Troponin T or troponin I as cardiac markers in ischaemic heart disease

There is increasing awareness of the limitations of standard biochemical markers of cardiac damage in patients with acute coronary syndromes. A desire to improve sensitivity and specificity has led to the search for markers uniquely diagnostic of acute myocardial infarction (MI) varying from 11–30% in studies has varied from 20–48%, with death and cardiac troponin (cTn) as indicators of myocardial necrosis.1 Biochemical markers of cardiac damage in patients with acute coronary syndromes. A desire to improve sensitivity and specificity has led to the search for markers uniquely diagnostic of acute myocardial infarction (MI) varying from 11–30% in studies has varied from 20–48%, with death and cardiac troponin (cTn) as indicators of myocardial necrosis.1

Troponins have proven useful for the diagnosis and subsequent risk stratification of patients presenting with acute chest pain.4 A raised troponin concentration may also identify those who are most likely to benefit from additional therapeutic measures.5 Nevertheless, is cTnT superior to cTnI?

Biochemistry and release kinetics

The troponin complex is situated on the thin filament of the striated muscle contractile apparatus and consists of troponin T (39 kD), troponin I (26 kD), and troponin C (18 kD), each coded by a separate gene.8 Specific cardiac and skeletal muscle isoforms are expressed in cardiac and skeletal striated muscle in adults. Troponins are mainly bound to the myofibrils, although 6–8% of cTnT and 2.8–4.1% of cTnI is cytosolic.9 This affects release kinetics. There is rapid early release of cytosolic cTnT after ischaemic injury, followed by more prolonged release of myofibrillar troponin, resulting in a biphasic release pattern. As cTnI has a smaller cytosolic pool, release is likely to be monophasic. Concentrations of both begin to rise in the 4–8 hours following injury and peak at 12–24 hours.5 cTnT may remain raised for more than two weeks and cTnI for more than 5–7 days.

Analytical methods

Only one assay for cTnT is available.9 The first generation of this assay has undergone upgrading. The present generation assay employs an immunoelectric technique using two cardiac specific antibodies directed against epitopes in part of the cTnT molecule differing significantly between cardiac and skeletal muscle isoforms.7 A test strip reader is also available. In contrast, there are several different cTnI assays available, which use mono- or polyclonal antibodies against different antigenic determinants and hence have varying sensitivities and discriminant values. A bedside assay for troponin I is also available. Thus clinicians need to be aware of the reference range and diagnostic cut off of the specific assay that they are using.

Troponin T and I in diagnosis

Comparisons of the sensitivities and specificities of troponin T and I for the diagnosis of acute MI have been made. Hetland and Dickstein looked at 170 consecutive patients with suspected acute MI.7 Of these, 68 had an acute MI (defined as two or more of the following: history, CK-MB rise, new Q waves and/or ST elevation or depression ≥ 0.1 mV in two or more leads). An ELECSYS 2010 system was used to measure cTnT (cut off 0.1 µg/l) and an Access system was used for cTnI (cut off 0.1 µg/l). At 4–8 hours after admission, sensitivities of cTnT and cTnI were 99% and 96%, respectively, and specificities were 78% and 88%, respectively. Zimmerman and colleagues studied 955 patients, aged ≥ 21 years, within 24 hours of suspected ischaemic pain lasting at least 15 minutes.9 Of these, 119 had an acute MI (defined as CK-MB mass ≥ 7 ng/ml and CK-MB mass:CK ratio ≥ 2.5% in two or more samples in the first 24 hours of onset of symptoms). cTnT cut off was 0.1 ng/ml (Boehringer assay) and the cut off for cTnI was 1.5 ng/ml (Stratus-Dade assay). At 10 hours after symptom onset, cTnT and cTnI sensitivities were 87% and 96%, respectively, and specificities were 93% for both.

Because cTnT and cTnI can detect myocardial necrosis below the detection limit of CK-MB, use of CK-MB as the gold standard for diagnosis of acute MI may lead to patients with a normal CK-MB but raised cTnT or cTnI being classified as false positives.

Troponin T and I for prognosis

Many studies have looked at cTnT and cTnI in isolation to stratify risk in acute coronary syndromes,2 11 12 and a smaller number of these studies have directly compared cTnT with cTnI in risk stratification (table 1). Hamm and colleagues used bedside cTnT and cTnI tests to triage 773 consecutive patients with chest pain of ≤ 12 hours duration with no ST elevation on the initial ECG.5 Those with an acute MI within two weeks were excluded. Among 47 patients diagnosed as having an acute MI (creatine kinase more than twice the upper limit of normal with raised CK-MB), 44 had raised cTnT (94%) and all had raised cTnI. Among 315 patients diagnosed as having unstable angina, cTnT was positive in 22% and cTnI in 36%, but only 16 patients (5%) had raised CK-MB. During 30 days follow up, of those with raised cTnT, 22% (27/123 patients) died or suffered an acute MI, compared with 19% (32/171 patients) with raised cTnI. The event rates in those patients with negative troponin tests were only 1.1% for cTnT and 0.3% for cTnI. The TRIM trial enrolled 516 unstable angina patients.3 Cardiac troponin T and I concentrations were measured at inclusion and six hours later, and were raised in 48% and 41%, respectively. During 30 days follow up, 11% of patients in each group died or suffered an acute MI. In the FRISC I study, for those with raised cTnT, the risk of death
or acute MI was 16.7% during five months’ follow up, compared to 17.3% for those with raised cTnT. In GUSTO IIa, troponin T was positive in 36% and cTnT in 29%. During 30 days follow up, of those who were cTnT positive, 34 patients (12%) died or suffered an acute MI compared with 28 patients with raised cTnT (13%). Although these figures were similar, cTnT showed a slightly greater association with 30 days mortality alone than cTnT (p < 0.001 and p = 0.002, respectively). Ottani and colleagues performed cTnI estimation at admission and eight hours later on 812 consecutive patients with chest pain lasting up to 12 hours. They were measured at admission and eight hours later. Each was raised in 24% of patients. Death or acute MI during 30 days follow up occurred in five patients (28%) with raised cTnT, but only in three patients (17%) with raised cTnT.

**Table 1 Summary of direct comparisons of cTnT with cTnI in risk stratification in acute coronary syndromes**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>cTnT (cut off)</th>
<th>cTnI (cut off)</th>
<th>Positive cTnT (patients)</th>
<th>Positive cTnI (patients)</th>
<th>Follow up</th>
<th>Death/AMI in cTnT positive patients</th>
<th>Death/AMI in cTnI positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamm et al</td>
<td>Any age, ≤ 12 h chest pain, no ST elevation, no AMI within 14 days</td>
<td>Bedside (0.18 ng/ml)</td>
<td>Bedside (0.1 ng/ml)</td>
<td>70 (22%)</td>
<td>114 (36%)</td>
<td>30 days</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>TRIM (n = 516)</td>
<td>25–80 years, &lt; 24 h chest pain, ST depression, T wave inversion or proven IHD</td>
<td>ES 300 (0.1 µg/l)</td>
<td>Opus Magnum (2.0 µg/l)</td>
<td>249 (48%)</td>
<td>213 (41%)</td>
<td>30 days</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>FRISC II (n = 823)</td>
<td>&gt; 40 years, &lt; 72 h chest pain, ST depression or T wave inversion</td>
<td>Enzymun (0.1 µg/l)</td>
<td>Access (0.1 µg/l)</td>
<td>66%</td>
<td>5 months</td>
<td>16.7%</td>
<td>17.3%</td>
<td></td>
</tr>
<tr>
<td>GUSTO IIa (n = 770)</td>
<td>Any age, ≤ 12 h chest pain, &gt; 0.05 mV ST depression or elevation, LBBB or T wave inversion</td>
<td>ES 300 (0.1 µg/l)</td>
<td>Stratus II (1.5 µg/l)</td>
<td>278 (36%)</td>
<td>220 (29%)</td>
<td>30 days</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Ottani et al (n = 74)</td>
<td>Any age, &lt; 48 h chest pain, &gt; 0.05 mVST depression or elevation, or T wave inversion</td>
<td>ES 300 (0.1 µg/l)</td>
<td>Baxter Stratus (3.1 µg/l)</td>
<td>18 (24%)</td>
<td>18 (24%)</td>
<td>30 days</td>
<td>17%</td>
<td>28%</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; IHD, ischaemic heart disease; LBBB, left bundle branch block.

**Troponin T and I in other diseases**

There are concerns that cTnT is re-expressed in skeletal muscle in renal failure and muscular disease, with implications for specificity. Patients with renal failure may have raised cTnT concentrations in the absence of myocardial ischaemia. It has been suggested that this may be caused by the antibody used in first generation cTnT assays cross reacting with skeletal muscle troponin T. In addition, there is controversy as to whether cross reactivity occurs in the absence of myocardial ischaemia. It has been suggested that this may be caused by the antibody used in first generation cTnT assays cross reacting with skeletal muscle troponin T.17 Apple and colleagues prepared skeletal muscle biopsies from 45 chronic renal disease patients for Western blotting in 4/5 skeletal muscle biopsies.18 There is controversy as to whether cross reactivity occurs in the absence of myocardial ischaemia. It has been suggested that this may be caused by the antibody used in first generation cTnT assays cross reacting with skeletal muscle troponin T.17

During 30 days follow up, of those who were cTnT positive, 34 patients (12%) died or suffered an acute MI compared with 28 patients with raised cTnT (13%). Although these figures were similar, cTnT showed a slightly greater association with 30 days mortality alone than cTnT (p < 0.001 and p = 0.002, respectively). Ottani and colleagues looked at patients presenting with chest pain and ECG changes, but whose total CK was < 200 IU during the first 16 hours.15 Troponins T and I were measured at admission and eight hours later on 812 consecutive patients with chest pain lasting up to 12 hours. They were measured at admission and eight hours later. Each was raised in 24% of patients. Death or acute MI during 30 days follow up occurred in five patients (28%) with raised cTnT, but only in three patients (17%) with raised cTnT.

**Cost efficacy**

Cost efficacy has now been shown for troponin I. Hoese and colleagues performed cTnI estimation at admission and four hours later on 812 consecutive patients with chest pain of up to 12 hours duration.16 No patient with negative cTnI and a normal or uninterpretable ECG had a cardiac event during the next 30 days. By restricting admissions using these criteria, substantial savings could be made. Collinson has shown that similar savings can be achieved using cTnT.17

**Conclusions**

From the published literature it is clear that in the management of acute coronary syndromes and acute MI in clinical practice, cTnI is comparable in diagnostic and prognostic efficacy to cTnT. Any variation in results is likely to be caused by differences in patient populations, blood sampling timing, and analytical methods. In renal impairment, even against second generation cTnT assays, cTnT is superior. In muscle damage, cTnI is at least as useful as cTnT.

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Glossary
FRISC: Fragmin In Unstable Coronary artery disease
GUSTO Global Use of the Strategies to Open occluded Ila: coronary arteries in acute coronary syndromes
TRIM: Thrombin Inhibition In Myocardial Ischaemia


STAMPS IN CARDIOLOGY

Congress

This 1979 stamp from Brazil featuring the clover flower with hearts as leaves was produced to mark the 35th Brazilian Cardiology Congress, which is signified in the inscription on the left side of the stamp. The inscription underneath the stamp design indicates that this stamp is also a tribute to Carlos Ribeiro Justinianno Chagas (1879–1934) who described the clinical and cardiac manifestations of Trypanosoma cruzi infection (Chagas disease).

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