Diagnostic application of CK-MB mass determination

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Abstract

Recent advances in analytic techniques have increased the diagnostic value of creatine kinase MB (CK-MB), enabling earlier and more sensitive results. The CK-MB mass immunoassays, that utilise the monoclonal anti-CK-MB in conjunction with anti-M or anti-B antibodies, are able to measure accurately small changes during the early hours after myocardial infarction (MI). CK-MB has two main limitations in diagnosing MI neither of which however undermines its established clinical value: CK-MB is not perfectly specific to cardiac injury, with increase occurring also during massive musculoskeletal injury; furthermore, the early release pattern of CK-MB limits its value for the late MI diagnosis. For the foreseeable future evidence is compelling for greater access to rapid testing capabilities in emergency situations, using protocols incorporating CK-MB mass evaluation together with other biochemical markers, i.e. myoglobin and troponins. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

The MB isoenzyme of creatine kinase (CK-MB) is the biochemical marker currently used for the evaluation of patients with suspected acute myocardial infarction (MI) [1]. The value of CK-MB has been recognized for more than 20

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years and the test is still used widely today. In 1996, the 85% of the cardiac marker’s market in Italy is still represented by the MB assay. CK-MB’s unique value in the diagnosis of MI is related to its characteristic rise following myocardial injury (Fig. 1). Damaged myocardial tissue releases CK-MB in a characteristic fashion following injury, enabling clinicians to reach conclusions about the extent and timing of myocardial injury through analysis of CK-MB serum kinetics. Increases in plasma levels usually occur between 3 to 5 h after the onset of infarction, peak at 16–20 h, and return to normal by 48 to 72 h. For all these reasons, CK-MB analysis has been the ‘gold standard’ for confirming MI for at least two decades [2]. However, classic analytic techniques, such as manual electrophoresis or immunoinhibition, used to quantitate CK-MB catalytic activity, were not sensitive enough for early use, relatively nonspecific, and results frequently required long turnaround times [3]. Thus, in the 70’s and 80’s, CK-MB has been used primarily for confirming MI at 24 h post-injury [4].

2. Assays for the determination of CK-MB mass

Recent advances in analytic techniques, enabling earlier and more sensitive results, have increased the value of CK-MB as a diagnostic tool [5]. The CK-MB immunoassays, that utilize monoclonal anti-CK-MB in conjunction
Table 1
Commercially available immunoassays for CK-MB determination that utilize monoclonal anti-CK-MB antibody

<table>
<thead>
<tr>
<th>Method</th>
<th>Detection</th>
<th>Antibody anchor</th>
<th>Antibody tag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott / IMx</td>
<td>Fluorescence</td>
<td>Anti-CK-MB, latex microparticles</td>
<td>Anti-CK-M, alkaline phosphatase</td>
</tr>
<tr>
<td>Bayer / Immuno 1</td>
<td>Colorimetric</td>
<td>Anti-CK-MB, paramagnetic particles</td>
<td>Anti-CK-B, alkaline phosphatase</td>
</tr>
<tr>
<td>Becton Dickinson / Affinity</td>
<td>Colorimetric</td>
<td>Anti CK-MB, goat IgG anti-mouse</td>
<td>Anti-CK-M, peroxidase</td>
</tr>
<tr>
<td>Behring / Opus</td>
<td>Fluorescence</td>
<td>Anti-CK-MB, glass fiber paper</td>
<td>Anti-CK-M, alkaline phosphatase</td>
</tr>
<tr>
<td>Boehringer / Elecsys</td>
<td>Electrochemiluminescence</td>
<td>Anti-CK-MB, paramagnetic particles</td>
<td>Anti-CK-MB, ruthenium-tris(bipyridyl)</td>
</tr>
<tr>
<td>Chiron / ACS:180</td>
<td>Chemiluminescence</td>
<td>Anti-CK-B, paramagnetic particles</td>
<td>Anti-CK-MB, acridinium ester</td>
</tr>
<tr>
<td>Dade / Stratus</td>
<td>Fluorescence</td>
<td>Anti-CK-MB, glass fiber paper</td>
<td>Anti-CK-B, alkaline phosphatase</td>
</tr>
<tr>
<td>Diagnostic Products / Immulite</td>
<td>Chemiluminescence</td>
<td>Anti-CK-MB, beads</td>
<td>Anti-CK-B, alkaline phosphatase</td>
</tr>
<tr>
<td>Johnson &amp; Johnson / Vitros</td>
<td>Chemiluminescence</td>
<td>Anti-CK-B, solid-phase</td>
<td>Anti-CK-MB, peroxidase</td>
</tr>
<tr>
<td>Organon Teknika / Auraflex</td>
<td>Fluorescence</td>
<td>Anti-CK-MB, paramagnetic particles</td>
<td>Anti-CK-B, alkaline phosphatase</td>
</tr>
<tr>
<td>Sanofi / Access</td>
<td>Chemiluminescence</td>
<td>Anti-CK-B, paramagnetic particles</td>
<td>Anti-CK-MB, alkaline phosphatase</td>
</tr>
<tr>
<td>Tosoh / Aia</td>
<td>Fluorescence</td>
<td>Anti-CK-B, magnetic beads</td>
<td>Anti-CK-MB, alkaline phosphatase</td>
</tr>
</tbody>
</table>

with anti CK-M or anti CK-B antibodies, measure mass concentration for MB instead of enzyme activity, but excellent concordance has been shown between mass and activity concentrations [6]. The CK-MB mass immunoassays have analytical sensitivities under 1 ug L⁻¹, are fully specific for CK-MB, and, therefore, are able to measure small changes during the early hours following the onset of acute MI [7–9]. This determination is now available on many different automated analytical systems and can be performed at any time of day on a ‘stat’ basis, specific results being obtained within 15–30 min of specimen receipt (Table 1).

3. Time to positivity for CK-MB mass

It is now clear that the mass assay for CK-MB will become ‘positive’ earlier than the traditional CK-MB activity assays [10], with as many as 50% diagnostic at 3 h and in excess of 80% ‘positive’ at 6 h (Table 2). Nevertheless, serial
Table 2
Indicative average percent of patients with early acute myocardial infarction recognized using CK-MB mass immunoassay

<table>
<thead>
<tr>
<th>Hours after onset of pain</th>
<th>Sensitivity (% of patients with CK-MB mass &gt; URL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>80%</td>
</tr>
</tbody>
</table>

* URL, upper reference limit.

CK-MB measurements in patients admitted with recent onset of pain (generally, in the previous 12 h) have shown greater sensitivity and specificity than single CK-MB measurements performed within the first 3 to 4 h after the onset of symptoms [11–13]. Applying the principle of serial CK-MB measurements, the concept of measurement of slope and the rate of increase has been developed and several authors have proposed practical diagnostic strategies. In 1988, Collinson et al. [14] first proposed a strategy with a two-step approach: in the first step, the determination of the slope of total CK was carried out, and the measurement of CK-MB slope was performed only when the total CK slope was elevated, to increase the specificity. Probably the direct CK-MB mass slope measurement is however the most efficient strategy, and estimates of the change in CK-MB per hour should be made for all patients with suspected early MI (Fig. 2). What this demonstrates is that the traditional serial rise and fall pattern of CK-MB over a 24-h period may be replaced with three early serum CK-MB

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Fig. 2. Diagnostic strategy for the early diagnosis of acute myocardial infarction by assessment of the CK-MB mass slope.
measurements (at 0, 2, and 4 h after admission) to examine the appearance rate of the enzyme.

Some reports threw doubt on the efficacy of the slope technique in categorizing patients with possible MI [15]. However, if the CK-MB slope assay is correctly used in the early time-interval after MI (0 to 12 h after onset), rapid and accurate diagnostic categorization of the patients is obtained [16]. With regard to this point, Lott et al. [17] recently confirmed that use of the cut-off values for single CK-MB results is less effective than the use of slope in the diagnosis of suspected MI in the first 12 h after admission.

4. Limitations of CK-MB assay

The use of CK-MB testing has two main limitations in diagnosing MI, neither of which undermines however its established clinical value. First, CK-MB is not perfectly specific to cardiac injury, with release of the isoenzyme occurring in clinical situations where massive musculoskeletal injury has been sustained. Second, the early release pattern of CK-MB limits its value for the late diagnosis of MI.

Skeletal muscles contain small but significant amounts (1 to 3%) of CK-MB. Thus, skeletal muscle damage can result in increased concentrations of MB in plasma [18]. This can cause diagnostic confusion in patients after surgery or trauma [19]. Various authors proposed the use of the CK-MB/total CK ratio, on the basis of the general principle that a greater proportion of CK-MB favours origin from a myocardial source [20,21]. The rationale for the use of this ratio was clearly stated in 1980 by Lott and Stang [22]: ‘Reporting CK-MB as a percentage of total CK has merit because after massive skeletal muscle injury, both total CK and CK-MB may be increased in serum, but the percentage that is CK-MB typically will be less than 3–4% of total CK and the source of the increased serum enzymes is skeletal muscle’. With the recent advent of mass assays, the conversion has been made to an index based on the mass assay expressed in ug L$^{-1}$ divided by CK total activity in enzyme units: the ‘relative index’. However, it is important to note that in the face of skeletal muscle damage as a source of a large amount of CK, the resulting reduction in the percentage of CK-MB can produce a loss of sensitivity for concurrent myocardial injury. In other words, the large amount of total enzyme, the denominator of the ratio, may obscure a smaller, but significant, pathophysiologic source of CK-MB from the heart [23]. Again, it should not be forgotten that regenerating skeletal muscle produces increased amounts of the B subunit, resulting in increased amounts of CK-MB in myofibers and consequently in the sera of patients with skeletal muscle myopathies [18]. CK-MB concentrations therefore are elevated in patients with inflammatory muscle disorders and dystrophies and
cannot be used in themselves as indicators of cardiac damage in such cases [24]. The use of more specific markers, such as cardiac troponin I, in these patients should allow for a more effective determination of whether concomitant cardiac injury is present [25].

Data also suggest that the CK-MB content of the myocardium varies with its prior pathology [26]. In particular, coronary occlusion appears to induce synthesis of CK-MB [27]. However, this does not appear to distort estimates of myocardial damage, judging from the good correlations reported between CK-MB concentrations and morphology [27].

The early release pattern of CK-MB limits its value for the late diagnosis of MI. Because of this narrow time window, there is however a definite place for using CK-MB assays for the diagnosis of reinfarction. Without exception, the decline of CK-MB follows a predictable course. If the decline deviates from this course by showing a sudden increase, a reinfarction usually has occurred. Using CK-MB, some authors reported an incidence of approximately 30% of MI extensions, that suggests that CK-MB monitoring has a significant place beyond initial diagnostic classification [28].

5. Prognostic value of CK-MB mass

Increased CK-MB mass results can also have an important prognostic value. In patients with unstable angina, two temporal patterns can be observed using CK-MB mass assay—one with stable CK-MB values and one with fluctuating CK-MB concentrations [29]. Ravkilde et al. [30] showed that, after a 28-months follow-up of such patients, those with CK-MB concentrations higher than the upper reference limit had a significantly higher risk of cardiac events than those with normal values, and in the former group the risk was not significantly different from that in patients with evidence of classic MI. Therefore, in this group of patients, CK-MB mass can provide essentially the same prognostic information of the newer, nonenzymatic, markers of cardiac damage, such as troponins [31].

6. CK-MB in reperfusion following myocardial infarction

Regarding the prognostic value of CK-MB, there is an empirical relationship between the amount of enzyme released, represented by the 'peak value', and the size of a MI [32]. After a therapeutic recanalization, the peak of enzyme appears to double because of the 'washout' phenomenon, limiting the use of this qualitative estimate of infarct size in these patients [33]. This increase in the rate of CK-MB egress into the circulation after reperfusion can be used as an aid in
the noninvasive detection of coronary recanalization following thrombolytic therapy [34]. However, very early detection of reperfusion is not possible with CK-MB [35]. As Zabel et al. [36] clearly showed, the sensitivity of the CK-MB slope calculation, 90 min after thrombolysis, is relatively low (approximately 58%). Conversely, it may be possible to use the myoglobin slope to determine the presence or absence of reperfusion as early as 90 min after the initiation of thrombolytic therapy with a good efficiency (area under ROC curve, 0.89) [36]. Since the time is critical, following the rate of appearance of myoglobin should replace the assessment of the rate of CK-MB increase in these patients [37].

7. Conclusion

Based on the well-known benefits and on the widespread use of the test, CK-MB remains an essential diagnostic element in the detection of myocardial injury. For the foreseeable future, evidence is compelling for greater access to rapid testing capabilities in emergency situations, using chest pain assessment protocols incorporating CK-MB mass evaluation together with other biochemical markers, i.e., myoglobin and/or troponins, allowing simultaneous analysis of clinical findings, biochemical test results, and electrocardiograms at the patient’s bedside [38].

References


