

## Requiem for a Heavyweight The Demise of Creatine Kinase-MB

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The development of rapid, automated, and accurate laboratory testing for creatine kinase MB (CK-MB) revolutionized the treatment of patients with acute cardiac events in the 1970s and 1980s.<sup>1</sup> To clinicians, CK-MB values augmented a thorough history, physical, and ECG findings, and elevations rapidly became the gold standard for identifying cardiac injury.<sup>1</sup> CK-MB allowed earlier diagnosis of acute myocardial infarction (AMI), and detection of reinfarction, and measurements could be used to provide a facile clinical estimate of infarct size. Elevations of CK-MB were never intended to be synonymous with myocardial infarction, only indicative of cardiac injury.<sup>1</sup> However, because of the relative insensitivity of measurements, increased concentrations occurred predominantly with larger insults such those associated with acute ischemic heart disease. For that reason, AMI was rarely diagnosed, assuming appropriate timing of the samples, in the absence of a CK-MB elevation.<sup>2,3</sup>

CK-MB assays initially relied on the measurement of enzyme activity, but over time, improved accuracy and ease of use were established by the use of mass assays. Mass assays allowed earlier detection of abnormal values and improved both clinical sensitivity and specificity. However, mass assays unmasked an increased frequency of CK-MB elevations due primarily to skeletal muscle injury because of their increased sensitivity.<sup>4-6</sup> Clinical use of the percent relative index was then initiated. This approach improved the specificity of elevations for cardiac muscle injury but was insensitive when concurrent cardiac injury and skeletal muscle injury were present because elevations from skeletal muscle often are of a large magnitude.<sup>7-10</sup> A large number of analytical confounds such as macrokinases and interfering substances also were substantial problems with these assays.<sup>10,11</sup> Attempts to standardize assays<sup>12</sup> have been partially successful, but differences still exist between manufacturers and even between the same testing antibodies used on different analytical platforms (ie, small versus large automated instruments). A frequency of up to 20% “false-positive” levels, thought to be due to skeletal muscle injury, was reported in patients with renal failure.<sup>13,14</sup> This was only one of many conditions such as noncardiac surgery, chest trauma, asthma, pulmonary embolism, chronic and acute muscle disease, head trauma, hyperventilation, and hypothy-

roidism in which CK-MB was elevated in the absence of cardiac injury.<sup>11</sup> In some ways, analytical tribulations and the lack of cardiac specificity provided clinicians with more flexibility in their decision-making processes. Enough analytical and physiological reasons not related to cardiac injury were available that elevations of CK-MB in any given patient could be considered false positives if the physician did not believe the assay results fit the clinical presentation. It was clear that cardiac biomarkers with better specificity and sensitivity were needed.

### Transformations Caused by the Advent of Troponin

The development of cardiac troponin I and T assays has revolutionized this arena. Troponin elevations are nearly totally specific for cardiac injury<sup>15,16</sup> except for infrequent analytical false positives caused by fibrin interference and/or cross-reacting antibodies, interferences that are far less frequent with contemporary assays and are inherent to any immunoassay testing. In high-quality clinical laboratories, these issues are recognized and easily dealt with by repeat centrifugation, testing on alternative platforms, dilution studies, and/or the use of heterophile blocking agents. In addition, troponin is substantially more sensitive than CK-MB,<sup>8,17</sup> related to the fact that more troponin is found in the heart per gram of myocardium and that a greater percentage depleted from the heart by cardiac injury arrives in the blood.<sup>9,18-21</sup> It is now clear that minor cardiac injury occurs in many situations, and in most circumstances, the associated increases in troponin values correlate with adverse short- and long-term outcomes.<sup>22-30</sup> This fact demonstrates that cardiac injury is a component of many nonischemic syndromes, but it also makes it difficult for physicians to disregard any elevated troponin values. Clinicians are forced to deal with new and at times undefined causes of the discernible elevations for which little practical guidance is available on how to proceed with patient care. This phenomenon is likely to continue as analytical detection limits, accuracy, and precision of troponin immunoassays constantly improve. It suggests the need for more research in these important areas.

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**Table. Use of Troponin**

Situation	Criteria
AMI	Rising or falling values with at least 1 value above the 99th percentile of the reference range
Reinfarction	An increase of values >20% over a 6-h period
Post-PCI	Normal baseline cTn; increases >3-fold (by convention) above the reference range Baseline cTn elevated but stable; use criteria for reinfarction Baseline cTn elevated but changing; no criteria can distinguish injury related to the index event from that potentially caused by PCI
Post-CABG AMI	A 5-fold increase in cTn with other clinical evidence (eg, ECG or imaging)
Infarct size	Correlation best with 72- to 96-h troponin concentration
Renal failure	All elevations of cTn are highly prognostic Patients with acute events have changing values despite the elevated baseline
Chronic elevation not associated with renal failure	All elevations of cTn are highly prognostic Patients with acute events have changing values despite the elevated baseline
Critically ill	Elevations predict short- and long-term outcomes; therapy if AMI is not present is usually oriented toward the underlying disease
Extreme exercise	Elevations are transient (24 h) and are not associated with an increased incidence of short-term cardiac events

PCI indicates percutaneous coronary intervention; cTn, cardiac troponin; and CABG, coronary artery bypass graft surgery.

## Use of Troponin in 2008

### Diagnosis of AMI

When troponin assays were first introduced clinically, it was unclear how to properly interpret values. In addition, a surfeit of data existed on the estimation of infarct size, diagnosis of reinfarction, and use of troponin after interventional procedures. Extensive data now indicate that troponin, because of its better sensitivity and specificity, provides at least comparable and often superior information than can be gleaned from CK-MB once it is appreciated how to use the marker (the Table). Troponin is the preferred marker of both the clinical (American College of Cardiology/European Society of Cardiology/American Heart Association [ACC/ESC/AHA])<sup>31</sup> and biochemical (National Academy of Clinical Biochemistry) guidelines groups.<sup>32,33</sup> With the use of contemporary high-sensitivity troponin assays and the 99th percentile cutoff values advocated by these groups,<sup>31-33</sup> it has been observed that troponin levels rise by 2 to 3 hours after the onset of chest discomfort. Thus, in upwards of 80% of patients, a definitive rule-in diagnosis can be made in 2 to 3 hours with troponin.<sup>34</sup> A definitive rule-out diagnosis takes longer, and the most recent guidelines suggest that samples be obtained at baseline, at 6 hours, and again at 12 hours in occasional patients

in whom suspicion is very high.<sup>31,33</sup> For those who wish to facilitate the movement of patients from an emergency department setting, a 2- or 3-hour sample may be considered.<sup>34</sup> No evidence exists that CK-MB adds to the accuracy and/or rapidity of this serial sampling approach. Approximately 10% of an acute coronary syndrome population is made up of individuals with normal troponin values and increased CK-MB,<sup>35</sup> and these patients have excellent outcomes,<sup>36</sup> confirming the lack of specificity of CK-MB in this situation. Thus, CK-MB adds only increased cost. Furthermore, because of the ability to make an early diagnosis with troponin, several studies suggest that the previously touted "rapidly rising" markers that lack specificity such as myoglobin, CK-MB, and fatty acid binding protein are no longer needed.<sup>37-40</sup> Patients who have an elevated troponin but not an elevated CK-MB have an increased risk for developing future cardiac events, morbidity, and mortality.<sup>25,34</sup> Several studies suggest that the use of these more sensitive assays and cutoff values identifies many more (30% to 130%, depending on the study) patients who meet the criteria for AMI and are at risk.<sup>35,41-48</sup> Prognostic studies suggest that this group is very similar to those with non-ST-segment elevation myocardial infarction identified by CK-MB. In some studies, these patients have been shown to have a worse prognosis,<sup>49</sup> but that finding may be due to differences in treatment before the potent prognostic effects of troponin were recognized. Other studies have shown slightly lower event rates after non-ST-segment elevation myocardial infarction defined by troponin concentrations alone,<sup>50</sup> but in each study, the time course of events has been similar between groups. Of equal importance is the fact that troponin elevations in patients with acute coronary syndrome have been shown to predict benefit from specific anticoagulant, antiplatelet, and invasive therapies in multiple large randomized clinical trials.<sup>31,33</sup>

Despite the fact that CK-MB values are no longer necessary to make the primary diagnosis of AMI, clinicians continue to use it. One reason is that tests that have assisted us for many years are hard to give up. A second reason is that clinicians, despite nearly 15 years of experience with troponin measurements, are still not comfortable with how to use the data in certain clinical situations. Thus, many do not make the diagnosis of AMI even when criteria with troponin have been met.<sup>50</sup> Some of this is appropriate because it is integral to the diagnosis of AMI for biomarker elevations to occur in the appropriate clinical context; ie, the clinical circumstances and ECG are key to the diagnosis of AMI.<sup>31,33</sup> If the clinical situation is not one in which acute ischemia is suggested clinically, another explanation for the troponin elevation should be sought.<sup>51</sup> We would contend that investing in learning how to use troponin concentrations properly will result in better clinical care and a reduction in cost owing to the elimination of the need for other biomarkers, including CK-MB.

### Estimation of Infarct Size

Prognosis after AMI is closely related to the extent of myocardial damage. Calculations based on the analysis of serial levels of total CK or CK-MB have provided this estimate for many years since the pioneering work of

Geltman et al,<sup>52</sup> Roberts et al,<sup>53,54</sup> and Marmor et al.<sup>55</sup> For clinicians, peak values provide a reasonable clinical estimate if sufficient samples are present<sup>56</sup> and if factors such as reperfusion (which changes the kinetics and magnitude of CK-MB release) are considered. For some, this has been a rationale for retaining the use of CK-MB. Recent data comparing cardiac troponin concentrations with imaging suggest that troponin values provide similar, and indeed often superior, estimates of infarct size. Ingkanisorn et al<sup>57</sup> published the first work investigating the association between early troponin values and infarct size in patients with acute coronary syndromes. They reported that peak troponin I correlated with acute infarct mass in patients undergoing acute primary percutaneous coronary intervention ( $r=0.83$ ,  $P<0.001$ ;  $n=23$ ). These data have been confirmed in a recent study by Younger et al<sup>58</sup> in which a significant relationship was found between infarct size and troponin in both thrombolized and nonthrombolized patients. Further data by the group from Heidelberg<sup>59</sup> are consonant with these findings and indeed suggest that one can use any of the values found on day 1, 2, 3, or 4 for such estimates, although values at 72 to 96 hours are best.<sup>60</sup> In most comparative studies, troponin concentrations provided a better estimate of infarct size than CK-MB.<sup>61,62</sup> Explanations for the differences between troponin estimates and CK-MB estimates are articulated more fully elsewhere.<sup>63</sup> These data do not necessarily imply that troponin values should become the gold standard for infarct size, but they do suggest that, with experience, clinicians can obtain facile estimates from the concentrations obtained for clinical use.

### Diagnosis of Reinfarction

Some still rely on CK-MB to diagnose reinfarction because troponin elevations may persist for many days or even weeks after an acute event. The updated ACC/AHA guidelines for acute coronary syndrome suggest that 2 samples for CK-MB may be helpful in diagnosing reinfarction.<sup>64</sup> We respectfully dissent. The literature validating the use of CK-MB for the diagnosis of reinfarction was reported before the aggressive use of interventional strategies and at a time when patients were hospitalized for many days and recurrent chest discomfort rarely triggered coronary angiography and/or intervention. In the initial validation studies of CK-MB, the mean time of reinfarction was 10 days, and it occurred predominantly in obese women with multiple episodes of recurrent chest discomfort.<sup>55</sup> Even then, the criteria required a rise from a prior baseline sample, which was performed commonly because in those studies CK-MB values were being monitored every 12 hours. The criteria proposed for CK-MB when values were elevated<sup>65</sup> have been modified by many clinical trial groups and have never, to the best of our knowledge, been validated. Contemporary therapy is predicated on the use of troponin, and current intervention strategies for AMI are rapid and aggressive. Literature comparing CK-MB and troponin for the diagnosis of reinfarction is sparse because of this aggressive interventional approach, with the most comprehensive article coming from Apple and Murakami.<sup>66</sup> From the Apple and Murakami data, it is clear that using 2 values for troponin allows the facile diagnosis of reinfarction. True

elevations are easy to discern because of the increased sensitivity of troponin. As in patients with renal failure and chronic troponin elevations,<sup>13</sup> when acute events occur, marked increases in troponin are easily observed despite the abnormal baseline value.<sup>67</sup> They also document the need in the modern era for 2 values of CK-MB to make such a diagnosis.<sup>66</sup> Given the improved sensitivity and specificity of troponin for cardiac injury, one would expect better information from troponin values. Cognizant of these data, the recent ACC/AHA/ESC Task Force for the Redefinition of Myocardial Infarction embraced the use of troponin over CK-MB for this purpose.<sup>31</sup> If used for reinfarction, a 20% change in troponin values is required for diagnosis (roughly 3 SD of the variability of the method once values are greater than the 99th percentile).<sup>31</sup> For reinfarction, changes in troponin values must correlate with the clinical status of the patient because an occasional patient will have a secondary rise in troponin (especially with cardiac troponin T) after ST-segment elevation myocardial infarction in the absence of symptoms.<sup>19</sup> Importantly, in the present interventional era in which most patients receive invasive reevaluations when they have recurrent symptoms, this diagnostic paradigm will likely be applied only to those with questionable histories and unclear ECG changes, situations in which the increased specificity of troponin will be of benefit.

### Use of Troponin in Patients Undergoing Percutaneous Coronary Intervention

The data in regard to the utility of troponin values after percutaneous coronary intervention is growing rapidly. It is now clear that most of the marked elevations of CK-MB and/or troponin after intervention are related to elevations of troponin at baseline<sup>45,68</sup> and are missed by the less sensitive marker, CK-MB. If baseline values are included in the analysis, the prognostic importance of the postintervention value is ablated.<sup>69,70</sup> When the baseline value is rising, distinguishing the troponin elevation related to the procedure from those that are due to the original presenting symptoms can be problematic. Key to this analysis is use of the 99th percentile cutoff value because concentrations greater than the 99th percentile have prognostic significance.<sup>69</sup> Because of these data, the recent AHA/ACC/ESC Task Force for the Redefinition of Myocardial Infarction suggested that post-percutaneous coronary intervention values are of use only if the baseline troponin value is within the normal range or remains unchanged over time.<sup>31</sup> If the baseline value is normal, a 3-fold increase is advocated by convention to diagnose a postprocedure AMI.<sup>31</sup> If the baseline value is elevated but stable, criteria for reinfarction are advocated.<sup>31</sup> Many now are ready to move to a troponin standard for post-percutaneous coronary intervention evaluation.<sup>71</sup> We believe that such a change is appropriate.

### Evaluation of Chronic Troponin Elevations

Many clinicians still believe that CK-MB assists in evaluating subsets of patients who have chronic troponin elevations such as those that occur in renal failure patients, the critically ill, and those who exercise.<sup>13,72</sup> We are unclear how. CK-MB is frequently elevated in patients with renal failure<sup>13</sup> and, in

contrast to troponin, has not been reported to help distinguish patients at risk from those who are not. In this group, the key to interpreting the troponin elevation lies in detecting a changing pattern of troponin to identify those with acute versus chronic disease. In regard to critically ill patients, literature confirming the diagnostic importance of troponin elevations is robust.<sup>24,73–75</sup> We are unaware of any information suggesting that the use of CK-MB helps to identify subsets of patients who are at risk for future cardiac events. After rigorous exertion, CK-MB release occurs ubiquitously, thought to be a result of skeletal muscle release.<sup>72</sup> How such a finding would help distinguish the individual with minor elevations in troponin from those without is unclear. At the present time, it appears that these transient elevations of troponin that occur 24 hours after exercise are not of short-term consequence, but further studies are needed.

Finally, it may be suggested that CK-MB is necessary for diagnosing AMI after coronary artery bypass graft. The original ESC/ACC task force opined that criteria for this clinical scenario were impossible.<sup>76</sup> The latest guidelines<sup>31</sup> suggest a reasonably low cutoff value for all biomarkers with advocacy for the use of additional clinical criteria. They also refer to many articles documenting that the magnitude of troponin elevations is associated with patient prognosis.

### Does CK-MB Still Have a Role?

Despite the large amount of data published indicating how troponin can be used without measurement of CK-MB, an analysis of current ordering patterns finds that many clinicians are still ordering CK-MB and troponin simultaneously. At the Mayo Clinic, CK-MB is tested  $\approx 33\,000$  times per year, slightly less frequently than troponin T at 44 000 tests per year. It is unlikely that this is unique to the Mayo Clinic, although we are sure that some heterogeneity of ordering patterns exists. Several concerns relate to these facts:

- **Cost.** If laboratory testing yields important additional diagnostic information for patients, then cost should not be an issue. However, in the case of CK-MB when little or no incremental information is provided, such testing, especially in such proliferation, is not cost-effective for institutions or patients.
- **Quality control of CK-MB assays.** There has been increasing difficulty in controlling the quality of current CK-MB assays, and there often is considerable machine-to-machine variability. It is clear that the level of commitment by industry to the quality assurance of CK-MB has waned significantly as it becomes clear that its use should be ending in the near future.
- **Incorrect use of CK-MB.** In many places, CK-MB is not being used correctly. Recent data from Apple et al<sup>77</sup> have reiterated the need for gender-specific reference ranges and cutoffs if CK-MB is to be used. However, it is rare for published studies to take this issue into consideration. We suspect the same is true in most patient care facilities.
- **Confusion.** Using CK-MB keeps some clinicians from learning how to use troponin properly and effectively because learning new paradigms takes time and effort. Eventually, however, clinicians need to learn how to use

troponin properly. Others have never learned how to use CK-MB properly because they have relied on troponin and are thus confused when elevations occur in the absence of troponin increases. We are aware of situations in which such confusion has negatively affected patient care.

Some of these problems are due in part to confusion about which cutoff values should be used, a lack of knowledge about how to translate values from 1 assay to another, and the large number of assays marketed, all of which claim high sensitivity and predictive accuracy. Some of these issues have now been clarified. Specifically, both major guidelines groups now endorse the use of the 99th percentile of the reference range as the appropriate cutoff value to use.<sup>31–33</sup> However, some challenges remain, including the lack of correspondence of values between assays and the lack of a facile way to distinguish assays that are adequately sensitive from those that are not. In general, point-of-care assays currently are not nearly as sensitive as laboratory-based assays,<sup>78</sup> and several studies have demonstrated that acute coronary syndrome patients are at increased risk by discordant results between point-of-care and central laboratory testing.<sup>79–81</sup>

### Conclusions

The Mayo Clinic in Rochester recently removed CK-MB from its cardiac biomarker panel after extensive collaboration with clinicians. Several other institutions have taken similar actions without any discernible negative effects on clinical care. We suspect that clinical care would be simplified and improved if this step were taken more widely because, as we have attempted to underscore above, the clinical issues that we need to address are best addressed by the use of troponin, and try as we might, it has been hard to find situations in which CK-MB adds substantially. It adds only cost and, from our perspective, confusion. Accordingly, after >10 years of experience using troponin in the clinical arena, it is time for clinicians to learn how to use cardiac troponin properly and, in doing so, let our old friend CK-MB rest.

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## Requiem for a Heavyweight: The Demise of Creatine Kinase-MB

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