High-sensitivity troponin T for early rule-out of myocardial infarction in recent onset chest pain

Sally Aldous,1 Chris Pemberton,2 A Mark Richards,2,3 Richard Troughton,1 Martin Than4

ABSTRACT

INTRODUCTION

The drive to improve the analytical sensitivity of cardiac troponin (cTn) assays for the diagnosis of acute myocardial infarction (AMI)1 has led to the development of new high-sensitivity assays based on humanised monoclonal antibodies. Recent studies assessing both late generation contemporary2–5 and high-sensitivity6–8 assays have demonstrated significantly improved sensitivity for the early diagnosis of AMI.2–13 Higher sensitivity assays therefore have the potential to change current chest pain assessment pathways,11,14 but no formal recommendations to reduce the time interval between baseline and follow-up cTn have been made to date. There is also concern that early measurements of the cTn concentration may be falsely negative in those presenting early because cTn levels may not have risen by the time of sampling.

The current definition of AMI requires a rise and/or fall in the cTn concentration,9 which helps distinguish acute elevations from chronically raised levels in conditions such as cardiomyopathy, valvular disease and renal dysfunction.5,9,13,15,16 Emphasis on the dynamic change in cTn concentrations from baseline to follow-up ("delta") has intensified as more patients with non-ischaemic conditions have elevations when high-sensitivity assays are used.11 However, the degree to which the cTn concentration must change and the optimum timing over which dynamic changes should be calculated has not been specified. Previous studies have used various delta criteria including $\geq 10–30\%$ deltas,4,7,8 receiver operating characteristics (ROC) curves to derive optimum percentage changes17 and standard deviations.7 The National Academy of Clinical Biochemistry laboratory medicine practice guidelines recommends the use of $\geq 20\%$ delta (the level exceeding that due to analytical variation at the 99th percentile) for cTn concentrations from elevated baseline values,18 but the evidence for such a strategy has yet to be confirmed.

The primary aim of this study was to investigate whether early measurements of high-sensitivity troponin T (hsTnT; Roche Diagnostics, Indianapolis, Indiana, USA) could be used in a new accelerated strategy for the diagnosis of AMI in patients presenting within 4 h from symptom onset. The secondary aim was to compare assays of hsTnT and troponin I (TnI; Abbott Diagnostics, Chicago, Illinois, USA), a late generation cTn assay, at matched time points.

METHODS

Patients attending the emergency department (ED) at Christchurch Hospital, New Zealand, were prospectively recruited from November 2007 to April 2010 between 05:30 h and 20:00 h. Patients were included if they presented within 4 h of symptom onset and had ischaemic-type pain, defined as acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without an apparent non-cardiac source (American Heart Association (AHA) guidelines).19 Patients were excluded if they were aged <18 years, were unable to provide informed consent or were unwilling to participate.

No formal recommendations to reduce the time interval between baseline and follow-up cTn had been made at the time of writing. Further investigations such as stress testing and coronary angiography were at the discretion of the attending clinician.


Reference standard (adjudication)
All investigations and diagnoses were reported using a predefined objective-structured adjudication process. Patient risk factors and diagnoses were based on American College of Cardiology (ACC) definitions 2001. A diagnosis of AMI was made if there was a rise and/or fall in cTn concentration (with a ≥20% change from baseline to peak) with ≥1 value of cTn ≥99th percentile. In patients with elevated cTn concentrations but without a rise and/or fall of ≥20%, a diagnosis of AMI was still made if there was objective evidence of myocardial ischaemia including: new ischaemic ECG changes (ST deviation ≥0.5 mm or T wave inversion ≥1 mm in two or more contiguous leads); positive stress testing (ischaemic symptoms and horizontal or down-sloping ST depression ≥1 mm or ST depression >2 mm without symptoms); or significant coronary artery disease on coronary angiography (with at least one area of coronary stenosis of ≥70% or revascularisation with percutaneous intervention or coronary artery bypass surgery). All investigations and final diagnoses were reported independently by a cardiologist (SA) and a second physician blinded to the hsTnT results but with knowledge of the TnI results. The primary end point was diagnosis of AMI.

Troponin assays
Blood samples for use in clinical management were sent in lithium heparin tubes to the central hospital laboratory for measurement of TnI (Abbott Diagnostics Architect system; limit of detection 0.01 μg/l, 99th percentile 0.025 μg/l, coefficient of variation <10% 0.032 μg/l). Ethylene diaminetetraacetic acid samples were centrifuged with plasma, frozen at −80°C and later assayed for hsTnT (Roche Diagnostics Elecsys 2010 system; 99th percentile 0.014 μg/l (14 ng/l); limit of detection 0.005 μg/l (5 ng/l); coefficient of variation <10% 0.013 μg/l (13 ng/l)) in a blinded manner in batches at a dedicated research laboratory.

Statistical analysis
Variables were analysed with conventional descriptive statistics (medians and interquartile ranges which were compared using the Mann–Whitney U test for continuous variables and numbers and percentages which were compared using the χ² test for categorical variables). Sensitivities and specificities for AMI were calculated for hsTnT and TnI (using the ≥99th percentile as a decision cut-off point) for all patients and then by categories by time of symptom onset to presentation. The peak 24 h TnI measurements (and peak 24 h hsTnT measurements, see data 1 in online supplement) were used as the reference standard for these calculations. The percentage delta was calculated for each patient using the following equation: 2 h or 12–24 h (cTn) minus the 0 h (cTn) divided by the lower of the 2 and subsequently multiplied by 100. Sensitivities and specificities for hsTnT and TnI were calculated for AMI with the following delta criteria: (a) ≥20% delta alone; (b) both ≥20% delta and cTn ≥99th percentile; and (c) either ≥20% delta or cTn ≥99th percentile. Sensitivities and specificities were compared using the McNemar test. Receiver operating characteristic (ROC) curves (see data 2 in online supplement) were constructed to assess the diagnostic test performance of hsTnT and TnI for AMI at all time points for all patients and then by categories by time of symptom onset to presentation, with peak 24 h TnI as the reference standard (or peak 24 h hsTnT, see data 1 in online supplement). The areas under the ROC curve (AUC) were compared. All hypothesis testing was two-tailed with p values <0.05 considered significant. All analyses were performed with SPSS for Windows software V19.0.

RESULTS
The characteristics of the 385 patients recruited to the study are summarised in table 1. The median values of hsTnT and TnI are plotted according to diagnosis in figure 1A. In figure 1B the median values of hsTnT and TnI in 82 patients who developed AMI (21.3%) are plotted against time of sampling.

Sensitivity
The sensitivities, specificities, positive predictive values, negative predictive values and diagnostic accuracies of hsTnT and TnI (≥99th percentile) for the diagnosis of AMI (at 0 h and at 0–1 h, 0–2 h and 0–24 h) are shown in table 2 (ROC curve analysis is presented in data 2 in the online supplement). Of the 82 patients with AMI, the numbers with elevated hsTnT and TnI values, respectively, were 74 (90.2%) and 61 (74.4%) at 0 h (p=0.005); 77 (95.9%) and 68 (82.9%) by 1 h (p=0.018); 78 (95.1%) and 71 (86.6%) by 2 h (p=0.065); and 80 (97.6%) and 82 (100%) by 12–24 h. Peak 0–24 hsTnT values trended to superiority compared with values at 0 h (p=0.063) but not compared with 1 h or 2 h values.

Specificity
The numbers of patients in the whole cohort with positive (≥99th percentile) hsTnT and TnI at different time points, respectively, were 128 (33.2%) and 70 (18.1%) at 0 h; 140 (36.4%) and 80 (20.8%) at 1 h; 145 (37.7%) and 86 (22.3%) at 2 h; and 150 (39.0%), and 99 (25.7%) at 12–24 h (p<0.001 for all). There were more positive hsTnT values than TnI values in patients without AMI, resulting in a reduction in overall specificity (table 2).

Time to presentation
If patients are subcategorised according to time from symptom onset to presentation, the sensitivity for hsTnT and TnI measurements by 2 h after presentation, respectively, was as

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 385)</th>
<th>Patients with AMI (n = 82)</th>
<th>Patients without AMI (n = 303)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>65 (56–76)</td>
<td>67 (59–78)</td>
<td>64 (55–75)</td>
<td>0.084</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>233 (60.5)</td>
<td>59 (72.0)</td>
<td>174 (57.4)</td>
<td>0.022</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>305 (79.2)</td>
<td>61 (74.4)</td>
<td>244 (80.5)</td>
<td>0.223</td>
</tr>
<tr>
<td>Other European</td>
<td>50 (13.0)</td>
<td>13 (15.9)</td>
<td>37 (12.2)</td>
<td>0.362</td>
</tr>
<tr>
<td>Maori/Pacific Islander</td>
<td>18 (4.7)</td>
<td>7 (8.5)</td>
<td>11 (3.6)</td>
<td>0.076</td>
</tr>
<tr>
<td>Other</td>
<td>12 (3.1)</td>
<td>1 (1.2)</td>
<td>11 (3.6)</td>
<td>N/A</td>
</tr>
<tr>
<td>Prior IHD, n (%)</td>
<td>201 (52.2)</td>
<td>36 (43.9)</td>
<td>165 (54.5)</td>
<td>0.105</td>
</tr>
<tr>
<td>Prior heart failure, n (%)</td>
<td>45 (11.7)</td>
<td>6 (7.3)</td>
<td>39 (12.9)</td>
<td>0.526</td>
</tr>
<tr>
<td>Prior revascularization, n (%)</td>
<td>126 (32.7)</td>
<td>20 (24.4)</td>
<td>106 (35.0)</td>
<td>0.088</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>6 (1.6)</td>
<td>0</td>
<td>6 (2.0)</td>
<td>0.192</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>16 (4.2)</td>
<td>3 (3.7)</td>
<td>13 (4.3)</td>
<td>0.808</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>262 (68.1)</td>
<td>59 (72.0)</td>
<td>203 (67.0)</td>
<td>0.180</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>239 (62.1)</td>
<td>48 (58.5)</td>
<td>191 (63.0)</td>
<td>0.799</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>239 (62.1)</td>
<td>52 (63.4)</td>
<td>187 (61.7)</td>
<td>0.538</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>58 (15.1)</td>
<td>10 (12.2)</td>
<td>48 (15.8)</td>
<td>0.984</td>
</tr>
<tr>
<td>Family history of IHD, n (%)</td>
<td>254 (66.0)</td>
<td>57 (69.5)</td>
<td>197 (65.0)</td>
<td>0.112</td>
</tr>
<tr>
<td>Creatinine, μmol/l, median (IQR)</td>
<td>89 (78–103)</td>
<td>95 (84–117)</td>
<td>88 (77–100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to presentation, h, median (IQR)</td>
<td>2.7 (2.0–3.3)</td>
<td>2.8 (2.1–3.3)</td>
<td>2.6 (2.0–3.3)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; IHD, ischaemic heart disease; NZ, New Zealand.
follows: 81.8% (55.0–97.0%) and 72.7% (44.1–90.1%) for patients presenting within 0–2 h (p<0.001) (n=11/84 with AMI); 100% (90.7–100%) and 84.8% (71.1–93.5%) for patients presenting within 2–3 h (p<0.001) (n=33/152 with AMI); and 94.7% (84.3–98.5%) and 92.1% (81.5–97.5%) for patients presenting within 3–4 h (p>0.1) (n=38/149 with AMI).
**Concordance**

There were 57 cases where hsTnT and TnI measurements were discordant. Fifty-four cases had elevated hsTnT and within range TnI. In three cases TnI was elevated but hsTnT was within range, two of whom were judged to have AMI. One was a 59-year-old man with a peak TnI of 0.170 µg/l and a peak hsTnT of 0.005 µg/l (5 ng/l) with coronary artery disease on angiography who did not require revascularisation. The second was a 44-year-old man who did not require revascularisation. The third case, without AMI, was a 42-year-old man with stable pain early after the onset of symptoms (<4 h) data indicating that early (0–2 h after presentation or by 6 h after symptom onset) measurements of hsTnT could be feasible in identifying patients with and without AMI.

**DISCUSSION**

We report for the first time in patients presenting with chest pain early after the onset of symptoms (≤4 h) data indicating that early (0–2 h after presentation or by 6 h after symptom onset) measurements of hsTnT could be feasible in identifying patients with and without AMI.

**Early ‘rule-out’ of AMI**

Given that New Zealand National Health targets for evaluation within the ED are ≤6 h, most patients with symptoms suggestive of acute coronary syndrome (ACS) are admitted, but the majority of these patients ultimately do not have ACS. An accelerated ‘rule-out’ strategy may allow discharge directly from the ED, thereby reducing hospital admission, overcrowding and reducing patient anxiety.

This study has shown that the sensitivity of peak 2 h hsTnT values is high (95.1%) compared with standard testing (86.6%). Also, importantly, the negative predictive value of hsTnT is very high (98.3%). Nevertheless, this still results in a false negative rate of 4.9% with 95% CIs up to 11.3%. This is a significant false negative rate given the increased risk of adverse events (and medicolegal implications) in those with missed AMIs. However, the overall performance of early hsTnT measurement is adversely affected by its poor performance in patients presenting very early after symptom onset. Online supplemental data 1 suggests a negative second hsTnT is 100% sensitive by 6 h after symptoms. However, 95% CIs still show false negative rates could be as high as 6.4%. CIs are probably affected by an underpowering of the study. Further prospective studies are therefore required to investigate whether this 6 h time frame is sufficient.
Despite good but suboptimal sensitivities by 2 h, these data indicate that later hsTnT samples are not statistically superior in sensitivity or by ROC curve analysis. However, this study may be underpowered for small improvements to be statistically significant, yet small differences would be significant clinically, given the high incidence of AMI.

Stress testing is recommended by ACC/AHA guidelines in those with negative serial cTn and ECG results. When accelerating serial measurements from 6–12 h to 2 h after presentation, the combination of hsTnT (including any value $>$99th percentile and any dynamic change between 0 h and 2 h of $\approx20\%$) and ECG results (including any ischaemic changes not known to be old), the false negative rate is 1.2% for AMI. Although stress testing has a sensitivity of only 70% for coronary artery disease which may be a concern when only early cTn measurements are being made, those with negative tests have a very low probability of subsequent complications. The safety of performing stress tests on patients with an AMI in whom there are negative early hsTnT values/deltas and ECGs has not been validated. However, Amsterdam et al. found no adverse effects of performing stress tests on admission in patients with no evidence of haemodynamic instability, arrhythmias or ECG signs of ischaemia. It would therefore seem reasonable to suggest that patients presenting to the ED with symptoms of ACS in whom both hsTnT values/deltas and ECGs are negative by 2 h after presentation (or 6 h after symptom onset) need not wait for a later hsTnT measurement before undergoing stress testing. Such a strategy requires further testing.

**Early ‘rule-in’ of AMI**

The use of accelerating ‘rule-in’ of AMI is as yet untested. It may improve patient disposition to monitored beds, but whether earlier diagnosis of AMI would improve outcomes is unknown. It might also prevent those without AMI from undergoing ultimately unnecessary investigations such as coronary angiography and treatments such as antiplatelet medications which carry risk.

The specificity of hsTnT for the diagnosis of AMI was lower than TnI, as expected for a high-sensitivity assay which is more likely to be raised in other conditions. The specificity may, however, be underestimated as a proportion of the surplus ‘false positives’ using hsTnT may actually be the true positives that cannot be recognised using the less analytically sensitive assay (see online supplemental data 1).

This study confirmed that a delta hsTnT of $\approx20\%$ in patients with peak 2 h or 24 h hsTnT ($\approx99$th percentile) increased the specificity for AMI significantly. This result is consistent with other studies suggesting that patients with raised hsTnT and dynamic changes of $\geq20\%$ are highly likely to have AMI and should be treated and investigated as such. However, sensitivity was markedly reduced, with a significant number of false negatives, which again is consistent with other studies. Consequently, it is possible that serial values of hsTnT with at least one value $\approx99$th percentile, irrespective of the delta (in a clinical context consistent with ACS), will perform well and largely obviate the need to distinguish a significant rising or falling pattern. However, deltas of $<20\%$ may be useful in alerting the physician to investigate for other causes of elevated hsTnT.

The sensitivity of the delta criteria in this study was improved by calculating a delta over the longer time period, 0 h to 12–24 h, without affecting the specificity. However, objective findings consistent with AMI, such as a significant delta, would be of more clinical importance at the early period after presentation when the diagnosis may not yet be evident.

**Comparison of hsTnT with TnI**

We compared hsTnT with TnI, even though this could not be done objectively as TnI performance was overestimated given its use for clinical decision-making and adjudication. TnI is an assay which has been shown in previous studies to perform well (although it does not quite conform to precision guidelines in that the 10% coefficient of variation is above the 99th percentile). hsTnT was more sensitive than TnI at the early time points, suggesting that the use of hsTnT is more reliable as an early rule-out tool. However, TnI is more specific.

In addition, because no two cTn assays are completely concordant, even hsTnT at 12–24 h would have led to missed AMIs (as adjudicated by peak 24 h TnI), yet it is an acceptable practice to test for only one cTn. Although it was much more likely that hsTnT had the positive bias, there were a small number of patients with elevated TnI concentrations but normal hsTnT concentrations.

Data in the online supplement show how the performance characteristics of early hsTnT and TnI measurements change if evaluated against peak 12–24 h hsTnT instead of peak 12–24 h TnI. This evaluation led to an increase in the number of AMIs diagnosed (by 50.0%), a great reduction in the sensitivity of TnI from 100% to 69.9%, and an increase in the specificity of hsTnT from 76.9% to 89.7%. These results highlight the difficulty of assessing a new test with equal—or possibly better—performance than the standard against which it is being assessed, but this method has been used in many other studies.

These findings are speculative but, if they are further corroborated, they mandate trials of early triage with the potential for appropriate and safe decisions regarding admission, early provocative testing and potentially early discharge, even with patients presenting within 4 h of symptom onset.

**Limitations of study**

Patient numbers in this study were limited by slow recruitment because the majority of patients tend to present more than 4 h after symptom onset. This was a convenience sample cohort as patients were not recruited 24 h a day, 7 days a week. Audit data from our institution suggest that only a small minority of patients present outside the hours of recruitment. The rate of AMI in the recruited population is consistent with audit data, but it may be higher or lower than other studies and other institutions, and this factor should be taken into account if applying these results to different populations.

**CONCLUSIONS**

The measurement of hsTnT on admission and at 2 h after presentation is not sensitive enough to identify all patients with AMI. However, serial measurements of hsTnT up to at least 6 h after symptom onset in combination with ECG recordings could potentially safely identify those suitable for early stress testing; such a strategy requires further prospective testing. The specificity of hsTnT could be improved by the use of a delta of $\geq20\%$ in patients with hsTnT $\geq99$th percentile, but at the cost of a major reduction in sensitivity.

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Original article

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Contributors All authors were involved in the design of the study. SA was responsible for the analysis and interpretation of the data and drafting of the manuscript. All authors were involved in manuscript revision and have read and approved the article.

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REFERENCES

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