Cardiac Troponin: a New Biochemical Marker for Peri-operative Myocardial Injury

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Key Words: Troponin; Aortic aneurysm; Peri-operative myocardial infarction.

Background

Peri-operative myocardial infarction (MI) occurs in 5–10% of patients undergoing major vascular surgery, is fatal in 50% of these cases and in total will account for more than 50% of all post-operative deaths.¹ An even larger proportion of operated patients will suffer cardiac complications, which may be fatal or non-fatal, that are not demonstrably related to peri-operative MI.² These complications may have metabolic causes, but are perhaps more likely to be due to myocardial infarction that cannot be detected by the standard diagnostic tests for peri-operative MI.³,⁴ This injury may be referred to as minor myocardial injury or micro-infarction.

Defining the aetiology, incidence, and treatment of peri-operative cardiac complications has been hampered by the limitations inherent in World Health Organisation (WHO) criteria for diagnosis of acute MI. The WHO criteria require that two of the following three features are present: a history of characteristic prolonged ischaemic chest pain; evolutionary changes on the electrocardiogram (ECG) and elevation of serial cardiac enzymes.⁵ However, in post-operative patients, symptoms may be masked by the use of opiate analgesia, and atypical or even absent in up 75% of patients who have objective evidence of MI.⁶ The ECG is difficult to interpret in the post-operative setting and often does not display the classical ST segment elevation of acute myocardial infarction.⁷ Lastly, even if there is a significant rise in creatine kinase leaked from dying myocardial cells (CK-MB) this may be masked by large quantities of creatine kinase (CK) released from skeletal muscle as the result of direct surgical trauma or ischaemia/reperfusion injury.⁸ This makes the CK/CK-MB ratio difficult to interpret.

Micro-infarction and the acute coronary syndromes

Recently it has become possible to detect micro-infarction by measuring cardiac structural proteins, such as cardiac troponin, that are released following myocardial cell death.⁹–¹¹ It has become apparent that even though the occurrence of micro-infarction may not lead to an acute deterioration of left ventricular function, it is associated with a very adverse longer term prognosis.⁹ Most studies conducted with regard to this have focused on the acute coronary syndromes. This is a group of conditions characterised by the spontaneous development of myocardial ischaemia due to the erosion, fissuring or rupture of coronary atherosclerotic plaque resulting in intra-vascular thrombosis.¹² At one extreme, this thrombosis will result in acute MI characterised by chest pain, ST-segment elevation on the
electrocardiogram, and the later development of Q waves as a result of myocardial scarring. At the other extreme, no infarction occurs, and the electrocardiogram usually shows non-specific changes such as ST depression or T wave inversion, and returns to normal once the symptoms settle. Between these two extremes lie a large group of patients who will have suffered micro-infarction.

While it was originally felt that their prognosis was more favourable in the absence of acute MI, it is now apparent that by 30 days they have a disturbingly high mortality that may actually exceed that of patients who present with full thickness MI. There appears to be a gradation of risk, with poorer outcome being associated with a larger micro-infarction. Recognition of the occurrence of micro-infarction and its seemingly poorer prognosis has led to a recent re-definition of term myocardial infarction so that some patients previously classified as suffering from unstable angina, are now re-classified as having had small myocardial infarcts. Though the mechanisms of peri-operative micro-infarction may differ from those of the acute coronary syndromes, the potential for similar adverse outcome is worrying.

There are now a number of therapies available that have been shown to reduce the mortality following an acute coronary syndrome that include the use of beta-blockers, low molecular weight heparins, the anti-platelet glycoprotein IIb/IIIa receptor antagonists and early coronary revascularisation. These therapies may have a similar important role in reducing the morbidity and mortality from peri-operative micro-infarction and the early accurate diagnosis of such injury is therefore critical. Cardiac troponin is one such marker that is currently under investigation with regard to its role in this diagnosis.

Structural aspects of cardiac troponin

The troponins are normal muscle proteins involved in the calcium regulated, actin-myosin interactions. Three sub-types exist. Troponin T binds to tropomyosin and attaches the troponin complex to the thin filament, troponin I binds to actin and inhibits actin-myosin coupling and troponin C binds to calcium and antagonises the effect of the troponin I. Most troponin is tightly bound to this troponin complex but about 6% of troponin T and 2–3% of troponin I is free in the cytoplasm.

Troponin as a specific marker of myocardial injury

Troponin I and T, but not C, exist as distinct cardiac specific sub-types. These structural, and therefore, antigenic differences have allowed the development of specific monoclonal antibodies to cardiac troponin I (cTnI) and T (cTnT). Both qualitative and quantitative assays based on these antibodies have been approved by the United States Food and Drug Administration (FDA) for use in clinical diagnosis. cTnI and T are released from myocardial cells early following cell necrosis and remain elevated in the circulation for a considerable time (Table 1).

Clinical experience with cTnT

To date, most experience has been gained with cTnT. There is one standardised assay for both qualitative and quantitative measurement that uses the same antibody pairs. Numerous studies in various groups of cardiac patients attest to the value of cTnT in the early and accurate diagnosis of micro-infarction. However, there have been reports of cross reactivity with skeletal muscle troponin T. This may have been due to a cross reactive antibody used with the original assay kit (Enzymun Test System ES22, Boehringer Mannheim). The newer kit available utilises two separate antibodies (ES300 Cardiac Troponin T, Boehringer Mannheim) and these are reported to be more reliable in their cardiac specificity. cTnT specificity may also be affected by the fact that it is expressed in normal foetal and neonatal skeletal muscle. Although its expression is normally suppressed in adult skeletal muscle it may also become elevated in disease states such as polymyositis and dermatomyositis. Unexplained elevations of cTnT have also been observed in patients with end stage renal failure undergoing renal replacement therapy. The possibility exists in these patients that myocardial injury undetected by other means is occurring, although of note in most of the patients studied cTnI was not elevated.

Clinical experience with cTnI

Numerous cTnI assay techniques are available (Table 2) that use differing antibodies pairs and differing methods. There has been concern raised over the direct comparison of the results obtained using these differing assays. However, as cTnI is not expressed
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Table 1. Characteristics of Cardiac Troponin I and T.

<table>
<thead>
<tr>
<th>Cardiac Troponin</th>
<th>Earliest elevation following necrosis</th>
<th>Peak level in circulation</th>
<th>Time detectable in circulation</th>
<th>Molecular mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI</td>
<td>3–12 h</td>
<td>12 h</td>
<td>5–10 days</td>
<td>24 kD</td>
</tr>
<tr>
<td>cTnT</td>
<td>3–12 h</td>
<td>12–48 h</td>
<td>5–14 days</td>
<td>37 kD</td>
</tr>
</tbody>
</table>

Table 2. Cardiac Troponin I assays currently available, the lower detection limits determined for myocardial injury and studies that have been conducted using the assays.

<table>
<thead>
<tr>
<th>cTnI kit</th>
<th>Manufacturer</th>
<th>Assay type</th>
<th>Lower limit of detection of assay</th>
<th>Studies using cTnI kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus antibody</td>
<td>Wellcome</td>
<td>Radioimmunoassay</td>
<td>10 ng/ml</td>
<td>Cummins et al. (1987)</td>
</tr>
<tr>
<td>Stratus</td>
<td>Dade</td>
<td>Immunofluorescence</td>
<td>1.5 ng/ml</td>
<td>Adams et al. (1993), Adams et al. (1994)</td>
</tr>
<tr>
<td>93PTG127B</td>
<td>Spectral Diagnostics</td>
<td>Fluorogenic ELISA</td>
<td>0.2 ng/ml</td>
<td>Bhayana et al. (1995)</td>
</tr>
<tr>
<td>cTnI</td>
<td>Baxter Diagnostics</td>
<td>2 step immunoassay</td>
<td>0.6 ng/ml</td>
<td>Kolle et al. (1997), Metzler et al. (1997)</td>
</tr>
<tr>
<td>OPUS cTnI</td>
<td>Dade Behring</td>
<td>Fluorogenic ELISA</td>
<td>0.5 ng/ml</td>
<td>Hegner et al. (1997)</td>
</tr>
<tr>
<td>AxSYM</td>
<td>Abbott Laboratories</td>
<td>Fluorometric</td>
<td>1 ng/ml</td>
<td>Heeschen et al. (1999)</td>
</tr>
<tr>
<td>Stratus II</td>
<td>Baxter Dade</td>
<td>Paramagnetic chemiluminescence immunoassay</td>
<td>0.35 ng/ml</td>
<td>Zaninotto et al. (1999), Khan et al. (1999)</td>
</tr>
<tr>
<td>cTnI Beckman Access</td>
<td></td>
<td></td>
<td>0.1 ng/ml</td>
<td>Neill et al. (2000)</td>
</tr>
</tbody>
</table>

Table 3. Peri-operative studies conducted using cardiac troponin as a marker for myocardial injury and its relation to cardiac events.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Follow-up period</th>
<th>cTnI measured</th>
<th>cTnI results</th>
<th>Clinical cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al. (1994)</td>
<td>108</td>
<td>36 h</td>
<td>I</td>
<td>9 (8.3)</td>
<td>90 (87.7)</td>
</tr>
<tr>
<td>Lee et al. (1996)</td>
<td>1175</td>
<td>3 days</td>
<td>T</td>
<td>199 (17)</td>
<td>976 (83)</td>
</tr>
<tr>
<td>Lopez et al. (1997)</td>
<td>772</td>
<td>6 months</td>
<td>T</td>
<td>92 (12)</td>
<td>580 (88)</td>
</tr>
<tr>
<td>Metzler et al. (1997)</td>
<td>67</td>
<td>7 days</td>
<td>T &amp; I</td>
<td>13 (19.5)</td>
<td>54 (80.5)</td>
</tr>
<tr>
<td>Neill et al. (2000)</td>
<td>80</td>
<td>3 months</td>
<td>T &amp; I</td>
<td>T-4 (5)</td>
<td>T-76 (95)</td>
</tr>
</tbody>
</table>

Cardiac troponin in the peri-operative patient

Few published studies have examined the use of troponin in the diagnosis of peri-operative MI in non-cardiac surgical patients (Table 3). Adams et al. reported on 108 patients of whom 96 had undergone major vascular surgery. Eight patients suffered a peri-operative MI as defined by echocardiographic detection of segmental wall defects. Of these, all had an associated cTnI rise, but only 6 had a CK-MB rise. A further 19 patients had a CK-MB rise with no echocardiographic changes, only one of whom had a cTnI rise. They concluded that cTnI is of most benefit in avoiding the false negative diagnosis of cardiac injury with a raised CK-MB, but with no echocardiographic evidence of wall damage.

Metzler studied 67 patients undergoing a variety of major abdominal, vascular and orthopaedic operations. With serial measurement over a 7 day period, 13 patients (19.5%) had an increase in both cTnI and cTnT. Eight patients had significant cardiac events and relatively higher (>0.2 μg l⁻¹) cTnT levels. They concluded that the degree of cTnI elevation reflects the severity of injury and also suggested that elevations of both cTnI and cTnT are necessary for diagnosis.

Lee et al. studied cTnT in 1175 patients undergoing major non-cardiac vascular surgery. cTnT was elevated in 87% of patients with a CK/CK-MB rise and...
ECG changes diagnostic of peri-operative MI. This compares with 16% of patients who had no evidence of peri-operative MI. In those patients who had other cardiac complications, cTnT was elevated in 62%, compared with 15% of those with no complications. These data indicate that cTnT had a similar performance for the diagnosis of definite MI as CK/CK-MB but a better correlation with major cardiac complications where no definite infarction could be identified.

They concede however that asymptomatic cTnT rise was common and that some 90% of patients with a rise suffered no apparent major cardiac complications. This suggests the following possibilities: a lack of specificity for the antibodies against cTnT used in their assay or sub-clinical myocardial micro-infarction that could not be detected otherwise. This question of the significance of an asymptomatic rise in troponin is addressed by a later study from the same group.40

In this study, they examined an asymptomatic group of 772 patients undergoing major surgery, of whom 92 (12%) and 211 (27%) suffered a cTnT or CK/CK-MB rise respectively.

They conclude that cTnT rise was associated with a higher relative risk of cardiac complications at 6 months follow up. cTnT rise was also correlated with in-hospital congestive failure, new cardiac arrhythmia or a raised CK/CK-MB suggesting that micro-infarction with cTnT release may have been the cause of these events. In a study by Neill et al. of 80 patients undergoing major vascular or orthopaedic surgery cTnT, cTnI and CK/CK-MB were examined.41 Silent myocardial ischaemia was found in 21 patients and elevations occurred in 4, 6 and 17 of these patients for cTnT, cTnI and CK/CK-MB respectively.

This study calculated the relative odds risk for major adverse cardiac events and found that, in keeping with the previous studies by Metzler and Lee, cTnT was a useful prospective marker for both major and minor cardiovascular complications.38,39

**Summary**

Cardiac troponin offers a new way to diagnose peri-operative MI, and is a far more sensitive and specific marker than CK/CK-MB. Measurement of circulating troponin levels has revolutionised the management of acute coronary syndromes, because even in the absence of CK elevation or ST segment elevation on the ECG, detection is clearly associated with micro-infarction and a disturbingly high incidence of late cardiac events. While it is not known if elevated troponin following surgery will have the same prognostic value as in an acute coronary syndrome, there is some evidence so far to support its use as a marker for adverse outcome. Using troponin measurement to diagnose peri-operative MI may allow for the early risk stratification and appropriate treatment of patients who may be at a higher risk of peri- and post-operative cardiac events. The main limitation to its clinical use to date has been its lack of general availability, the differing antibodies available and the lack of direct comparison between these. Troponin assays are also more expensive compared with other markers currently in routine clinical use. This increased cost must obviously be balanced against the potential reduction in morbidity, mortality and a reduced in-patient hospital stay that may result from earlier and more appropriate cardiac intervention.

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Accepted 25 June 2001