REVIEW

Cardiac Biomarkers: The Troponins and CK- MB

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Abstract
With the prevalence of ischemic heart disease, early diagnosis and management of myocardial infarction is important, and necessitates the need for cardiac biomarkers. Since several markers have evolved over time, it becomes important to understand which markers are best in different clinical situations. After a review of the literature, we have summarized the most frequent markers used. Though the search for an ideal cardiac biomarker remains, troponins seem to have evolved as the most advantageous. Features of troponins include high specificity, sensitivity, a wide diagnostic window allowing prompt, early diagnosis, as well as enhancing detection of myocardial injury in patients presenting late. Enabling risk stratification, estimation of infarct size, detecting reperfusion, usefulness in predicting prognostic outcomes, and offering therapeutic guidance also are among the advantageous features of troponins. Troponins also aid in detecting perioperative myocardial injuries and cardiac injury in renal failure patients. CK myocardial band (CK-MB), however, seems to be more advantageous in detecting reinfarction, though it has limitations in terms of early diagnosis. Troponins are being increasingly used, compared to other cardiac biomarkers, in the detection of acute coronary events and myocardial damage, though CK-MB is still preferred in selective situations.

Introduction

Acute coronary syndromes (ACS) represent a range of ischemic heart disease from unstable angina to myocardial infarction (MI), and may include large areas of cardiac necrosis (1). The symptomatic manifestations of an acute MI (AMI) may be varied, and ECG is also non-diagnostic in about 50% of cases, which poses a risk for potential misdiagnosis. Hence, biochemical markers and cardiac enzymes are considered not only important, butessential, for the diagnosis of myocardial infarction (2).

Initially, transaminases and creatine kinase (CK) were used as diagnostic markers, and gradually, improved markers like CK myocardial band (CK-MB) evolved and have

been used to diagnose AMI and assess cardiac damage. Their non-specificity has been an issue which has led to the introduction of more specific and sensitive cardiac biomarkers, (for e.g. troponins). Troponins are more efficacious than earlier markers because they aid not only in diagnosis, but also in risk assessment and therapeutic decision-making. However, the search for an ideal cardiac marker continues, although troponins seem to have many qualities of an ideal marker (3).

Characteristics of an Ideal Cardiac Marker

An ideal cardiac marker would guide physicians in evaluation, but such a marker does yet exist. Researchers have hypothesized several characteristics of such an ideal marker (4). High specificity is important for a cardiac biomarker to be ideal, and higher concentrations of the marker should be seen in the myocardium, with lower concentrations seen in non-cardiac tissue (2). Tissue distribution of the marker is important, both in physiological as well as pathological conditions. The speed with which the marker is released from injured myocardium is important. Appearance in the bloodstream soon after injury may facilitate early diagnosis. For e.g., troponins show an initial release with peak concentration at 12-24 hours of injury and a second peak 2-4 days after injury. The continuous breakdown leads to prolonged and sustained elevations of troponins which aids in diagnosis (3).

Assays also benefit if the marker has a short turn-around time, as it adds with both sensitivity and specificity within a clinical frame. Prolonged elevation, as seen in troponins, may be beneficial is diagnosing patients who present late; however, they have the disadvantage of not being able to detect reinfarction. In such situations, markers with a shorter time course, such as CK-MB are more useful and have been recommended in both early as well as recent guidelines (5,6).

Table 1. Comparative Efficacy of Cardiac biomarkers [8]

Markers	Sensitivity	Specificity
Total CK	73.5%	84.6%
CK-MB	88.2%	93.2%
Troponin I	100%	96.3%

Assessment of infarct size is possible by serial marker concentration vs. time; however, this has been found to be inaccurate in some situations (7). Though CK-MB was earlier used as a standard marker, troponins have more characteristics of an ideal marker and are now preferred, except in situations where CK-MB offers an advantage, as discussed. The present review will focus on the key, clinically useful, cardiac markers. Discussion about other uncommonly used markers would be beyond the scope of this review. Hence, our emphasis will be on the usefulness of troponins and CK-MB in different clinical situations. Our goal is that such a concise review would help physicians update their knowledge and enable them in early diagnosis/ management of patients with AMI which would allow minimization of associated morbidity/mortality.

Troponins

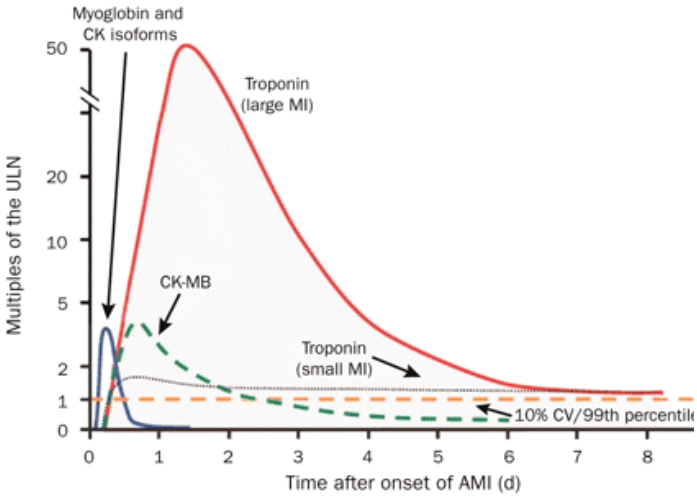

Fig 1. Wide diagnostic window of troponin (9)

Two types of troponins, troponin T (cTnT) and troponin I (cTnI) are ideal markers which are highly sensitive and specific for myocardial injury and have shown better efficacy than earlier markers (Table 1) (8). Elevated serum levels of troponin are detectable within 4 to 8 hours after the onset of chest pain, reaching peak concentration in approximately 12–24 hours (3), and remaining elevated for 3–10 days following AMI, giving them a wide diagnostic window which extends beyond the window of other cardiac markers giving them an advantage (Fig 1) (9). Troponins have been useful in a wide variety of clinical situations. CK-MB is also emphasized, wherever relevant; however, an exclusive attempt to give an overview of disadvantages/ advantages of CK-MB will be made later.

Role, Usefulness and Clinical Advantages of Troponins

Troponins offer several advantages over earlier markers like CK-MB and fulfill most of the requirements of an ideal marker. Hence, a joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) committee on redefinition of MI has proposed that troponins be the principal diagnostic marker of AMI, and furthermore recommended they be the chief markers to evaluate ACS because of their enhanced sensitivity and specificity (10). The low background concentration of troponins with the fact that they provide evidence of a myocardial infarct having developed up to 10 days earlier (in contrast to other markers), gives them an advantage. They have replaced CK-MB as the standard marker in ACS (11).

Chest pain and diagnosis of angina/ MI

Rapid and accurate diagnosis of chest pain is essential as thrombolysis or immediate therapeutic coronary angioplasty reduces morbidity and mortality, and both earlier and recent ACC/AHA guidelines emphasize this importance (12,13). Because of atypical presentation and non-diagnostic ECGs, diagnosis by cardiac markers has become vital. Once, CK-MB was considered the "gold standard" serum marker for MI. However, it lacks specificity for cardiac tissue and a raised value is not seen till 6–8 hours after onset of an AMI (14).

CK-MB is still used in the absence of troponins, but because of its limitations, research has paved the way for troponins to replace CK-MB as the 'gold standard' diagnostic marker. Myoglobin is also used as an early marker but lacks specificity and requires associated cardiac troponin measurements to confirm myocardial injury and eliminate myoglobin false-positives (15).

The high sensitivity of cardiac troponin assays enables it to be useful in patients with unstable angina, where the degree of cardiac injury is minor and considerably less than in AMI. Outcome studies have shown that patients with unstable angina and abnormal cardiac troponin levels have a 5-fold increased risk for AMI and cardiac death within 4 to 6 weeks than do patients with normal troponin levels (16). Thus, measurement of troponin in blood has a dual role: while abnormally high concentrations are indicative of AMI, mildly abnormal concentrations suggest a patient is at increased short-term risk for a future cardiac event. New antithrombotic and antiplatelet drugs reduce the risk of serious disease progression in unstable angina patients. Cardiac troponins are of great help in early identification and optimum therapeutic management of such patients. The role of troponins in the management of unstable angina and non-ST segment MI is now well-recognized and has since been incorporated in the updated management guidelines of "The Joint Committee of the ACC/AHA recommendations, 2002 (17)". The 2007 ACC/AHA guidelines for the management of MI also emphasizes troponins and CK-MB as potentially important markers of cardiac injury (13).

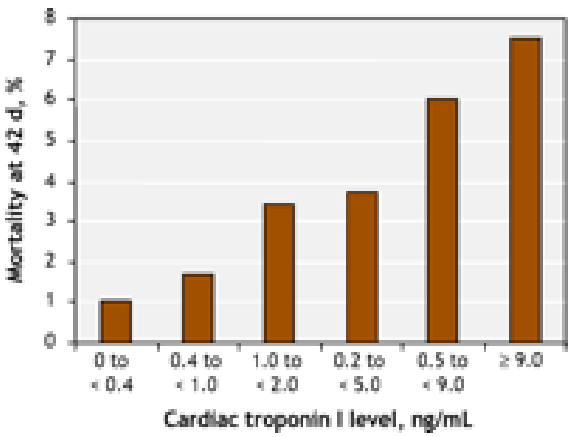

Fig 2. Increased mortality rates with increasing levels of cardiac troponin I (TIMI III B trial) (19)

Risk stratification and prognosis of ACS by Troponins

Troponin levels have been used to stratify those who are at risk for future cardiac events. Studies have demonstrated a strong association between the troponin values and both short- and long-term risk for new cardiac events in patients with coronary heart disease (CHD). The evidence that cTnT and cTnI elevations predict prognosis in patients with and without ST elevation in ACS is so comprehensive that it has led to the proposed redefinition of AMI, while recognizing troponins to be of great prognostic significance (18). Apart from showing considerable correlation in patients with ACS, troponins also have a prognostic role in other entities such as heart failure and pulmonary embolism. Serial measurements of troponins in patients with heart failure have been shown to be helpful to monitor their long-term progress (17).

Cardiac troponin-I levels of ≥0.4 mg/mL were associated with a significantly higher mortality rate within 42 days than lower levels. An excellent linear correlation between troponin levels and worsening outcome was shown in the TIMI-III B trial. A significant increase in mortality rates was found with increasing levels of cTnI (Fig 2) (19).

Therapeutically, patients stratified to high-risk groups benefit from aggressive treatment that includes early revascularization as opposed to those at lower risk for subsequent events treated more conservatively. The Fragmin During Instability in Coronary Artery Disease (FRISC) Study also suggested that measuring cardiac

troponin levels might have therapeutic value in patients with ACSs. Troponin elevations identify the group in which a more aggressive antiplatelet aggregation therapy is useful, and early coronary intervention attenuates the adverse prognostic outcomes (20).

In perioperative myocardial injury (cardiac and non-cardiac surgery)

Diagnosis of perioperative MI is problematic because of the markers released from the damaged skeletal muscle as well as from the myocardium during cardiac surgery (12). Consequently, non-specific markers are frequently elevated and are not of much use. Perioperative and immediate postoperative AMI in non-cardiac surgeries also pose a challenge as non-specific cardiac markers are frequently elevated due to skeletal muscle trauma during surgery. The measurement of troponins is sensitive and specific for the detection of perioperative MI following orthopedic, abdominal, and vascular surgery, as well as in coronary artery bypass surgery (CABG). It remains an important predictor of in-hospital mortality after cardiac surgery (21). Troponins have been reported to be an independent predictor of early postoperative cardiovascular complications following non-cardiac surgery, apart from being identified as an early predictor of short-term mortality in vascular surgery patients as well as a predictor of MI and death after CABG (17). ESC/ACC recommend the use of troponins for the detection of MI after cardiac surgery. The close correlation of troponin levels to development of new wall motion abnormalities having both short- and long-term prognostic value. This is a major step forward in the diagnosis of perioperative AMI in both cardiac and non-cardiac surgery (22).

Troponins: Salient features

- Fast results and diagnosis
- Improved diagnostic sensitivity and specificity.
- Prognostic indicator
- Detects perioperative MI
- Can predict cardiovascular risk
- Useful in detecting reinfarction
- Point of care availability
- Useful as a single marker

Role in percutaneous coronary artery intervention (PCI)

Myocardial damage after PCI (due to procedural complications such as incidental side branch occlusion and thrombus formation with embolization) is common and shows associated elevated troponin levels (23). Evaluation of prognostic values of troponins after PCI has shown a significant association between elevated troponins and major in-hospital complications, including mortality. Increase in troponin levels above the 99th percentile after PCI is indicative of post-PCI acute MI (24). Since patients with ACS may have elevated troponin levels at baseline because of an increase related to the continuing release of troponin (rather than the release after PCI-related cardiac injury), a baseline troponin level is essential for proper interpretation of post-PCI elevations (25).

Estimation of infarct size

Evaluation of infarct size after AMI aids in predicting the subsequent clinical course as it reflects the reduction of left ventricular function and risk of ventricular arrhythmias. Left ventricular ejection fraction (LVEF) was demonstrated to be inversely related to the troponin peak values, and elevated troponin levels are useful for estimating infarct size in a wide variety of circumstances (26). Infarct size can be estimated from troponin values measured at 72 hours post AMI. Estimates of infarct size by troponins have been found to be superior to those provided by CK or CK-MB (27).

Detecting myocardial reinfarction

Reinfarction is difficult to detect with any biomarker, and the same applies to troponins. An increased pattern of cTnI has been seen in patients with AMI who had a reinfarction, and re-elevations in cTnI was demonstrated to be substantial (28). Earlier findings have also suggested that changes in troponin levels are adequate to diagnose reinfarction. However, CK-MB appears more suited for detecting reinfarction.

Detection of reperfusion

Coronary recanalization occurs after AMI, and serial measurements of troponin levels can assess coronary artery patency and aid in biochemical assessment of reperfusion therapy (29). This is especially valuable at times when mechanical intervention, such as rescue angioplasty, could be of benefit to the patient, as troponin levels give a good index of reperfusion. Cardiac troponins have also been shown to be advantageous for the early, noninvasive determination of coronary reperfusion following thrombolytic therapy (30). Based on documented angiography, a significantly

larger percentage of change from baseline value in cardiac troponin concentrations with reperfusion has been demonstrated (31).

Role of troponins in renal failure

Troponins are the biomarker of choice for detecting cardiac injury in patients with renal failure, including those with end-stage renal disease (ESRD) receiving long-term dialysis. The Global Use of Strategies to Open Occluded Coronary Arteries IV (GUSTO-IV) trial found that elevated troponin levels predicted short-term prognosis regardless of creatinine clearance (32). Patients of ESRD with elevated troponin levels had an increased risk of death after 1, 2, and 3 years of follow-up, and increases in troponin levels in ESRD patients showed a 2- to 5-fold increase in mortality (32).

Limitation of Elevated Troponins as Cardiac Marker: False Positives

Troponin elevations may not be associated with ACS. Such false positives can be seen in a range of clinical situations (33). About 41% patients with elevations in troponin without ACS were seen to have other non-thrombotic conditions, including non-ischemic cardiac disorders, pulmonary embolism, sepsis, stroke, trauma, internal bleeding, and renal failure. Other related conditions where troponins may be elevated without ACS are with hypovolemia, atrial fibrillation, congestive heart failure, myocarditis, and myocardial contusions (34). Although troponins are specific for myocardial injury, they are non-specific for etiological cause (33). However, elevation of troponins in non-ACS patients are seen to be associated with poor outcomes; and should be alarming since it often indicates an underlying worsening clinical etiology, although not ACS.

Creatinine Kinase Myocardial Band

Though troponins offer several advantages over CK-MB, certain situations warrant CK-MB as the preferred marker. To have an insight, it is important to understand salient features of CK-MB and its mechanism of action.

Role and salient features

CK-MB was once considered the gold standard for diagnosis of MI. However, since it lacks specificity and levels may not be elevated even 6–8 hours after onset of symptoms, CK-MB isoforms have been used. CK-MB isoforms have reduced this time to 2 hours. The CK-MB isoform is twice as sensitive as conventional CK-MB. Its sensitivity in detecting AMI at 6 hours reportedly increased to 95.7% compared with 48% for conventional CK-MB (35). Thus, CK-MB is also an important marker used to evaluate ACSs and MI. CK-MB has 3 dimeric isoenzymes comprising total CK activity; CK-MM, CK-MB, and CK-BB isoenzymes, of which CK-MB is mainly cardiac specific. While CK-MM is predominantly seen with striated muscle and myocardium, CK-MB only constitutes 0–3% of CK in skeletal muscle and is elevated in myocardial disease. CK-MB isoenzyme comprises around 20% of total CK in myocardial tissue damage versus that of normal individuals whereby one would find it constituting a lower percentage (only around 1% in this tissue) (36).

Around 5% of all CK activity is from CK-MB in skeletal muscles, which are known to rise under certain physiologic conditions (heavy exercise/marathon runners), disease states (genetic/acquired myopathies), and even neoplasms (37). Though the circulating plasma catalytic activity of CK-MB limits its usefulness for assessing necrosis of myocardium, a way to improve the cardiospecificity of CK-MB was determined by expressing it as the quotient of total catalytic activity of circulating CK, and then a certain cut off plasma level in skeletal muscle could be considered as a sign of its being released from myocardium. Determining mass concentration of CK-MB by immunoassays, rather than catalytic activity, has also helped in adding to its increased sensitivity and accuracy (17).

CK-MB has been considered a benchmark marker. It has been used as a comparative value for other markers (36). Hence, though diagnostic of specific myocardial injury, skeletal muscle shows higher activity. However, the characteristic rise and fall of CK-MB measured serially is still considered pathognomonic in diagnosis of MI (36). The first elevation in CK-MB may be 4–6 hrs after onset of symptoms; however, for increased sensitivity and specificity, serial measurements over a period of 8–12 h are advised. Gibler *et al* (38). measured samples at presentation and then at 3, 6, and 9 hours in low-risk patients with MI (non-diagnostic from ECG), and demonstrated a sensitivity and specificity of 100% and 98.3% for MI diagnosis, respectively, in these chest pain patients (38).

Advantages within limitations of CK-MB in detecting re-infarction

As discussed, CK-MB concentration shows increased plasma levels beginning 4-6 hours after symptoms of AMI and remain elevated till 24–36 hours after onset of symptoms. Because of this sudden rise and subsequent early fall, CK-MB is often advantageous and used to detect reinfarction. However, since CK-MB is not an early marker

of infarcted myocardium, levels have been shown to be normal in 35–50% of AMI patients, an obvious limitation (17). Importantly, CK-MB is used to assess re-infarction or infarct extension. However, in spite of good performance, its rise may take 8–12 hours after onset of symptoms and its non-specificity make for bothersome issues (36). Despite the limitations, CK-MB has a crucial role in diagnosis, especially in absence of troponins, and in reinfarction cases.

Measuring CK-MB 2/CK-MB1 ratio

After tissue necrosis, CK-MB2 is quickly released to plasma and gets rapidly converted to CK-MB1. Normally, the tissue isoform variant (CK-MB2) is in equilibrium with the plasma isoforms (CK-MB1), with the ratio being close to 1.0. During AMI, large amounts of CK-MB2 are released which are not completely converted to CK-MB1 in plasma, leading to a higher ratio of CK-MB2/CK-MB1 (≥1.5). Presence of an increased ratio has high diagnostic sensitivity for necrosis of myocardial tissues, especially 0-6 hours after onset (39).

Measuring CK-MB isoforms has shown a significant (92%) diagnostic rate of MI within the first 6 hours after chest pain, though main diagnostic value is due to the high negative predictive value. CK-MB isoforms were shown to be quite sensitive (91%) in early diagnosis (<6 hours) of AMI in one study of emergency patients with chest pain (40). However, because of less cardiospecificity and levels not being easily obtained, it introduces subjectivity into the interpretation of results. These disadvantages have led to an increased use of troponins than CK-MB or its isoforms in diagnosing AMI. And as stated earlier, troponins have now replaced CK-MB as the 'gold standard' for diagnosis of myocardial injury (4).

Conclusion

Troponins have ushered in a new era of highly specific and sensitive cardiac markers used in various cardiovascular clinical situations. Having replaced CK-MB as the gold standard for diagnosis of MI, they have also proved to be a good prognostic indicator by risk stratification as well as a therapeutic guide used in high-risk patients with unstable angina. Troponins are shown to help in the diagnosis of post-PCI infarction and in perioperative cardiac and non-cardiac surgeries. They are also proving to be beneficial in estimation of infarct size, detection of reinfarction, and detection/evaluation of reperfusion and coronary recanalization. Their useful role in assessing cardiovascular morbidity in chronic renal insufficiency and patients with ESRD is proving to be an additional boon. With many qualities of an ideal marker, troponins are favorably set to significantly aid in the management of the rising cardiovascular morbidity and mortality. However, certain clinical situations still warrant CK-MB as the ideal choice of cardiac biomarker, especially in cases of detecting reinfarctions.

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