Biochemical Markers of Myocardial Injury
Is MB Creatine Kinase the Choice for the 1990s?

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Modern medical practice requires rapid decisions. Patients must be triaged faster, treated more expeditiously, and discharged earlier. Diagnostic tests used to evaluate patients with possible myocardial ischemia/infarction must be simple to perform and must rapidly and accurately accomplish several goals: (1) Differentiate patients with and without acute myocardial infarction (AMI). Only a small percentage (10% to 20%) of patients with chest discomfort or other symptoms compatible with ischemia have infarction.1 There is enthusiasm for the concept that molecular markers might be able to define this group rapidly enough to aid in deciding which patients should receive treatment with thrombolytic agents and which patients are at sufficiently low risk that they could be sent home or cared for in a less intensive and thus less costly facility than an intensive care unit. (2) Distinguish patients who have coronary recanalization after treatment with thrombolytic agents from those who do not so that those in need of additional treatment can be identified. (3) Permit estimation of the extent of myocardial damage, the most reliable predictor of survival after acute myocardial infarction.2

Although tests for the MB isoenzyme of creatine kinase (CK) in plasma have served all of these purposes for nearly three decades, increases in MBCK are not as specific for myocardial injury as first believed and occur too late for optimal early diagnosis of infarction or prompt detection of coronary recanalization. In addition, the complex kinetics of release and clearance after reperfusion confound analyses of infarct size. Because of these limitations, alternative markers have been investigated. Are they better, or will these markers have similar or even more significant limitations than MBCK?

Historical Perspective

The report of Karmen et al in 19543 that serum glutamate oxaloacetate transaminase (SGOT, now aspartate transaminase or AST) activity was increased in the serum of patients with AMI stimulated an explosion in diagnostic testing. Because of greater specificity for heart, measurement of lactate dehydrogenase (now designated LD) and then LD isoenzymes replaced AST for the confirmation of myocardial injury.4 However, the rapid appearance of CK in serum after AMI5 and the improved specificity for myocardial injury provided by measurement of the MB isoenzyme6 quickly established MBCK as the marker of choice. Nevertheless, it became clear that the ECG could be normal despite biochemical evidence of myocardial damage7 and that marked ECG changes could occur without increased concentrations of cardiac proteins in the blood.8 Thus, the current World Health Organization criteria for the diagnosis of AMI includes the presence of two of the following criteria: clinical symptoms compatible with acute ischemia, ECG abnormalities, and a pattern of enzyme release typical of myocardial injury. It has been suggested that a typical rising and falling pattern of MBCK alone in the proper clinical setting should suffice for confirmation of AMI.9

Characteristics of Markers of Myocardial Injury

An ideal marker of myocardial injury would (1) be found in high concentration in myocardium, (2) not be found in other tissues, even in trace amounts or under pathological conditions, (3) be released rapidly and completely after myocardial injury, (4) be released in direct proportion to the extent of myocardial injury, and (5) persist in plasma for several hours to provide a convenient diagnostic time window but not so long that recurrent injury would not be identified.

Determining Factors

The factors that determine these characteristics and the sensitivity and specificity of each marker are size, cellular localization, solubility, release ratio, clearance, specificity for myocardium, specificity for irreversible injury, and detectability.

Size. In general, the smaller the molecular marker, the more rapidly it is released into the circulation.10 Thus, levels of low molecular weight markers such as myoglobin are likely to be elevated earlier than higher molecular weight markers such as LD4 and CK.11

Cellular localization. Cytosolic proteins are released more rapidly than are structural proteins after damage to the sarcolemma, resulting in earlier plasma elevations.12

Solubility. Macromolecules of low solubility, including some cardiac contractile proteins, move slowly out of the myocardium.

Release ratio. Some macromolecules, eg, CK, may undergo local degradation after release.13,14 Thus, the amount of marker depleted from the heart may be substantially greater than the amount that can be measured in plasma. The release ratio is rarely 1; some protein usually remains within the central region of myocardium.
infarction where blood flow is the lowest. Changes in blood flow may alter the release ratio; e.g., reperfusion markedly increases the amount of CK depleted from heart that appears in plasma.16

Clearance. Smaller markers generally are cleared more rapidly than those of greater size.10,11 Thus, markers with shorter plasma half-lives are better for characterizing the timing of events such as reperfusion or reinfarction if frequent blood samples can be obtained.17 Markers with longer half-lives are better for integrating events over time with infrequent samples but often will be insensitive to new release, e.g., from recurrent myocardial injury. In addition, a marker’s clearance is a critical determinant of detectability (see below).

Specificity for myocardium. Most macromolecules in the heart also are abundant in skeletal muscle, especially under pathological conditions. After injury, cells alter the molecular species they produce, recapitulating production of proteins produced in utero or early in life (a “return to ontogeny”).18-21

Specificity for irreversible injury. It is controversial whether the release of cytosolic proteins indicates cell death. Although the sarcolemma must be damaged for release to occur, it is not clear whether the damage must be so extensive that the cell is irreversibly injured.22-25 Specificity for irreversible injury has been difficult to define because of limitations in the detectability of marker proteins in plasma, which is related to the plasma levels normally present and the sensitivity of the assay, and because of limitations in the morphological detection of myocardial necrosis. Release of small amounts of proteins could be undetectable after reversible ischemia if baseline levels are too variable, if assays are not sufficiently sensitive, or if the increment in the plasma level does not exceed the upper bound of the physiological range of the marker, leading to the erroneous conclusion that only irreversible injury causes enzyme release. Conversely, if the release ratio is high or levels of the marker in plasma are low and thus detectability high, protein levels in plasma rather than morphological assessment may be more sensitive for the detection of myocardial necrosis, especially if areas of cell death are not contiguous. The majority of the evidence supports the latter hypothesis, in our view. Prolonged release of structural proteins should be highly specific for irreversible injury.

Detectability. In addition to the issues noted above, detectability requires accurate and easy-to-use assays with high sensitivity and low variability. In general, markers that under normal circumstances are present in very low levels in plasma provide the best diagnostic accuracy. The assumption that detection of markers by different assays is equally precise or that the results of activity and mass assays are equivalent is not necessarily valid.26

The above considerations must be understood in their clinical context. The accuracy of diagnosis and especially the specificity of any test are dependent in large part on the patient population to which they are applied. Thus, increases in the levels of molecular markers of cardiac injury have better specificity for the diagnosis of AMI when symptoms characteristic of ischemia are present. Conversely, improved analytic sensitivity may reduce specificity of a given assay for AMI.

The following review summarizes what is known about several conventional and some new molecular markers of myocardial injury to provide a structure within which to consider the biological and clinical importance of markers available in the 1990s. It also summarizes the practical applications of molecular markers for the diagnosis of AMI, for early detection of infarction, for detection of coronary artery recanalization after treatment with thrombolytic agents, and for estimation of infarct size. Finally, it provides a discussion of possible changes in the use of these markers during the 1990s.

The markers to be considered are CK isoenzymes, CK isofoms, myoglobin, myosin fragments, LD, troponins, heart fatty acid binding protein, and enolase. Their characteristics are detailed in Table 1.

Creatine Kinase

The molecular marker of choice for the evaluation of patients with suspected AMI has been the MB isoenzyme of CK. CK isoenzymes are dimers composed of 39 000 to 42 000 D subunits synthesized in the cytosol of myocytes. CK catalyzes the transfer of a high-energy phosphate from ATP to creatine, producing creatine phosphate.27 Isoenzymes are composed of two M subunits (MMCK), two B subunits (BBCK), or one M and one B subunit (MBCK). Single subunits are enzymatically inactive. A unique dimeric mitochondrial form not composed of either M or B subunits also exists.28 BBCK is most abundant in brain, MMCK in striated muscle, and MBCK in the heart.19,29 Controversy exists as to whether substantial amounts of MBCK are intrinsic to normal myocardium or whether only trace amounts occur physiologically and that increases are produced in response to recurrent ischemic insults.30 Autopsy data, data from other primates, and the documented ability to diagnose myocardial injury in patients whose myocardium was known to be normal before injury favor the former hypothesis.31 After myocardial injury, the concentration of MBCK in myocardium increases; elevated levels have been observed in humans with hypertension, left ventricular hypertrophy, and coronary artery disease.30 In experimental animals, coronary occlusion appears to induce synthesis of MBCK.32 This may improve the sensitivity for detection of AMI in these groups but does not appear to distort estimates of infarct size, judging from the excellent correlations reported between MBCK estimates and morphology.33,34

CK is inactivated by proteolysis in lymph.34 In experimental animals, CK clearance is not affected by changes in heart rate, blood pressure, or cardiac output. CK is not excreted in urine, and its levels are not influenced by changes in renal or hepatic blood flow in experimental animals.35 Hypothyroidism retards and administration of exogenous thyroid hormone increases clearance of CK.36 Nonspecific reticuloendothelial blockade (with zymozan) also retards clearance.35

Tissue Distribution of CK and MBCK

CK is abundant in most tissues. Activities as high as 12 000 IU/g and as low as 225 IU/g have been reported in striated muscle.19,29 There are approximately 1600 IU of CK activity per gram in myocardium, 15% to 30% of which is MBCK.35 Results with sensitive mass assays have shown that most skeletal muscles contain small
Table 1. Molecular Markers Used or Proposed for Use in the Diagnosis of Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Marker</th>
<th>MW (D)</th>
<th>Range of times to initial elevation (h)</th>
<th>Mean time to peak elevations (nonthrombolysis)</th>
<th>Time to return to normal range</th>
<th>Most common sampling schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>hFABP</td>
<td>14 000-15 000</td>
<td>1.5</td>
<td>5-10 h</td>
<td>24 h</td>
<td>On presentation, then 4 h later</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17 800</td>
<td>1-4</td>
<td>6-7 h</td>
<td>24 h</td>
<td>Frequent; 1-2 h after CP</td>
</tr>
<tr>
<td>MLC</td>
<td>19 000-27 000</td>
<td>6-12</td>
<td>2-4 d</td>
<td>6-12 d</td>
<td>Once at least 12 h after CP</td>
</tr>
<tr>
<td>cTnI</td>
<td>23 500</td>
<td>3-12</td>
<td>24 h</td>
<td>5-10 d</td>
<td>Once at least 12 h after CP</td>
</tr>
<tr>
<td>cTnT</td>
<td>33 000</td>
<td>3-12</td>
<td>12 h-2 d</td>
<td>5-14 d</td>
<td>Once at least 12 h after CP</td>
</tr>
<tr>
<td>MBCK</td>
<td>86 000</td>
<td>3-12</td>
<td>24 h</td>
<td>48-72 h</td>
<td>Every 12 h x3^*</td>
</tr>
<tr>
<td>MBCK tissue isoform</td>
<td>86 000</td>
<td>1-6</td>
<td>12 h</td>
<td>38 h</td>
<td>60-90 min after CP</td>
</tr>
<tr>
<td>MBCK tissue isoform</td>
<td>86 000</td>
<td>2-6</td>
<td>18 h</td>
<td>Unknown</td>
<td>60-90 min after CP</td>
</tr>
<tr>
<td>Enolase</td>
<td>90 000</td>
<td>6-10</td>
<td>24 h</td>
<td>48 h</td>
<td>Every 12 h x3^*</td>
</tr>
<tr>
<td>LD</td>
<td>135 000</td>
<td>10</td>
<td>24-48 h</td>
<td>10-14 d</td>
<td>Once at least 24 h after CP</td>
</tr>
<tr>
<td>MHC</td>
<td>400 000</td>
<td>48</td>
<td>5-6 d</td>
<td>14 d</td>
<td>Once at least &gt;2 d after CP</td>
</tr>
</tbody>
</table>

hFABP indicates heart fatty acid binding proteins; MLC, myosin light chain; cTnI, cardiac troponin I; cTnT, cardiac troponin T; MBCK, MB isoenzyme of creatine kinase (CK); MMCK, MM isoenzyme of CK; LD, lactate dehydrogenase; MHC, myosin heavy chain; CP, chest pain.

^*Increased sensitivity can be achieved with sampling every 6 or 8 h.

Amounts (1% to 3%) of MBCK. Thus, skeletal muscle damage can result in detectable amounts of MBCK in plasma. This was unappreciated initially because dilution of samples to measure elevated total CK activity reduced MBCK activity below the limit of detectability of electrophoretic assays available at the time. In general, small amounts of damage to healthy skeletal muscle does not release enough MBCK into plasma to cause diagnostic confusion. For example, intramuscular injections and instrumentation during cardiac catheterization and uncomplicated coronary angioplasty do not result in increases of MBCK despite marked increases in total CK.

When skeletal muscle is injured, it produces increased amounts of B subunits, just as it does during fetal development. Transient increases in the percentage of MBCK in skeletal muscle and elevations in circulating levels occur after acute muscle injury (including extremely rigorous exercise). For example, increases of the skeletal muscle concentration of MBCK in marathon runners are maximal 24 hours after a marathon. Increases of MBCK in plasma also have been documented in professional football players after skeletal muscle injury. Persistent increases in MBCK resulting from chronic myopathies also occur and are probably the cause at least in part of the increases in patients with chronic renal failure and hypothyroidism. Persistent increases of MBCK in plasma in patients with chronic myopathic insults usually allow differentiation of acute from chronic injury. Whether an occult skeletal myopathy can occasionally lead to transient increases in MBCK is controversial.

Increases in MBCK in plasma usually are attributable to release from myocardium in the absence of conditions known to increase MBCK in muscle or abnormalities of clearance. Patients with a rising and falling pattern of MBCK and a peak value that exceeds the upper limit of the reference range should be considered to have had an AMI until shown otherwise.

Specificity of CK for Irreversible Injury

In most studies, release of MBCK into plasma correlates with other evidence of myocardial injury. In addition, increases in MBCK do not occur after ischemia evoked by stress testing or in most patients with severe unstable angina. However, in some experimental studies, small amounts of MBCK have been detected in lymph, coronary sinus effluent, and plasma in the absence of characteristic histological evidence of myocardial damage. However, it is not possible to exclude the possibility that minute amounts of nonconfluent myocardial damage (that were not detectable by random sampling and light microscopy) could have led to the release of small amounts of MBCK. This argument cannot be adjudicated definitively at present. However, CK release after rigorous exercise is associated with skeletal muscle necrosis. Similar physiology may exist in myocardium as well. This is consistent with data demonstrating that patients with chest pain and minor increases in MBCK indicative of AMI but without marked elevations in total CK are at increased risk for subsequent cardiac events.

Techniques of Measurement

Assays of CK activity and/or mass can be done on either plasma or serum. Samples should be maximally reduced with β-mercaptoethanol to protect against oxidation of sulfhydryl groups in the active center, which leads to loss of activity. Commercial kits contain reagents to inhibit adenylate kinase, which can be released by red blood cells, resulting in artifactual elevations of CK activity. Assays for total and MBCK activity and mass have been reviewed extensively elsewhere. Artifacts can
occur with any assay but are particularly common with electrophoresis. Naturally fluorescing compounds such as bilirubin, benzodiazepines, antidepressants, pyridoxime, and aspirin in high doses can produce artifactual bands by electrophoresis. Patients with renal failure can also manifest artifactual bands that comigrate with MBCK and BBCK.44 Carryover of MM into the MB fraction is a common problem with “column” methods,52 and assays that detect B subunits53 can measure elevated levels that are the results of brain injury; pregnancy; carcinoma of the prostate, lung, or gastrointestinal tract; tuberculosis; or uterine abnormalities. Up to 3.2% of hospitalized patients have detectable circulating levels of BBCK.45 Because BB is cleared rapidly, it usually is only detectable in patients with disease processes that result in continuing release.

Assays based on monoclonal antibodies that measure MBCK mass are rapid, highly sensitive and specific, and are now the analytic method of choice.55 However, monoclonal antibodies directed against different epitopes of the same marker may be affected differently by pathological and/or artificial processes.26 Recently, it was found that elevations in MBCK mass were produced by cross-reactivity of atypical forms of alkaline phosphatase in plasma with the alkaline phosphatase used to stabilize the reagents for the assay.56 Similar artifactual results can occur with all assays using monoclonal antibodies. In general, mass and activity assays yield comparable results, with the occasional exception of samples with very high total and MBCK values.57

Macrokinases, including immunoglobulin G bound to BBCK (macro-CK1) or aggregates of mitochondrial CK (macro-CK2), are detected with many assays.58,59 In a prospective study of 3000 hospitalized patients,58 macrokinases were detected in 4.2% (1.0% had type 1 and 3.4% had type 2), but for patients with cardiovascular disease, this may be a substantial overestimation.26 Macro-CK1 migrates close to and is often indistinguishable from MBCK on electrophoretic separations, thus markedly increasing the percentage of MBCK with respect to total CK. Macro-CK1 is detected most often in chronically ill older women. Macro-CK2 migrates near MMCK, resulting in elevations in total CK activity.59 The presence of macro-CK2 is associated with chronic disease (especially liver cirrhosis and malignancy) and severe acute illness. In contrast to free CK enzyme, macrokinases are heat stable. The persistence of enzyme activity after incubation for 20 minutes at 45°C has been used to verify the presence of macrokine activity.26 Although it is hoped that the newer assays based on mass will be less affected by macrokinases, cross-reactivity may still occur.

**Diagnosis of AMI**

Measurement of MBCK is currently the test of choice to confirm the diagnosis of an AMI.11 (See Table 1.) Increases in plasma levels usually occur between 6 to 10 hours after the onset of infarction (in the absence of thrombolysis), peak at 24 hours, and return to normal by 36 to 72 hours.60 Given these kinetics, measurement of MBCK every 12 hours is an adequate and cost-effective method for diagnosis of AMI. Obtaining values more frequently will increase diagnostic sensitivity.61 Levels of MBCK peak slightly earlier, and the MB fraction disappears slightly more rapidly than total CK. The time to peak enzyme concentration is earlier for small infarctions,42 leading some to hypothesize that non-Q wave infarctions, which also tend to be smaller, result from occlusion and reperfusion.43 This is an interesting but unproven speculation. Recanalization increases the rapidity with which MBCK appears in plasma, permitting earlier diagnosis of AMI. Enzyme levels in plasma are abnormal within 2 hours after coronary recanalization in experimental animals and when recanalization is confirmed in patients by cardiac catheterization.54,60 In the absence of recanalization, there usually is a return to baseline values by 24 hours, representing a shorter period of enzyme release rather than a change in the rate of clearance.66

**Processes Associated With Elevations of MBCK in the Absence of AMI**

Myocardial cell death of any cause will result in a rising and falling pattern of MBCK. This has been observed in patients with cardiac contusion after chest wall trauma, electrical injury, and pericarditis with concomitant myocardial involvement.67-69 As discussed above, sufficient MBCK can be released from damaged skeletal muscle to elevate circulating levels. This can cause diagnostic confusion in patients after surgery or trauma, requiring noninvasive tests (such as echocardiography) to confirm the diagnosis.67,70 Some have proposed that an MBCK/total CK percentage of 3% to 5% or an MBCK mass/CK activity ratio of 80 ng/U or 2.5% differentiates a myocardial from a skeletal muscle source.71,72 However, results of a large study of trauma patients did not support this approach.73 When high levels of total CK are present because of skeletal muscle injury, a large amount of MBCK has to be released from myocardium to meet percentage criteria, decreasing sensitivity, whereas chronically injured muscle may release large amounts of MBCK, decreasing specificity. The failure of percentage criteria to differentiate skeletal from myocardial release of MBCK has been confirmed recently in a large study of patients with acute and chronic skeletal muscle abnormalities.73 In general, when MBCK is released because of skeletal muscle injury, it is released for a longer period of time. Thus, plasma levels decline more slowly than after an AMI. The use of more specific markers (such as cardiac troponin I) in these patients should allow for a more facile determination of whether concomitant cardiac injury is present (see below).

Patients with hypothyroidism have increased levels of MBCK in plasma because of skeletal myopathy and a decreased rate of clearance.13 Administration of exogenous thyroid hormone increases the disappearance rate of CK and usually rapidly normalizes circulating levels of CK and MBCK.15

**Detection of Reperfusion**

Early detection of failure of recanalization could allow for mechanical intervention to reperfuse ischemic myocardium. After reperfusion, the release ratio of CK appears to double, and the rate of egress into the circulation increases,16 which aids detection of reperfusion. (See Table 2.)

Very early detection is not possible with total CK, but it does have moderate sensitivity for the detection of
reperfusion late after treatment. Although a time to peak CK of less than 4 hours is highly predictive of recanalization, most patients have peak CK levels at 4 to 16 hours, when the predictive power is between 40% and 60%.64,74 The usefulness of the measurement can be improved by definition of peak levels and determination of the time required to reach a percentage of it.75

Early detection of reperfusion is possible with measurement of MBCK. An early increase in MBCK levels and a shorter time to peak MBCK have been found to be indicators of reperfusion.65,75 A 2.2-fold increase in MBCK in patients with inferior myocardial infarction and a 2.5-fold increase in those with anterior myocardial infarction during the initial 2 hours of treatment are adequately sensitive (85%) and 100% specific for the detection of recanalization.65,74 However, measurement of MBCK 1 hour after thrombolysis does not differentiate between those in whom recanalization is and those in whom it is not successful.74

**Estimation of the Size of AMI**

Infarct size can be estimated after AMI if the amount of enzyme lost from the myocardium, its volume of distribution, and its release ratio are known. Extensive modeling of the volume of distribution and disappearance rate have facilitated calculations.15 Infarct size as assessed by MBCK closely correlates with the volume of the infarction, the ejection fraction, the incidence of ventricular arrhythmias, and prognosis.2,76 Initially, it was believed that 30% of the MBCK depleted from heart appears in plasma.78 These data at present stand alone against previous results and the known proteolysis of MBCK in lymph.14 Approximately 15% of CK activity remains in heart even after infarction while some of the remaining 85% is deactivated in lymph.13 Calculations are further complicated by release of MMCK from skeletal muscle in patients with large infarctions, making estimates based on total CK larger than those based on MBCK.79 Thus, in plasma, the percentage of MBCK with respect to total CK fluctuates, depending on the presence of concomitant skeletal muscle disease, the amount of MBCK in muscle, the size of the infarction, and regional blood flow.

After recanalization, the amount of enzyme released into plasma appears to double, limiting the use of calculations of infarct size as defined in its absence.16,77,80 It is unclear whether a continuum exists in the amount of enzyme that reaches the circulation as a function of the total ischemic time and the amount of reflow or whether in some way this response is a “step function.” It is likely that the release of smaller cumulative amounts of MBCK in patients undergoing early thrombolysis compared with those not treated with thrombolytic agents is indicative of salvage of myocardium. However, comparisons of enzyme levels between untreated patients and those with late recanalization are less useful.

**CK Isoforms**

Isoenzyme subforms with similar enzymatic activity but different isoelectric points (thus isoforms) have been identified for both MMCK and MBCK.61 The tissue distribution and specificity of CK isoforms for irreversible injury are the same as those for CK. Three

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**TABLE 2. Molecular Markers and Criteria Proposed for Noninvasive Detection of Coronary Recanalization**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Proposed criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>Minimal rate of rise &gt;2.6 ng · mL⁻¹ · min⁻¹ at 1-2 h²⁴</td>
<td>92%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>4.6-Fold increase over 2 h²⁴</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Rate/initial value &gt;0.015²⁴</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>CK</td>
<td>Time to peak &lt;4 h²⁴</td>
<td>10%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>Time to peak &gt;16 h²⁴</td>
<td>39%</td>
<td>81%</td>
</tr>
<tr>
<td>MMCK isoforms</td>
<td>Minimal rate of decline of MM3% &gt;3.1%/h⁶⁶</td>
<td>87%</td>
<td>74-90%</td>
</tr>
<tr>
<td></td>
<td>MM3%/MM1% &gt;0.35 at 60 min¹⁷³</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Rate of rise of MM3% &gt;0.18%/min⁷⁴</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>MBCK</td>
<td>Minimal rate &gt;0.04 IU · L⁻¹ · min⁻¹ at 1 h²⁴</td>
<td>92%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>2.2-Fold increase over 90 min (inferior MI)⁶⁵</td>
<td>77%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>2.5-Fold increase over 90 min (anterior MI)⁶⁵</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Appearance rate constant (k₁) &gt;0.185⁷⁵</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>MBCK isoforms</td>
<td>Peak MB2/MB1 ratio &gt;3.8 at 2 h¹⁰³</td>
<td>82%</td>
<td>78%</td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>Peak concentration/concentration at 32 h &gt;1.1⁷⁴</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Concentration at 14 h/concentration at 32 h &gt;1.0²⁴</td>
<td>87%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CK indicates creatine kinase; MMCK, MM isoenzyme of CK; MBCK, MB isoenzyme of CK; MI, myocardial infarction.
isoforms of MMCK are known to exist,\textsuperscript{81,82} and at least three are known for MBCK.\textsuperscript{83} Isoforms represent post-translational modifications of the carboxyterminus of the M and B monomers. They are numbered by their relative electrophoretic migration to the anode with those migrating furthest toward the anode having the lowest number.\textsuperscript{83}

In tissue, greater than 95% of MMCK is comprised by the tissue isoform designated MM3,\textsuperscript{82} i.e., it remains near the origin on electrophoresis. Structurally, it has a lysine residue on the carboxyterminus of each subunit.\textsuperscript{84} Once released into plasma, carboxypeptidase-N sequentially removes the carboxyterminal lysines from MMCK by hydrolytic cleavage, generating an intermediate designated MM2 and an ultimate conversion product designated MM1.\textsuperscript{85} Each lysine cleaved removes one positive charge from the molecule, resulting in an anodal electrophoretic shift.\textsuperscript{81} The conversion\textsuperscript{86} and rapid clearance\textsuperscript{86} of MM3 result in its swift disappearance from plasma.

MBCK isoforms should be more specific for cardiac injury than MMCK isoforms. The MB tissue isoform (designated MB2) has lysines on the carboxyterminals of both M and B monomers. Although four isoforms could exist theoretically, electrophoretic separations have delineated only two forms, and it has been presumed that the second form (designated MB1) represents cleavage of the carboxyterminal lysine from the M monomer by carboxypeptidase-N.\textsuperscript{87,88} With chromatography and monoclonal antibodies to the MB carboxyterminal lysine, it is now clear that at least three isoforms circulate in vivo; the tissue isoform, a form with a lysine on the M subunit but not on the B subunit, and a form with lysines absent from both carboxyterminals.\textsuperscript{83,88} Thus, cleavage of the M monomer lysine is favored. Comigration on electrophoresis of the tissue isoform and the isoform with a lysine removed from the B monomer appears to account for the separation of only two species.\textsuperscript{83}

Techniques of Measurement

Samples should be collected in ethylene diamine tetraacetic acid (final concentration 7 to 10 mmol/L) to inhibit in vitro conversion.\textsuperscript{80} MMCK isoforms vary with respect to charge, allowing separation by prolonged electrophoresis, high-voltage rapid electrophoresis, nonequilibrium pH gradient electrophoresis, isoelectric focusing, or chromatofocusing.\textsuperscript{51,66,91} The high-voltage electrophoretic methods are the most rapid and least difficult. However, these methods tend to underestimate MM3 and overestimate MM1 compared with chromatofocusing (A.S. Jaffe and D.A. Abendschein, unpublished observations).

Electrophoresis also has been used to separate isoforms of MBCK.\textsuperscript{81,87,88} However, as described above, this method only delineates two of the three forms known to exist in plasma in vivo.\textsuperscript{83}

Diagnosis of AMI

Measurement of MMCK isoforms is highly sensitive for the early detection of AMI.\textsuperscript{92} The sensitivity of MMCK isoforms is due to the fact that the tissue isoform (MM3) is abundant in myocardium, but because of conversion of MM3 to other forms and its rapid clearance from the circulation, MM3 comprises only 15% of MMCK activity in plasma under physiological conditions.\textsuperscript{92} The ratio of MM3 to MM1 averages 0.33.\textsuperscript{92} Thus, the release of only small amounts of MM3 will dramatically increase its percentage in plasma and the MM3 to MM1 ratio that has been used for diagnosis. When a ratio of MM3 to MM1 > 0.5 is used as the upper limit of the reference range and patients who present late are diagnosed by increases in MBCK, 94% of patients who fulfill subsequent criteria for AMI can be identified by analysis of MMCK isoforms and MBCK in the first sample of blood drawn on presentation.\textsuperscript{92} By 12 to 16 hours, the conversion and clearance of MM3 return the ratio to normal or near-normal values,\textsuperscript{92,94,95} but by this time MBCK levels usually are elevated so that a diagnosis can be made early with analysis of MMCK isoforms and later with MBCK.\textsuperscript{93} Since MMCK isoforms are not specific for myocardium, their utilization for the diagnosis of AMI requires that acute skeletal muscle damage be excluded. Even then, the specificity of MMCK isoforms for the early diagnosis of AMI varies between 77% and 94%, depending on the specific criteria used.\textsuperscript{92,93}

Measurement of MBCK isoforms could be more specific than MMCK isoforms for the diagnosis of AMI. Because the absolute levels of MBCK in plasma are low (much lower than MMCK), the release of small amounts of the tissue isoform (MB2) will result in a marked change in the ratio of MB2/MB1 hours before elevations of circulating MBCK are manifest. However, it may be that the small amounts of MB2 contained in skeletal muscle could deleteriously affect cardiac specificity by the same mechanism. This issue is yet to be resolved. Application of MB isoforms in patients with a high pretest probability of AMI, as with all such tests, improves the cardiac specificity. The presence of elevated levels of MBCK isoforms, defined as a plasma MB2 activity > 1.0 U/L and a MB2/MB1 ratio > 1.5, has a 59% sensitivity for the diagnosis of AMI at 2 to 4 hours and a 92% sensitivity at 4 to 6 hours after the onset of symptoms.\textsuperscript{96} The early accuracy of these criteria may improve if separation of all the isoforms known to circulate in plasma can be accomplished. Myocardial injury that is not due to AMI may also be detectable by analysis of CK isoforms. The proportion of MB2 to total MBCK in plasma has been found to be elevated in patients with cardiac transplant rejection and cardiomyopathy.\textsuperscript{97,98} Whether this is due to skeletal muscle or cardiac release is unclear at present.

Detection of Reperfusion

The presence of the combination of relief of chest pain, normalization of ST-segment changes, and reperfusion arrhythmias has been found to be indicative of coronary recanalization, but these criteria are not sensitive because all three occur in only 15% of patients.\textsuperscript{99} Results with CK isoforms have been far more promising (Table 2).\textsuperscript{100,101} An accelerated rate of increase of MM3% in plasma reliably distinguishes animals with and without coronary recanalization by 30 minutes after reflow is established\textsuperscript{100} and identifies patients with recanalization within 1 hour of the administration of thrombolytic agents.\textsuperscript{74,101,102} The rate of rise in MM3% not only permits a very early determination in experimental animals but is less affected by residual high-grade acute or chronic coronary stenoses.\textsuperscript{100} Currently, the best criteria
for the detection of reperfusion with MMCK isoforms is a rate of rise of MM3% ≥0.18%/min.74 Criteria based on both the rate of rise and absolute values of MM3% in plasma may be capable of distinguishing patients with persistent recanalization from those with transient reperfusion followed by reclosure.

MB isoforms also have been used to detect coronary recanalization. A ratio of MB2 to MB1 ≥3.8 has been established as the upper limit of the reference range.103 Preliminary results suggest that substantial overlap exists between levels of this marker in patients with and without recanalization.103 Conjoint use of the rates of rise of MM3% and either the ratio of MB2 to MB1104 or the rate of rise of MB2%,105 may produce more accurate results by detecting more patients who recanalize. For isoform assessment of recanalization, samples should be obtained before treatment and at 60 to 90 minutes after treatment. Early sampling and rapid turnaround for the assays are essential if additional interventions are to be implemented based on the results.

Myoglobin

Myoglobin is a low-molecular-weight heme protein (17 800 D) that is abundant in cardiac and skeletal but not smooth muscle. Thus, it is a sensitive but not specific marker of AMI, requiring the exclusion of skeletal muscle injury.106 Myoglobin is rapidly released from necrotic myocardium, with subsequent rapid renal clearance.10 Decreased renal function can result in elevated levels.106 Because of its rapid kinetics, myoglobin can define the timing of myocardial events if frequent samples are obtained.17,107,108 Myoglobin is often detectable 2 hours after coronary occlusion, with peak levels occurring at 3 to 15 hours. Sixty-five percent of patients with AMI have elevated levels of myoglobin in their initial samples.108,109

A pattern of discontinuous release of myoglobin consisting of multiple peaks, or the “staccato phenomenon,” can occur in patients who have suffered AMI.17,110 This pattern of myoglobin elaboration may reflect cyclical spontaneous coronary reclosure and reperfusion of the ischemic myocardium, leading to bursts of myoglobin release. Early treatment with either nifedipine (within 6 hours of the onset of symptoms) or thrombolytic therapy has been shown to decrease the number of staccato peaks.111,112

When used for the early detection of coronary recanalization after thrombolysis, the lack of specificity of myoglobin for myocardium is less problematic. In both experimental and clinical studies, a rate of change of myoglobin concentration >2.6 ng·mL⁻¹·min⁻¹ over 60 minutes or a 4.6-fold rise over 2 hours allows detection of coronary recanalization with an accuracy comparable to MMCK isoforms.74,113 In animals, this determination can be made as early as 30 minutes.74 However, because of the rapid clearance of myoglobin, criteria based on myoglobin concentrations are less precise at 120 minutes. The rapid release of myoglobin also seems to make criteria with it more prone to be met by increases associated with transient rather than sustained restorations of blood flow.74,113 Elevated levels of myoglobin have been reported in patients with unstable angina, perhaps reflecting small areas of otherwise undetected myocardial cell death or the release of myoglobin from skeletal muscle in critically ill patients.114,115

Myosin Fragments

Myosin consists of six proteins: two heavy chains (MW, 200 000 D each) and two pairs of dissimilar proteins (MW, 20 000 to 26 000 D each) designated myosin light chain I and II (MLC-I and MLC-II). Both participate in regulation of the interaction of actin and myosin predominantly by modulating changes in calcium flux.

Myosin Light Chains

At least two forms of MLCs exist in the ventricles and atria, and at least three forms of MLCs are found in skeletal muscle. These forms have similar structures, and the amino acid sequences of ventricular MLC-II and slow skeletal MLC-II are identical.116,117 Given the close or identical structures of cardiac and skeletal muscle forms of MLCs, the specificity of MLCs for myocardial injury both in normal and pathological situations is limited.117,118 This problem has been accentuated in some studies by the use of polyclonal antibodies that cross-react with troponin T.119 Both types of MLC fragments (MLC-I and MLC-II) dissociate from the contractile apparatus after cell necrosis.120 Although most of the MLC fragments are noncovalently linked to myosin heavy chains, a smaller pool (perhaps present in the cytosol after synthesis) is available for early release.122,124 Thus, MLC fragments generally are detectable in plasma within 6 hours of the onset of infarction.118 Elevated levels are present for more than 7 days and are thought to represent continuing dissociation and release from the contractile apparatus.121,122 MLCs are cleared by the kidneys.123

MLC fragments are sensitive markers of myocardial injury, in part because prolonged elevations permit retrospective detection for up to 2 weeks.118 The contention that measurement of MLC is more sensitive for the detection of AMI than either total CK or MBCK114 probably is due to this prolonged diagnostic window rather than a greater amount of protein release per gram of injured tissue. Patients with unstable angina who have elevated levels of MLC, perhaps indicating myocardial injury that occurred before admission, have more severe coronary artery disease and a higher incidence of subsequent AMI and/or death.45,114 Because of their long half-life, monitoring of MLC levels is not a sensitive way to detect recurrent AMI.

Measurement of MLC can be used to estimate infarct size. The release ratio is close to unity if samples are obtained until values return to baseline and it is unaffected by reperfusion.122,124 However, the need to obtain multiple samples over at least a 7-day period lessens the attractiveness of this technique. In addition, cross-reactivity between antibodies with both skeletal muscle and cardiac forms of MLC may also impair the accuracy of such estimates.

Myosin Heavy Chains

Myosin heavy chains (MHCs) are larger (MW, 200 000 D)116 fragments that dissociate from other structural proteins before release.125 Levels of MHC are not present in plasma until 2 days after the event; peak levels occur 5 to 6 days later.126 Elevations persist for up to 10 days, allowing for a prolonged retrospective determination of myocardial necrosis.126 In contrast to
other structural proteins, an early releasable pool of this protein does not appear to exist. Although monoclonal antibodies to MHCs have been developed, the existence of multiple variants in atria, ventricles, and skeletal muscle with similar structures has limited cardiac specificity.116,125,127 All patients have elevated levels of MHCs after cardiovascular surgery, but patients with clinical evidence of perioperative AMI have significantly greater elevations.125

**Lactate Dehydrogenase**

LD is a tetramer composed of "M" (muscle; MW, 34,000 D) and "H" (heart; MW, 34,000 D) subunits. The two subunits are encoded by different genes and give rise to five distinct isoenzymes that provide LD with an element of tissue specificity.51 The molecular weight of the LD tetramers is approximately 135,000 D. LD-1 contains four H subunits; LD-2, three H subunits and one M subunit; LD-3, two H and two M subunits; LD-4, one H subunit and three M subunits; and LD-5, four M subunits. Individual chains lack biochemical activity. LD is responsible for the interconversion of pyruvate and lactate as the final step in glycolysis.

LD-1 is the predominant form in heart but also occurs in erythrocytes, brain, pancreas, kidney, and stomach. LD-2 is also abundant in heart; LD-3, LD-4, and LD-5 are found in only trace amounts. All LD isoenzymes are abundant in many tissues, whereas LD-5 is the predominant isoenzyme in skeletal muscle. Clearance of LD is via the reticuloendothelial system.128

**Techniques of Measurement**

Differences in amino acid composition of M and H chains result in alterations in charge that can be detected by electrophoresis.126 The isoenzymes are designated according to electrophoretic migration, with the lowest number moving closest to the anode. Total LD usually is measured as enzymatic activity, and levels of its isoenzymes can be quantified after separation by electrophoresis. LD isoenzymes (especially those rich in M subunits) are inactivated when chilled or frozen but are stable at room temperature for several days.130 Care must be taken to avoid hemolysis, which will markedly increase LD activity. The details of the various techniques used for the assay of LD and its isoenzymes have been reviewed recently.51

**Diagnosis of AMI**

In human plasma, LD-2 is normally found in greater abundance than LD-1. A normal LD-1/LD-2 ratio is <0.76. When myocardial necrosis occurs, more LD-1 than LD-2 is released, and the percentage of LD-1 relative to LD2 increases. Ratios >0.76 are considered by some to be suggestive of AMI, but others require a value of >1.0, which appears to improve specificity.1,4,131 Alternatively, an LD-1/LD-4 ratio >3.0 (when LD-1 is <40% of total LD) or >4.0 (when LD-1 is >40% of total LD) has been proposed as a more accurate and earlier criterion for AMI than LD-1/LD-2.132 Plasma LD is increased above the upper limit of the reference range 8 to 12 hours after the onset of AMI, peaks at 28 to 48 hours, and is normal by day 10.51 A persistent abnormality in the LD-1/LD-2 ratio may indicate reinfarction.

**Processes Associated With Increased LD-1/LD-2 Ratio in the Absence of AMI**

Although an elevated LD-1/LD-2 ratio may indicate AMI, there are other possible causes of an abnormal ratio. Erythrocytes are an abundant source of LD-1 and LD-2, and intravascular or extravascular hemolysis will increase LD-1 and LD-2 levels. In patients with chronic muscle disease or recurrent skeletal muscle injury, LD-1 and LD-2 are reexpressed in skeletal muscle;133 elevated LD-1/LD-2 ratios occur in healthy, well-trained athletes.134 Other causes of abnormal LD-1/LD-2 ratios include germ cell tumors (testicular seminomas and dysgerminomas) and diseases of the pancreas, stomach, and kidney.135 The presence of macroenzymes of LD, which are probably complexes of LD with IgG or IgA, increase total LD.58

**Estimation of Size of AMI**

A good correlation has been found between LD (and α-hydroxybutyrate dehydrogenase [HBDH], which is equivalent to LD-1 plus LD-2) and anatomic estimates of infarct size.136 It is possible that the release ratios of LD and HBDH are less affected by reperfusion, and estimates of infarct size by these markers thus are superior to those based on CK and MBCK in patients treated with thrombolytic agents.137,138 Definitive studies are lacking.

**Troponins**

Troponins are a complex of regulatory proteins uniquely present in striated muscle that regulate the calcium-mediated interaction of actin and myosin. Troponin T binds the tri-protein complex to tropomyosin, troponin I inhibits coupling of actin and myosin, and troponin C binds to calcium, inducing a sterically shifted and reversing the inhibitory activity of troponin I. There are tissue-specific isoforms of troponin I, T, and C. Different isoforms of troponin I and T are expressed in slow-twitch, fast-twitch, and cardiac muscle, whereas troponin C has only a fast-twitch and a slow-twitch/cardiomyocardial isoform. Troponin isoforms are the products of different genes; they have unique structures and different regulatory effects on calcium binding.139-142

Cardiac troponins are tightly complexed to the contractile apparatus. Circulating levels are normally low, but they rise relatively rapidly after AMI, suggesting the presence of a more accessible pool, perhaps troponin synthesized in the cytosol.143 This hypothesis has not been proven definitively. If a cytosolic pool of troponin does exist, then its usefulness as a marker is subject to questions about whether increases are specific for myocyte death. That continuing release for days caused by dissociation of the contractile apparatus indicates cell death is less controversial. The existence of tissue-specific isoforms with unique structures has allowed the development of tissue-specific assay methods.

Cardiac troponin I (cTnI) is not expressed in skeletal muscle throughout ontogeny.144 Fetal rat, chick, and human heart contain both slow-twitch and cTnI initially. After the ninth postnatal month, only cTnI is expressed in myocardium.145,146 Thus, the presence of cTnI in the circulation above the reference limit is highly specific for myocardial injury and allows for MBCK elevations resulting from skeletal muscle damage to be distin-
guished from those resulting from cardiac injury.\textsuperscript{147} Elevations in cTnI do not occur in marathon runners or patients with acute or chronic muscle disease or in patients with renal failure unless concomitant acute cardiac damage has occurred.\textsuperscript{147,149} The specificity of cardiac troponin T (cTnT) for myocardium has not been fully delineated. Skeletal muscle troponin T (sTnT) and cTnT are coexpressed in fetal heart muscle, with the skeletal muscle form being suppressed during ontogeny and reexpressed in stressed human heart.\textsuperscript{150,151} In contrast to cTnI, cTnT is expressed in fetal skeletal muscle and is reexpressed in adult rat skeletal muscle after injury or denervation.\textsuperscript{152} Since the troponin system is highly conserved across species, cTnT could be reexpressed in injured human skeletal muscle, with a decrease in its specificity for AMI. Most\textsuperscript{151,153} but not all investigators\textsuperscript{154} have found multiple isoforms of cTnT, some of which are expressed in skeletal muscle.\textsuperscript{151} In two studies in which assays were based on polyclonal antibodies with a 1% to 3% cross-reactivity with sTnT, 16% of patients with skeletal muscle disease and 15% of patients with chronic muscle disease had elevations of cTnT without any evidence of myocardial injury.\textsuperscript{155,156} There appears to be less analytic cross-reactivity with the monoclonal antibody used by Katus et al.\textsuperscript{159} In a study of patients undergoing surgery either for forearm fractures or noncardiac thoracic surgery, no elevations were detected despite obvious acute skeletal muscle damage.\textsuperscript{157} However, in another study using the same monoclonal antibody-based assay for cTnT, three of 14 patients with normal ECGs and low levels of MBCK relative to total CK had elevated levels of cTnT.\textsuperscript{159} This could be due to increased sensitivity or decreased specificity, since no other cardiac evaluations were performed. In addition, 27% of patients with polymyositis/dermatomyositis have been reported to have elevations of cTnT in the absence of detectable cardiac injury.\textsuperscript{158} Although elevations of cTnT have not been found in athletes with elevations in MBCK, important details regarding how well trained the subjects were, the exercise involved, and the methods have not been reported.\textsuperscript{159} A proper understanding of the cardiac specificity of cTnT will be necessary to interpret recent findings that patients with unstable angina and increased levels of cTnT have a poorer prognosis than similar patients without elevations of cTnT.\textsuperscript{160} It is likely that the measurement of cTnT permitted detection of patients with AMI before presentation to the hospital (since MBCK was not elevated) and that patients with unstable angina after infarction are at greater risk than those with unstable angina alone. However, it is also possible that cTnT is released from poorly perfused skeletal muscle in some critically ill patients.

Detection of AMI

The sensitivity of measurement of cTnI has been reported to be comparable to that of MBCK for the diagnosis of AMI in canine studies and in patients admitted with chest pain; elevations of cTnI above the upper bound of the reference range occur a few hours later than those of MBCK.\textsuperscript{149,161} Increased levels persist for up to 1 to 2 weeks after AMI, facilitating retrospective identification of AMI.\textsuperscript{143,156,161} In addition, the short half-life of cTnI in plasma and the small amounts present in plasma in the absence of infarction result in very low circulating levels (undetectable: <1 ng/mL for cTnI) in normal volunteers, enhancing sensitivity of elevations for detection of infarction.\textsuperscript{161}

cTnT also is a sensitive marker for the detection of AMI in humans\textsuperscript{156,157,162}; some have claimed it to be more sensitive than MBCK.\textsuperscript{160} This apparent superiority probably is due to a longer diagnostic window rather than to more release of protein per gram of damaged tissue. The cardiac specificity of cTnT in patients with skeletal muscle disease and therefore the accuracy of measurement of cTnT for the diagnosis of AMI in this population has not been defined (see above).

Heart Fatty Acid Binding Proteins

Heart fatty acid binding proteins (FABPs) are abundant cytosolic proteins of low molecular weight (14 000 to 15 000 D) that are thought to be important intracellular fatty acid carrier proteins. Three different FABPs are found in heart, liver, and intestine, although each is also present in other tissues that use fatty acids as metabolic substrates.\textsuperscript{163} Heart FABP (h-FABP) has a unique structure and is abundant in myocardium, but detectable amounts also are present in skeletal muscle and kidney.\textsuperscript{165} Serum h-FABP is elevated after myocardial injury in rats, and serum and urine levels are elevated in humans after myocardial infarction.\textsuperscript{164,165} Initial and peak elevations occur earlier than increases in MBCK consistent with the smaller size of FABP. Measurement of h-FABP may have comparable sensitivity to that of myoglobin for the detection of reperfusion after thrombolytic therapy.\textsuperscript{166} The tissue distribution for h-FABP requires determination, but because of its abundance and potential sensitivity, this marker could have exciting clinical applicability if it is adequately specific.

Enolase

Enolase is an abundant glycolytic enzyme present in all tissues. It catalyzes the interconversion of 2-phosphoglycerate and phosphoenolpyruvate. The enzyme exists as a dimeric structure composed of three distinct subunits, \(\alpha, \beta,\) and \(\gamma\), with an approximate molecular weight of 90 000 D. Each subunit is the product of a different gene.\textsuperscript{167} Five isoforms of enolase (\(\alpha\alpha, \alpha\beta, \beta\beta, \alpha\gamma,\) and \(\gamma\gamma\)) have been described. \(\alpha\beta\)-Enolase is the predominant form in myocardium, \(\beta\beta\)-enolase represents the predominant form in skeletal muscle, and the \(\gamma\gamma\)-subunit isoforms (\(\alpha\gamma\) and \(\gamma\gamma\)) are present in neuronal tissue.\textsuperscript{168} The \(\beta\beta\)-subunit represents 90% of total enolase in humans.\textsuperscript{168} Total and “muscle-type” (\(\alpha\beta\) and \(\beta\beta\)) enolase can be measured with assays based on polyclonal antibodies and are elevated 12 to 48 hours after AMI.\textsuperscript{169,170} Levels of \(\beta\)-enolase also are elevated after open heart surgery, which some investigators interpret as being indicative of myocardial injury.\textsuperscript{171} Enolase undergoes postsynthetic modifications similar to those of MMCK.\textsuperscript{172}

At present, it appears that measurement of \(\beta\)-enolase will not enable differentiation of skeletal muscle from myocardial damage. An assay specific for \(\alpha\beta\)-enolase might be more useful. However, even this strategy may not result in a method with adequate specificity if pathological states that affect either the myocardium or skeletal muscle alter the distribution of
isoforms. Since the diagnostic window of enolase is comparable to that of MBCK, enolase probably will not have significant clinical utility.

**Recommendations for the 1990s**

**Acute Myocardial Infarction**

*Routine diagnosis.* The measurement of MBCK remains the test of choice for the confirmation or exclusion of AMI and probably will remain the test of choice throughout early 1990s. Samples obtained every 12 hours provide adequate sensitivity and are cost-effective.

*Retrospective diagnosis.* LD still is useful, but it probably will be replaced by more specific long-lived markers (eg, the troponins) in the near future. Samples for these long-lived markers can be done daily.

**Diagnosis when skeletal muscle injury is present.** More specific assays (eg, cardiac troponin I) will in the future be useful conjointly with MBCK. Because cardiac troponin I persists in plasma for prolonged periods of time, it cannot replace the use of MBCK when timing of AMI is necessary.

**Very early diagnosis.** Several approaches are possible. The conjoint use of MBCK isoforms and myocardin or MMCK isoforms could be a very sensitive approach and will compete with MBCK. Serial measurements over several hours are likely to be most useful; however, it is unclear how earlier diagnosis based on multiple samples would impact on patient care. The application of serial measurements to the large number of patients in whom one might wish to exclude AMI may not be cost-effective and would delay the initiation of early treatment. In addition, decisions regarding who should be admitted and who should be discharged should not be based on the presence or absence of these markers of infarction alone. The most promising role at present for this approach is in distinguishing patients with possible AMI who may need admission to an intensive care unit from those who can be treated in a less intensive facility. Whether use of markers other than MBCK to shorten the time to diagnosis to <12 hours is clinically necessary and/or cost-effective remains to be shown.

**Detection of Coronary Recanalization After Thrombolysis**

Criteria based on isoforms of MM and MBCK and myoglobin appear to hold the most promise. It is possible that conjoint use of two markers, eg, myoglobin or MBCK isoforms combined with MMCK isoforms, will emerge as the best strategy.

**Estimation of Infarct Size**

Longer-lived structural protein markers such as the troponins or MLC, whose release ratios are less affected by alterations in blood flow, probably will replace MBCK for this use. However, because of the prolonged release of these markers, blood samples will have to be obtained for an extended period of time for these studies. These techniques require further validation.

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