among healthy adults, a very low cut-off range can be used to define elevation, leading to higher sensitivity than CK-MB. Patients who in the past would have been classified as unstable angina with normal CK-MB values may have minor myocardial necrosis detected by an elevation in cTnI or cTnT [10,11]. Introduction of widespread troponin testing resulted in up to a 25% increase in the detection of MI in patients with normal CK-MB values [12]. With the newer, more sensitive cTn assays the increased frequency of the diagnosis of MI may even be higher, estimated at 28% to 195% depending on the cut-point used [13]. Cardiac troponin measurement yields fewer false-positive results in the setting of trauma, surgery, and renal failure as compared to CK-MB [14,15].

The recommended cut-off value for an elevated cardiac troponin is the 99th percentile of a control reference group at a precision level of $\leq$10% Coefficient of Variation (CV, which is a measure of precision and is defined as standard deviation/mean) [2]. Although these low-level cardiac troponin elevations are very specific for myocardial damage, troponin elevation in itself does not indicate the mechanism of injury. Pulmonary embolism, congestive heart failure, and myocarditis can all lead to cardiac troponin elevation [16]. In addition, diabetes mellitus, left ventricular hypertrophy, chronic kidney disease, and congestive heart failure can all lead to minor cardiac troponin elevation in an asymptomatic, ambulatory population [17].

Myoglobin

Myoglobin is a 17,800 Dalton hemoprotein that is found in all tissues. Myoglobin has been used in the diagnosis of MI because it is an early marker that can be detected 1–2 hours after symptom onset, and remains elevated for up to 24 hours; studies have shown that myoglobin offers high sensitivity for detecting MI in the first few hours after presentation [18]. However, the use of myoglobin as a stand-alone marker has significant limitations including low-specificity for MI in patients with renal failure or skeletal muscle trauma [19]. Also, given that myoglobin rises and falls rapidly in the setting of MI, the level may normalize in patients that present >24 hours after symptom onset [20]. Considering its rapid rise and fall, and limited specificity, myoglobin has usually been used in combination with CK-MB or cTn.

Point-of-care testing

There are several assays that can measure cardiac markers at the point-of-care (POC). These include assays that measure myoglobin, CK-MB, and cTnI or cTnT. As cTn is the preferred cardiac marker for evaluating patients with possible MI, all manufacturers of POC cardiac markers include either cTnI or cTnT. The POC assays can be either quantitative or qualitative and some have corresponding

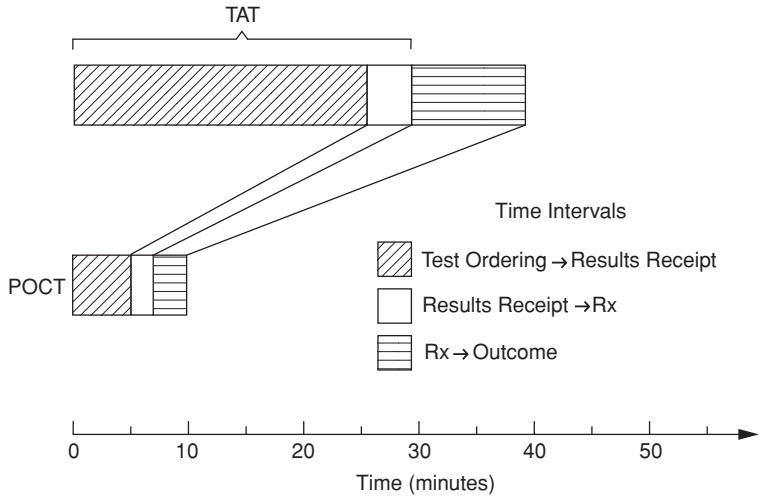

Fig. 1.2 Time intervals influencing therapeutic turnaround time (TAT) for central laboratory (top) and point of care (POCT) (bottom) testing strategies. Rx = therapy. Kost G. *Chest* 1999; **115**: 1140–1154.

central laboratory analyzers that yield similar results. If an institution uses a POC device that does not have a corresponding central laboratory analyzer, this is important to realize as the same specimen will yield different results on POC and central lab tests, and the cut-points for determining abnormal results will be different, which may lead to clinical confusion. Although in general central laboratory systems offer greater precision at low levels of biomarkers, some studies have shown equivalent clinical performance between POC technology and central laboratory assays [21–27]. However, one study of 4447 patients with acute coronary syndrome demonstrated that a significant number of patients that had a positive central laboratory cTnT assay did not have elevated values as measured by a cTnI POC device [28]. Thus, it is critical to know the diagnostic performance of the particular assay that is being used.

The promise of POC testing of cardiac markers is a more rapid turnaround time (TAT) leading to possible faster triage and treatment of patients evaluated for MI. Factors that affect TAT are delays in delivery of the sample to the central laboratory, preanalytical steps necessary to prepare sample, analysis time, and delivery of results to the ordering physician (Fig. 1.2). The National Academy of Clinical Biochemistry (NACB) [29] and the International Federation of Clinical Chemistry (IFCC) [30] have recommended 60 minutes or less from the time that blood is drawn to the reporting of results. The American College of Cardiology/American Heart Association (ACC/AHA) have also recommended a 60-minute TAT, but state 30 minutes is preferred [31].

Table 1.1 Turnaround time (in minutes) for point of care testing compared to central laboratory

Reference #	POCT	Central Laboratory	Time Reduction
Cargher [32]	38	87	49
Lee-Lewandrowski [35]	17	110	93
Collinson [36]	20	79	59
McCord [37]	24	71	47
Singer [40]	15	83	68
Sieck [39]	20	90	70
Gaze [34]	20	85	65
Altinier [38]	17	82	65
Hsu [33]	26	65	39

POCT = Point-of-Care Testing

Numerous studies have shown that when using POC devices the TAT for cardiac marker results can be decreased in the range of 39 to 93 minutes when compared to a central laboratory strategy [32–40] (Table 1.1). This time savings can translate into more rapid triage and medical decision making. In a randomized controlled study in the ED by Murray [41], 93 patients had blood testing at the POC and 87 patients had samples sent to the central laboratory. Blood tests that were available at the POC included electrolytes, glucose, hematocrit, and qualitative CK-MB and myoglobin. Patients were only entered into the trial if all blood tests ordered were available POC. This was a heterogeneous population and did not require that the patient was being evaluated for possible MI. The median length of stay (LOS) of patients in the POC group was 3.5 hours and in the central laboratory group 4.4 hours ($p = 0.02$). The difference was greater in discharged patients who comprised 75% of all patients: POC 3.1 hours versus central laboratory 4.3 hours ($p < 0.001$). In a study by Singer [40] of patients evaluated for MI in the ED, 232 patients had cTnI measured in the central laboratory in the initial phase and subsequently 134 patients had cTnI measured at the POC. No other tests were measured at the POC. The median LOS in the POC group was 5.2 hours versus 7.1 hours in the central laboratory group. The time to results reported in the POC group was 14.8 minutes as compared to 93 minutes in the central laboratory group. In addition, the time to call for admission in the POC group was 2.7 hours as compared to 4.7 hours in

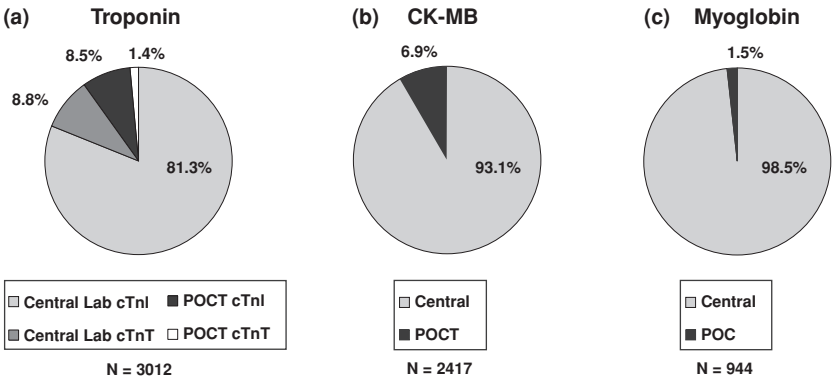

Fig. 1.3 Survey performed by the College of American Pathologists in 2005 to evaluate utilization of central laboratory compared to point of care testing (POCT) for cardiac markers. Wu A. *Point of Care* 2006; **5**: 20–24.

the central laboratory group. Thus, in this study measurement of POC cTnI led to faster medical decision making and decreased LOS. POC testing of cardiac markers has been used in the prehospital setting in ambulances and in remote locations such as cruise ships [42–45]. Although POC testing of cardiac markers is more expensive per unit test, the decrease in LOS may make a POC strategy financially appealing in certain institutions.

Although it is intuitively appealing that the more rapid identification and treatment of non–ST-segment elevation myocardial infarction (NSTEMI) patients by cTn measured at the POC can improve patient outcomes, there are no compelling data to validate the 30–60 minute recommended TAT for cardiac markers. Time to identification and treatment of patients with ST-segment elevation myocardial infarction (STEMI) is crucial as improved patient outcomes are clearly very time dependent [46], but initial decision making is based on electrocardiographic findings rather than biomarker levels. In contrast, although patients with NSTEMI identified by an elevated cTn benefit from glycoprotein IIb/IIIa inhibitors, low-molecular weight heparin, and cardiac catheterization with percutaneous intervention [47–50], there are insufficient data to conclude that these therapies delivered 60 minutes or so earlier, afforded by POC measurement of cTn, improve patient outcomes. Although POC testing of cardiac markers are used in some centers, most institutions measure cardiac markers in the central laboratory (Fig. 1.3). Although it is hoped that POC testing will eventually impact outcomes in ACS, at the present time the most compelling reason to use POC testing is to more rapidly identify high- and low-risk patients, which may lead to shorter LOS. The exact affects of POC testing will likely be specific to certain institutions and depend on factors such as volume, patient acuity, and staffing.

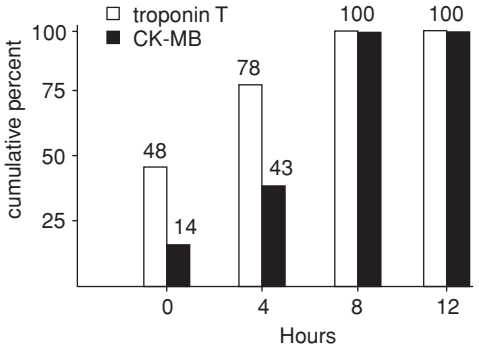

Fig. 1.4 Proportion of patients with elevation of troponin T or CKMB through 12 hours in a chest pain observation unit. Newby. *Am J Cardiol* 2000; **85**: 801–805.

Serial sampling of cardiac markers

Elevations of cTnI and cTnT are not sufficiently sensitive at presentation in the ED and must be measured serially over time to adequately exclude MI. Numerous professional organizations agree that cTn should be measured over at least 6 hours. Although some guidelines state that 6 hours is adequate [51], others suggest 6–9 hours [52,53], or even 6–12 hours [54]. Newby [55] evaluated 383 consecutive patients in a chest pain observation unit that had nondiagnostic electrocardiograms, no high-risk clinical features, and normal CK-MB values at presentation. There were eight (2.1%) patients that had MI. Patients had serum CK-MB and cTnT measured at 0, 4, 8, and 12 hours. All patients who were positive by either CK-MB or cTnT at 12 hours were already identified by both positive CK-MB and cTnT at 8 hours (Fig. 1.4). Hamm [56] evaluated 773 patients with chest pain of less than 12 hours duration and without ST-segment elevation on their electrocardiograms. There were 47 (6.1%) patients with a diagnosis of MI. Samples were taken for cTnI at presentation and at 4 hours. If the patient presented within 2 hours after chest pain onset, then a third sample was drawn at least 6 hours after symptom onset. Therefore, all patients had at least 2 samples, the last being at least 6 hours after symptom onset. Among the 47 patients with MI, 31 (66%) had a positive cTnI at presentation and all 47 (100%) had an elevated cTnI at 4 hours. Herren [57] evaluated a 6-hour "rule-out" MI strategy in 292 consecutive patients evaluated in the ED with nondiagnostic electrocardiograms who presented within 12 hours of symptom onset. All patients had CK-MB measured at arrival. If patients presented <3 hours after symptoms onset, there was a CK-MB measured at 6 hours. Patients that presented within 3–12 hours of symptom onset had a second CK-MB measured at 3 hours after presentation. Patients then had a cTnT measured at 48 hours. Of the 238 patients that had all normal CK-MB values, there was only 1 that had an elevated cTnT

of 0.11 ng/dl. On review at 1 month this one patient was doing well with no electrocardiographic evidence of MI. The negative predictive value for MI of serial CK-MB over 6 hours was 99.6%.

The study by Newby suggests there is no reason to measure cTn beyond 8 hours. Although in the Hamm study cTnI was not measured in general beyond 6 hours after symptom onset, there were only 2 adverse events at 30 days (1 death and 1 MI after discharge) in the 602 patients that had negative cTnI, yielding a 0.3% adverse event rate. Thus, an adequate sample set for evaluating patients for possible MI is a sample at presentation and a second at least 6 hours after symptom onset. Patients that present >6 hours after symptom onset may proceed to stress testing, if clinically indicated, with 1 normal cTn value at presentation. With newer, more sensitive and precise cTn assays the necessary time period for serial testing will likely shorten (see next section).

Multimarker strategies and analysis of dynamic change in markers over time

Taking advantage of the different release kinetics of the various cardiac markers, studies of combinations of markers have evaluated the ability to rapidly exclude MI in less than 6 hours. A cardiac marker that rises early in the setting of MI, most commonly myoglobin, combined with one that increases later, CK-MB or cTn, allows MI to be identified more rapidly and, therefore, excluded in less time. A patient who has completely normal myoglobin and CK-MB or cTnI over the first few hours after presentation to the ED could proceed to their final disposition more rapidly. Patients that have only an elevated myoglobin would require serial testing over a longer period to confirm myocardial necrosis. Kontos [58] evaluated 101 patients admitted from the ED for possible MI. Blood samples for CK-MB and myoglobin were taken at 0, 4, 8, 16, and 24 hours. There were 20 MIs. The individual sensitivities for myoglobin and CK-MB at 0 and 4 hours were 85% and 90%, respectively. The combined sensitivity for both markers over 4 hours was 100%. McCord [37] studied 817 patients in the ED where myoglobin, cTnI, and CK-MB were measured at 0, 1.5, 3, and 9 hours. There were 65 patients with MI. The combined sensitivity of myoglobin and cTnI over 90 minutes was 96.9% (negative predictive value 99.6%). Measurement of CK-MB and blood sampling at 3 hours did not improve sensitivity. It should be noted that these studies used CK-MB as the gold standard for MI detection, and thus sensitivity may not be quite as high if a troponin-based standard was used.

A dynamic change (delta) in any cardiac marker can identify a patient earlier in the setting of MI. Various strategies utilizing delta markers alone or in combination with typical abnormal cut-off values have been studied. Ng [59] studied 1285 consecutive patients in the ED. There were 66 (5.1%) patients diagnosed with MI. Myoglobin, cTnI, and CK-MB were measured at 0, 0.5, 1.0, 1.5, 3, and 6 hours. At 90 minutes the combined sensitivity of CK-MB, cTnI, and delta-myoglobin (defined as >25% increase over 90 minutes) was 100%. Kontos

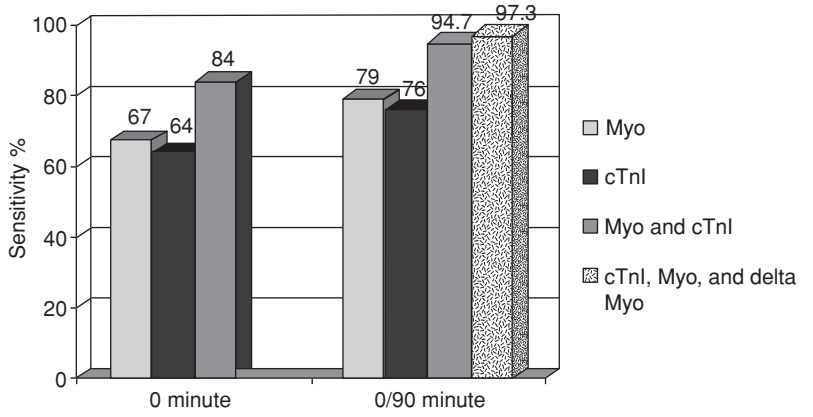

Fig. 1.5 Sensitivity of myoglobin, cTnI, and delta myoglobin (increase > 20 ng/ml from baseline to 90 minutes) to detect myocardial infarction within 90 minutes of presentation. Sallach. *Am J Cardiol* 2004; **94**: 864–867.

[60] evaluated 2093 patients who were admitted to the hospital for possible MI. There were a total of 186 (8.9%) MIs. The combined sensitivity at 3 hours for the combination of CK-MB ≥8.0 ng/mL, relative index (CK-MB × 100/total CK) ≥4.0, or at least a 2-fold increase in CK-MB without exceeding the upper range of normal was 93% over 3 hours. Fesmire [61] studied 710 patients evaluated in the ED who had a baseline CK-MB <2 times the upper limits of normal (12 ng/mL) and blood draws at 0 and 2 hours. A CK-MB was considered positive at 6 ng/mL and a delta-CK-MB was positive if there was a change from 0 to 2 hours of ≥1.6 ng/mL. There were 113 patients diagnosed with MI (68 NSTEMI and 45 STEMI). The sensitivities of CK-MB and delta-CK-MB at 2 hours were 75.2% and 92%, respectively. The specificity of 2-hour delta-CK-MB was 95.3%. These studies, and many others, although of conceptual interest, also employed a CK-MB definition of MI and thus have limited clinical application in the modern era. Few studies have evaluated multimarker or delta-marker strategies in the context of cTn-defined MI.

Sallach [62], in a retrospective reanalysis of a prior study [37], analyzed 817 consecutive patients evaluated in the ED. MI was defined in accordance with the ESC/ACC 2000 guidelines concerning the redefinition of MI and required at least one cTnI >0.4 ng/mL. Blood samples were taken at 0, 1.5, 3, and 9 hours for myoglobin and cTnI. A delta-myoglobin >20 ng/mL increase over 90 minutes was considered positive. There were 75 patients (9%) who had MI. The sensitivities for the various combinations are shown (Fig. 1.5). The combined sensitivity of cTnI, myoglobin, and delta-myoglobin >20 ng/mL was 97.3% at 90 minutes. There were only 2 patients with MI not identified within 90 minutes with this strategy. One patient had intermittent chest pain consistent with unstable angina that led to an MI. The myoglobin rose from 144 ng/mL

at 90 minutes to 233 ng/mL (>200 ng/mL abnormal) at 3 hours and cTnI was abnormal at 9 hours. The other patient actually had a decrease of myoglobin >20 ng/mL at 90 minutes, and if this patient was considered positive the early sensitivity would be even higher. This patient likely had a very early peaking myoglobin that was already decreasing. Fesmire [63] reported on 975 patients evaluated in the ED that had blood samples drawn at 0 and 2 hours for cTnI, CK-MB, and myoglobin that had a cTnI at presentation ≤1.0 ng/mL (Abbott Axym). MI was defined as either cTnI >1.0 mg/mL, new significant Q-waves in 2 contiguous leads, cardiac death, or death for unknown reason. They reported that the sensitivity of delta- CK-MB >0.7 ng/mL at 2 hours of 93.2% was higher than delta-myoglobin >9.4 ng/mL of 77.3%.

Improved troponin assays: cut-points, precision, and implications for the role of myoglobin and CK-MB

The recommended cut-point for an abnormal cTn is at the 99th percentile of a reference control group with an acceptable CV ≤10%. [2] Earlier cTn assays had such a high degree of analytical imprecision at low levels that none met the stringent precision requirements at these low levels, so a higher cut-point than the 99th percentile was used to meet the ≤10% CV precision requirement. However, assays have now been developed that are close to or meet the criterion for <10% CV at the low 99th percentile level. Most published studies have used the less precise and less sensitive cTn assays. However, a few studies have investigated the early diagnostic utility of these new sensitive and precise cTn assays. MacRae evaluated the need for measuring cTnI over 6 hours when evaluating patients for possible MI in the ED [64]. The assay used the AccuTnI (Beckman Coulter) with the 99th percentile level of 0.04 ng/mL. This was a retrospective study performed using stored samples from 1996. There were 258 patients enrolled and specimens were collected at presentation and then hourly until 6 hours after symptom onset, and thereafter at 9, 12, 24, and 48 hours. MI was defined as at least 1 sample >0.04 ng/mL and at least 20% change between specimens. There were 92 MIs. There was not a significant difference in the proportion of patients with troponin elevation when comparing patients who had cTnI measured ≥3 hours as compared to ≥6 hours (Fig. 1.6). This study suggests that with the newer, more sensitive, and precise assays that a "rule-out" MI protocol may be able to be reduced from 6 hours to 3 hours. However, these findings need to be corroborated in other studies before any change in current clinical algorithms should be considered.

The diagnostic utility of myoglobin and CK-MB has been studied with the newer cTn assays. Eggers [65] studied 197 consecutive patients in the ED with nondiagnostic electrocardiograms. There were 43 patients (22%) with MI. Blood samples were drawn at time of presentation, every 30 minutes during the first 2 hours, and then at 3, 6, and 12 hours. The samples were analyzed on the Stratus

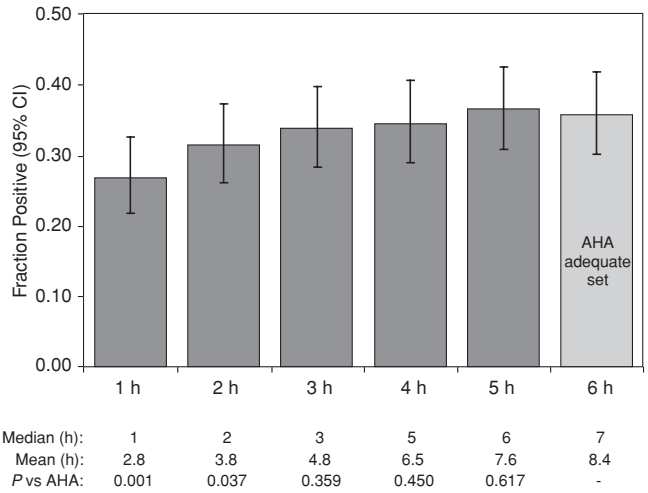

Fig. 1.6 Fraction of patients positive by hour with an assay for cTnI that meets the precision of < 10% coefficient of variation (CV) at the 99^{th} percentile (0.04 ng/ml). MacRae. *Clin Chem* 2006; **52**: 65.

CS device (Dade Behring). The 99^{th} percentile for this assay has been reported at 0.07 ng/mL [66] and the 10% CV is 0.10 ng/mL [67]. The cumulative sensitivity was highest for cTnI at 0.10 ng/mL at all time points (Fig. 1.7). Importantly, the measurement of CK-MB or myoglobin did not improve sensitivity. However, the specificities of cTnI and CK-MB at 6 hours were 76% and 88%, respectively. Amodio [68] reported on 516 patients evaluated for possible MI. A cTnI-based definition for MI was used. Blood samples were drawn at presentation and every 6 hours thereafter; cTnI and myoglobin were measured on the Dade Stratus CS. There were 110 patients (21.3%) with MI. The sensitivity of cTnI was reported at very low values, including those below the 10% CV. Although in this study there was not early frequent sampling of myoglobin, the measurement of myoglobin at 6 hours did not improve early sensitivity. Kavsak [69] retrospectively analyzed 228 patients who were evaluated for possible MI in 1996 and had stored samples. Specimens were drawn at presentation and then hourly until 6 hours, and thereafter at 9, 12, 24, and 48 hours after symptom onset. In the original study CK-MB isoforms were measured, and in the reanalysis myoglobin and cTnI were measured on the Accu cTnI assay (Beckman Coulter). The new definition of MI was retrospectively applied to cases after cTnI measurement and the prevalence of MI increased from 46 patients (20%) to 91 (40%). The measurement of myoglobin or CK-MB did not improve early sensitivity.

When cTn assays are available, the routine measurement of CK-MB to evaluate patients for possible MI is unnecessary. However, the measurement of CK-MB still may be helpful in particular situations such as determining reinfarction in

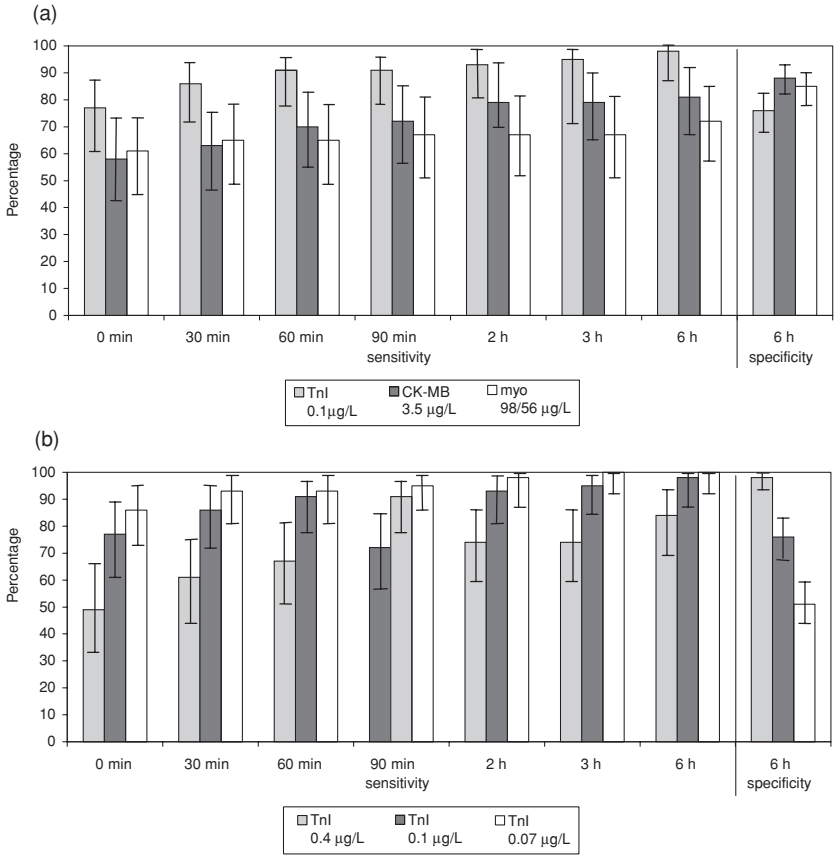

Fig. 1.7 Comparison of sensitivities of myoglobin, CK-MB, and a sensitive assay for cTnI at various cut-points and time intervals. Note the improved sensitivity for the lower cTnI threshold of 0.1 ng/mL early after presentation. Eggers. *Am Heart J* 2004; **148**: 574–581.

patients already with an elevation of cTn. Prior studies performed even before the newer, more sensitive, and precise cTn assays were available suggested that CK-MB did not improve sensitivity for MI detection [37]. An argument for the routine use of CK-MB in evaluating patients with possible MI is lessened further with the 3rd generation cTn assays. Presently many institutions routinely measure CK-MB in combination with cTn. This strategy is unnecessary and a poor use of resources. During the transition period with the new cTn assays, a "reflexive" cTn strategy may be reasonable. The laboratory measures cTn only if the cTn value is normal. However, the laboratory will automatically run and report CK-MB if the cTn is even mildly elevated. This enables the clinician to

have at their disposal a CK-MB value when attempting to sort out a patient with any level of cTn elevation. Several institutions use this strategy presently (e.g., Mayo Clinic, Henry Ford Hospital). Similarly, a few recent studies suggest that myoglobin measurement in a multimarker strategy may not improve early sensitivity as low levels of cTn can be detected early after MI by these more sensitive cTn assays. The diagnostic utility of myoglobin, or change in myoglobin, early on in the setting of MI needs to be investigated further in the context of the new cTn assays.

A change over time in low-level cTn levels may assist in the identification of MI, particularly among patients who have equivocal historical or ECG evidence to support MI. A dynamic change in low-level cTn levels over time would suggest acute active myocardial necrosis and distinguish these patients from those that have chronic elevations. Low-level cTn elevations can be detected in asymptomatic ambulatory patients with a history of diabetes mellitus, heart failure, renal insufficiency, or left ventricular hypertrophy [17].

Although low-level cTn detection may enable more rapid detection of MI, and therefore a faster "rule-out" MI process, low-level cTn detection has lower specificity for MI. Minor cTn elevation may be seen in multiple clinical scenarios where there is myocardial damage but not a clinical scenario of MI (pulmonary embolism, myocarditis, heart failure, and many others). With the ultra-sensitive cTn assays the frequency of abnormal cTn values in patients without MI will increase in the ED. In the era of ultra-sensitive cTn assays historical and electrocardiographic findings will be even more important in assessing patients for possible MI. If further studies of the new cTn assays demonstrate no incremental diagnostic utility of myoglobin, then the door is open for other multimarker strategies to be developed that include novel markers of ischemia together with highly sensitive cTns (see chapter 5).

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