EDITORIAL VIEWS

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Beyond CK-MB

Biochemical Markers for Perioperative Myocardial Infarction

I. Background

Myocardial infarction, whether occurring in the ambulatory or the surgical setting, has a substantial impact on mortality, resource utilization, and health-care expenditure. Although we continually seek improved methods for diagnosis and treatment of infarction, these remain challenging, especially in patients undergoing surgery.

Diagnosis of myocardial infarction is based on World Health Organization criteria, requiring two of three positive findings, including: (1) a clinical history of prolonged ischemic chest pain, (2) a characteristic sequence of electrocardiographic change, and (3) increased plasma concentrations of cardiac enzymes. However, each of these criteria has inherent limitations. Clinical symptoms of infarction often are masked or, even, silent. That is, 75% of documented episodes of myocardial ischemia are painless, and 30% of myocardial infarctions are silent or associated with atypical chest pain. The 12-lead electrocardiogram is indeterminate in approximately 20% of patients with myocardial infarction. Cardiac-specific enzymes, such as CK-MB, have sensitivity of 70% or less for acute myocardial infarction in certain populations. In high-risk patients undergoing surgery, these limitations are even more constraining, making diagnosis of perioperative myocardial infarction more challenging. Symptoms of ischemia or infarction are uncommon perioperatively; 95% of postoperative ischemia episodes are silent. Approximately 20% of preoperative electrocardiograms and an additional 25% of postoperative electrocardiograms are uninterpretable. Finally, the specificity of cardiac enzymatic changes in surgical patients is limited because of perioperative skeletal muscle CK-MB release.

In this issue of Anesthesiology, Mächler et al. examined the usefulness of a relatively new biochemical marker, troponin-T, for assessment of patients undergoing coronary artery bypass graft (CABG) surgery. Because of the potential of the new biochemical markers for assessment of injury or infarction and because of recent proliferation of data in this area, it would be useful to present a historical perspective and a brief review of these data, before discussing the Mächler et al. study.

II. Biochemical Markers for Myocardial Infarction

Over the past four decades, new methods for biochemical assessment of myocardial infarction have been investigated. The first markers suggested, SGOT, LD, and LD isoenzymes, were replaced approximately 25 yr ago by the more specific CK-MB isoenzymes. More recently, the tissue isoforms of CK-MB and CK-MM, as well as myoglobin, myosin heavy and light chains, fatty acid binding proteins, and enolase have been investigated (table 1), and over the last decade, the cardiac troponins (T, I, and C). From these studies, we have learned that the sensitivity and specificity of biochemical markers for myocardial injury are affected by a number of factors, including molecular size, cellular location, solubility, release ratio, clearance, detectability, and specificity for irreversible injury. For example, small proteins (fatty acid binding proteins and myoglobin) and cytosolic proteins (vs. structural proteins) are released into the serum soon after injury, whereas proteins undergoing local degradation (CK) are released later but may achieve higher serum concentration, because of other factors, such as reperfusion. The specificity of such proteins as markers for irreversible injury is limited by the difficulty of diagnosing irreversible intracellular damage and relating such damage to cytosolic and structural enzyme leakage. Thus, the dynamics of biochemical markers per se and the differing characteristics of presently available or newly developed markers of myocardial injury must be understood when considering their use.
Table 1. Biochemical Markers for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Marker</th>
<th>Molecular Weight (a)</th>
<th>Earliest Elevation (h)</th>
<th>Peak Elevation</th>
<th>Return to Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid binding protein</td>
<td>14,000–15,000</td>
<td>1.5</td>
<td>5–10 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,800</td>
<td>1–4</td>
<td>6–7 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Myosin light chain</td>
<td>19,000–27,000</td>
<td>6–12</td>
<td>2–4 days</td>
<td>6–12 days</td>
</tr>
<tr>
<td>Troponin I (cardiac)</td>
<td>23,500</td>
<td>3–12</td>
<td>24 h</td>
<td>5–10 days</td>
</tr>
<tr>
<td>Troponin T (cardiac)</td>
<td>33,000</td>
<td>3–12</td>
<td>12 h–2 days</td>
<td>5–14 days</td>
</tr>
<tr>
<td>CK-MB</td>
<td>86,000</td>
<td>2–6</td>
<td>24 h</td>
<td>48–72 h</td>
</tr>
<tr>
<td>CK-MB tissue isof orm</td>
<td>86,000</td>
<td>1–6</td>
<td>18 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>CK-MM tissue isof orm</td>
<td>86,000</td>
<td>1–6</td>
<td>12 h</td>
<td>38 h</td>
</tr>
<tr>
<td>Enolase</td>
<td>90,000</td>
<td>6–10</td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>135,000</td>
<td>10</td>
<td>24–48 h</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Myosin heavy chain</td>
<td>400,000</td>
<td>48</td>
<td>5–6 d</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Adapted with permission.8

III. Limitations of CK-MB

In general, the specificity and sensitivity of CK-MB for myocardial infarction generally are high but may be affected by certain conditions. For example, the myocardium contains approximately 10–30% CK-MB,16 whereas skeletal muscle contains 1–3%;17; thus, in patients with acute skeletal muscle injury (rigorous exercise) or chronic myopathies, total creatine kinase often is elevated and accompanied by elevations of CK-MB. Consequently, skeletal muscle injury induced during surgery may increase the postoperative concentration of CK-MB thereby decreasing CK-MB specificity for myocardial infarction. Similarly, sensitivity of CK-MB is time-constrained; that is, the increase persists for, at most, 72 h, mandating early and frequent assessment to optimize CK-MB effectiveness as a marker for injury. These not insignificant limitations necessitate investigation of alternative biochemical markers for use in high-risk surgical patients.

IV. The Cardiac Troponins

The troponins are a complex of regulatory proteins (T, I, and C) located in striated muscle, regulating actin-myosin interactions. In cardiac striated muscle, the troponins are tightly bound to the contractile apparatus, with troponin-T binding the triprotein complex to tropomyosin, troponin-I inhibiting the coupling of actin and myosin, and troponin-C binding to calcium and reversing the effects of troponin-I. Normally, because of the tight complexing of the troponins to the contractile apparatus, plasma levels are low. With acute myocardial infarction, plasma cardiac troponin concentrations increase rapidly within 3–5 h after surgery, suggesting a cytosol distribution.18 Following this early phase, a late phase, marked by continued release of troponin for 5 days or more, appears to be associated with destruction of the contractile apparatus, indicative of cell death.18 Thus, the greater sensitivity of the cardiac troponins relative to CK-MB allows for earlier detection of myocardial infarction, as well as late diagnosis.

Specificity of the cardiac troponin-T and -I also appears to be greater than that for CK-MB. Cardiac troponin-T has a number of isofoms that are expressed in skeletal muscle. Assays based on polyclonal antibodies demonstrate a 1–3% cross-reactivity between cardiac and skeletal troponin-T, resulting in false-positive rates of 15–27% in patients with skeletal muscle disease who do not have detectable cardiac injury.9,19 Cross-reactivity appears to be decreased when specific monoclonal antibodies are used; however, further investigation is necessary. Cardiac troponin-I is expressed only in the myocardium in adults, resulting in this protein being highly specific for myocardial injury and not skeletal muscle damage.7,9 Studies have demonstrated that, in contrast to CK-MB or troponin-T, troponin-I elevations do not occur in marathon runners or patients with acute or chronic muscle disease, unless cardiac injury has occurred.9,21

Several comparisons of these biochemical markers have been performed in patients with ischemic heart disease. Studies in patients with stable angina, unstable angina, and acute myocardial infarction suggest that cardiac troponin-T may be at least as sensitive as CK-MB for detection of these conditions, because of its longer diagnostic window.9,18,20,22,23 The specificity of troponin-T appears to be similar to CK-MB in patients

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with skeletal muscle disease.\textsuperscript{9,19} Cardiac troponin-I appears to have equivalent sensitivity to CK-MB, but greater specificity in patients with skeletal muscle disease, skeletal muscle injury, or renal failure.\textsuperscript{9,21,24–26}

In patients undergoing cardiac surgery, troponin-T appears to increase after reperfusion,\textsuperscript{27} but comparison of troponin-T or -I with CK-MB has not been performed. In patients undergoing noncardiac surgery, the sensitivity and specificity of cardiac troponin-I appear to be greater than those of CK-MB, suggesting use of troponin-I as the diagnostic biochemical marker.\textsuperscript{7}

V. The Present Study

The clinical investigation by Mächler \textit{et al.},\textsuperscript{8} measures troponin-T release in 21 patients with unstable angina and 31 patients with stable angina undergoing CAGB surgery. Their results suggest that the majority of CAGB patients with unstable angina, \textit{versus} those with stable angina, have increased cardiac troponin-T before (24 h) anesthesia, before induction of anesthesia, and even before cardiopulmonary bypass. CK-MB activity and CK-MB mass were increased in fewer than 25% of patients with unstable angina at these measurement intervals, and CK-MB results did not differ in patients with unstable \textit{versus} stable angina. Because of the limited size of this study, the usefulness of these biochemical markers for prediction of perioperative adverse events cannot be evaluated.

The findings of Mächler \textit{et al.}\textsuperscript{8} generally are consistent with those of previous investigations conducted in nonsurgical patients with unstable angina. Hamm \textit{et al.}\textsuperscript{22} and Katus \textit{et al.}\textsuperscript{23} have reported troponin-T elevations of 47\% and 39\%, respectively, in patients with unstable angina. These investigators also suggest an increase in adverse outcome in patients with unstable angina and elevated cardiac troponin-T levels. Mächler \textit{et al.} report higher incidences (62–90\%) of troponin-T levels in their CAGB patients with unstable angina, but this difference may be due to the diagnostic criteria they have used to define unstable angina and to differentiate it from chronic stable, accelerated, or subacute angina. Combined with previous findings, the work of Mächler \textit{et al.} suggests that the cardiac troponins may provide insight into preoperative risk stratification in patients with unstable angina undergoing CAGB surgery. Certainly, the enhanced sensitivity of cardiac troponin-T and -I and increased specificity of troponin-I suggest that further investigation using larger-scale trials is warranted to determine the prognostic value of the cardiac troponins for preoperative risk stratification, and to delineate the role of the troponins in diagnosing perioperative myocardial infarction.

VI. Summary

Diagnosis of perioperative myocardial infarction remains an important but challenging task. Both clinical symptoms and electrocardiographic changes have inherent limitations. Therefore, biochemical markers for myocardial injury are critical diagnostic tools. The use of creatine kinase isoenzymes (CK-MB) has enhanced detection of perioperative myocardial infarction; however, skeletal muscle damage during surgery limits CK-MB specificity. In this regard, the cardiac troponins appear to offer increased sensitivity, primarily because of their prolonged diagnostic window and even may offer enhanced specificity (especially troponin-I) in patients with surgical skeletal muscle damage. In addition, the convenience of relatively infrequent sampling (because of the prolonged diagnostic window), as well as potential cost savings, make use of the troponin markers attractive. However, definitive data in high-risk patients undergoing either cardiac or noncardiac surgery are still lacking, and significant questions remain regarding appropriate thresholds, specificity of troponin-T, and comparative accuracy of troponin-T, troponin-I, and CK-MB for diagnosis (and prognosis) of perioperative myocardial infarction.

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