

Editorial

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 expressed by the myocardium. The cardiac troponins T and I (cTnT and cTnI) have been found to have excellent sensitivity and specificity and are superior to creatine kinase-MB (CK-MB) as indicators of myocardial necrosis.¹ Using cTnT or cTnI as a diagnostic marker, the positivity rate in studies has varied from 20–48%, with death and acute myocardial infarction (MI) varying from 11–30% in 28 months follow up.^{2–4} These variations are largely caused by differences in risk among the populations studied and differing lengths of follow up.

Troponins have proven useful for the diagnosis and subsequent risk stratification of patients presenting with acute chest pain.^{5,6} A raised troponin concentration may also identify those who are most likely to benefit from additional therapeutic measures.⁷ 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.^{7–9} 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.⁸ 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.⁸ 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.⁵ 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 $\mu\text{g/l}$) and an Access system was used for cTnI (cut off 0.1 $\mu\text{g/l}$). 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.¹⁰ Of these, 119 had an acute MI (defined as CK-MB mass ≥ 7 ng/ml and CK-MB mass:CK ratio $\geq 2.5\%$ 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 misclassified 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.⁶ Those with an acute MI within two weeks were excluded. Among 47 patients diagnosed as having an acute MI (creatinine 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

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

Study	Study population	cTnT (cut off)	cTnI (cut off)	Positive cTnT (patients)	Positive cTnI (patients)	Follow up	Death/AMI in cTnT positive patients	Death/AMI in cTnI positive patients
Hamm <i>et al</i> ⁶ (n = 315)	Any age, ≤ 12 h chest pain, no ST elevation, no AMI within 14 days	Bedside (0.18 ng/ml)	Bedside (0.1 ng/ml)	70 (22%)	114 (36%)	30 days	22%	19%
TRIM ³ (n = 516)	25–80 years, < 24 h chest pain, ST depression, T wave inversion or proven IHD	ES 300 (0.1 µg/l)	Opus Magnum (2.0 µg/l)	249 (48%)	213 (41%)	30 days	11%	11%
FRISC I ¹³ (n = 823)	> 40 years, < 72 h chest pain, ST depression or T wave inversion	Enzymun (0.1 µg/l)	Access (0.1 µg/l)	66%		5 months	16.7%	17.3%
GUSTO IIa ¹⁴ (n = 770)	Any age, < 12 h chest pain, ≥ 0.05 mV ST depression or elevation, LBBB or T wave inversion	ES 300 (0.1 µg/l)	Stratus II (1.5 µg/l)	278 (36%)	220 (29%)	30 days	12%	13%
Ottani <i>et al</i> ¹⁵ (n = 74)	Any age, < 48 h chest pain, > 0.05 mV ST elevation or depression, or T wave inversion	ES 300 (0.1 µg/l)	Baxter Stratus (3.1 µg/l)	18 (24%)	18 (24%)	30 days	17%	28%

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

or acute MI was 16.7% during five months' follow up, compared to 17.3% for those with raised cTnI.¹³ In GUSTO IIa, troponin T was positive in 36% and cTnI in 29%.¹⁴ 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 cTnI (13%). Although these figures were similar, cTnT showed a slightly greater association with 30 days mortality alone than cTnI ($p < 0.001$ 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. Each was raised in 24% of patients. Death or acute MI during 30 days follow up occurred in five patients (28%) with raised cTnI, but only in three patients (17%) with raised cTnT.

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.¹⁶ 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.¹⁷ In addition, there is controversy as to whether cross reactivity occurs when the more specific second generation troponin T assay is used. Apple and colleagues prepared skeletal muscle biopsies from 45 chronic renal disease patients for Western blot analysis and blotted these with anti-cTnT antibodies, including those used in the second generation assay.¹⁸ They concluded that although cTnT isoforms are expressed in skeletal muscle from chronic renal disease patients, the antibody configuration of the second generation cTnT assay is such that if these isoforms were released into the circulation they would not be detected.

McLaurin and colleagues analysed cTnT and cTnI in 24 dialysis patients without ischaemic heart disease.¹⁶ First generation (ES 300 enzyme linked immunosorbent assay (ELISA)) and second generation (Enzymun) tests were used for cTnT (upper reference cut off 0.2 µg/l for both) and Stratus II was used for cTnI assay (upper reference cut off 0.8 µg/l). Using ELISA, 17/24 patients (71%) had raised cTnT, but this fell to 3/18 patients (17%) using Enzymun. However, only 1/24 patients had a raised cTnI (4%). In a separate group of five dialysis patients, expression of cTnT but not cTnI was observed using Western blotting in 4/5 skeletal muscle biopsies.

More recently, Musso and colleagues measured cTnT and cTnI in 49 renal patients (12 on medical treatment, 20

on haemodialysis, and 17 post-transplant with residual renal impairment).¹⁷ None had ischaemic heart disease, diabetes mellitus or muscular disorders. A second generation cTnT assay, Enzymun ES300 (upper reference limit 0.02 µg/l), and two cTnI assays, Stratus II and Access (upper reference limits 0.3 and 0.03 µg/l, respectively), were used. A cTnT concentration above the upper limit of normal was found in 23 patients (47%) and two had concentrations indicative of acute MI. However, only two patients (4%) had raised cTnI concentrations using Stratus II and none was raised using Access. There were no cardiac events during 18 months' follow up.

Troponin I is as effective as cTnT in diagnosing myocardial necrosis in the setting of trauma and coronary bypass grafting.^{19, 20} In percutaneous transluminal coronary angioplasty/stent, and in association with congestive heart failure, there are reports of raised cTnT and cTnI, while in DC cardioversion there is no increase in either.^{21–24}

Cost efficacy

Cost efficacy has now been shown for troponin I. Heesch and colleagues performed cTnI estimation at admission and four hours later on 812 consecutive patients with chest pain of up to 12 hours duration.²⁵ 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.²⁶

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, cTnI is superior. In muscle damage, cTnI is as 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

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STAMPS IN CARDIOLOGY**Congresses**

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 Justiniano Chagas (1879-1934) who described the clinical and cardiac manifestations of *Trypanosoma cruzi* infection (Chagas disease).

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