Elevation of troponin I in acutely ill medical patients: a pilot study and literature review

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Abstract

Previous studies have identified a significant incidence of clinically unrecognised myocardial ischaemia in intensive care unit (ICU) patients, as determined by elevation of serum troponin. This pilot study demonstrates a similar high frequency of such a phenomenon in patients who are acutely ill, but without clinical evidence of myocardial ischaemia, on the general medical wards of a large city hospital. Elevation of serum troponin in these patients is associated with higher hospital mortality and increased lengths of hospital stay. Recognition that slight elevation of troponin levels may occur in the context of significant medical illness in acute general medical ward patients is important as it may avoid erroneous diagnosis of myocardial infarction and subsequent unnecessary investigations. A literature review of the various causes of an elevated troponin result is then presented.

Key words: troponin, myocardial ischaemia, APACHE III score.

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Introduction

Acutely ill patients admitted to the medical wards often have risk factors for coronary atherosclerosis and may therefore be susceptible to silent myocardial ischaemia when placed under physiological stress.[1] Previous studies have demonstrated silent myocardial ischaemia, as determined by elevation of troponin, in ICU patients. This may indicate a poorer prognosis.[2-4] Currently, it is not clear what proportion of acutely ill medical ward patients have clinically unrecognised cardiac injury, as troponin assay is not usually indicated in their management.

Recognition that clinically unrecognised myocardial ischaemia may occur in some acutely ill medical patients is important as it may suggest an alternative rationale upon which to base the aetiology of elevated troponin in similar patients in the future. Furthermore, appreciation of a potentially distinct pathogenesis of myocardial ischaemia in these patients is likely to lead to a different management strategy compared to that for patients with elevation of troponin due to acute coronary syndromes. Identification of these patients may also be important as they may have a poorer prognosis than those without myocardial ischaemia.

The main purpose of this study was to determine the incidence and prognostic value of elevated troponin I in acutely ill general medical ward patients who do not have clinical evidence of myocardial ischaemia such as myocardial infarction or angina. The study would also investigate any association between troponin I level and degree of illness severity as defined by APACHE III score.[5] Assessment would be made of any association between elevation of troponin I, length of hospital stay and mortality.

Study methods

This study met local requirements for ethical approval. Patients included male and female adult admissions to the Acute General Medicine Unit in Southern General Hospital, Glasgow, between May 2003 and November 2003. Criteria used to identify clinical evidence of significant illness were based on the presence of several physiological abnormalities such as tachycardia, hypotension and dyspnoea. Severity of illness was graded according to APACHE III score, which can provide initial risk stratification for severely ill hospitalised patients.[5] Patients were excluded if they had clinical evidence of definite or possible myocardial ischaemia such as myocardial infarction, unstable angina or chest pain. Patients with clinical evidence of left ventricular failure, myocarditis, pericarditis, pulmonary embolism and cardiac arrhythmias were also excluded. Electrocardiograms were reviewed, if available.

Blood samples for troponin I were obtained at least 12 hours following admission. Serum troponin I was measured using the Beckman Coulter Access analyser Accu TnI assay. The upper limit of normal range for troponin I level was defined as 0.04 µg/L (99th percentile of the normal range). Analytical variability at cut-off was 14%.

Results

A total of 27 patients were prospectively evaluated in the study period. Two patients in the original analysis were excluded (one had myocardial infarction and one had pulmonary embolism). The incidence of myocardial injury as determined by elevation of troponin I greater than 0.04 µg/L was 40% (10 of 25 patients). Baseline characteristics of these patients are shown in table 1. Comparison is made of those patients with and without elevation of troponin I with regard to APACHE III score and other phys-

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Table 1. Baseline characteristics of patients in the pilot study according to the level of cardiac troponin I (cTnI). Results are expressed as medians (interquartile range) or absolute numbers (%)

Characteristic	All patients (n=25)	Normal cTnI (n=15)	Elevated cTnI (n=10)
TnI, µg/L	0.04 (0.02–0.06)	0.02 (0.02–0.03)	0.07 (0.06–0.08)
APACHE III score	40 (28–57)	40 (23–52)	44 (35–60)
Age, y	68 (62–76)	62 (60–71)	76 (71–82)
Male, n (%)	15 (60)	7 (47)	8 (80)
Female, n (%)	10 (40)	8 (53)	2 (20)
Mean arterial BP, mmHg	90 (80–100)	100 (90–105)	80 (76–88)
Heart rate, beats/min	95 (88–110)	100 (89–110)	93 (83–105)
RR, breaths/min	18 (16–20)	20 (16–30)	17 (16–20)
Temp = or > 38ºC, n (%)	7 (28)	3 (20)	4 (40)
PaO_2 = or < 8kPa, n (%)	7 (28)	3 (20)	4 (40)
Any renal impairment*, n (%)	8 (32)	3 (20)	5 (50)
Significant renal impairment**, n (%)	3 (12)	1 (7)	2 (20)

*Any renal impairment is defined as serum creatinine > 130 µmol/L; **Significant renal impairment is defined as serum creatinine > 200 µmol/L
Key: y = years; BP = blood pressure; RR = respiratory rate

Table 2. Patient outcomes by troponin I. Results are expressed as medians (interquartile range) or absolute numbers (%)

Patient outcome	Normal troponin I (n=15)	Elevated troponin I (n=10)
Length of hospital stay (days)	27 (15–46)	50 (27–62)
Hospital mortality	4 (28.6)	4 (44.4)

iological variables. In patients with elevated troponin, systemic sepsis was implicated more commonly (seven of 10 patients) than in patients with normal troponin (three of 15 patients). The three remaining patients with elevated troponin had either an exacerbation of chronic lung disease (chronic obstructive pulmonary disease or pulmonary fibrosis) or metabolic decompensation (hyperosmolar non-ketonic state).

None of the differences between variables reached statistical significance but patients with elevated troponin I tended to have a higher APACHE III score, be older, male, have lower mean arterial blood pressure, pyrexia, significant hypoxia and renal impairment. Patients with normal troponin I tended to be slightly more tachycardic and tachypnoeic.

Comparison is made between patients' level of troponin I and their outcome in table 2. Patients with raised troponin I were more likely to have longer hospital admissions and higher mortality.

A scatter plot of APACHE III score against troponin I level is shown in figure 1. There was a slight trend for troponin I to rise with APACHE III score.

Discussion

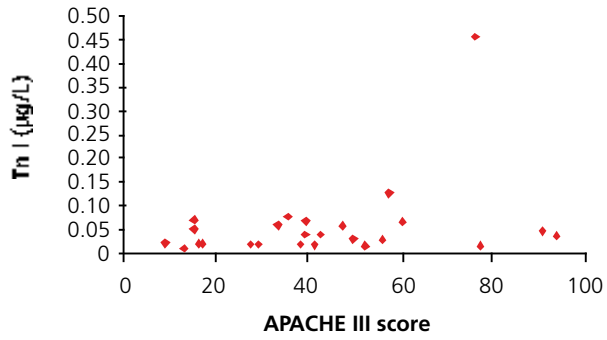
The main purpose of this study was to identify the proportion of patients with significant medical illness but no clinical evidence of myocardial ischaemia that would have an elevated troponin as a consequence of unrecognised cardiac injury. The observed frequency of this was 40% (10 of 25 patients). In one male patient with no prior history of atherosclerosis, who was suffering from a chest infection, troponin I was 0.46 µg/L. This was not associated with clinical or electrocardiographic features of myocardial ischaemia. Otherwise, elevated troponin I levels were not greater than 0.13 µg/L. Whilst there was a tendency for patients with raised troponin to have more deranged physiological variables, statistically significant results are precluded due to the sample size.

These results compare to previous ICU studies that identified 15.3% and 15.8% of medical ICU patients to have cardiac injury, as defined by elevation of troponin I.[3,4] The reason for the difference in this observation may be accounted for partly by the greater severity of illness of the study population. The overall hospital mortality in this group was 34.8%, compared to 18.7% and 17.7% in previous studies.[3,4] There was also a greater incidence of renal impairment in this study population, which is known to cause elevation of troponin.[6] However, even after excluding all patients with serum creatinine above the normal range, the incidence of raised troponin I was 29.4% (five of 17 patients). This study confirms previous associations between elevation of troponin I and patient outcomes such as length of hospital stay[3,4] and hospital mortality.[3]

An overview of elevated troponin

The cardiac structural proteins, troponin I and troponin T, represent a new generation of biochemical markers of myocardial cell injury and, due to their superior sensitivity and specificity compared to traditional cardiac enzymes such as creatine kinase MB (CK-MB), have recently become the preferred marker in the diagnosis of myocardial infarction.[7,8] Troponin measurement has now become an inte-

Figure 1. Scatter plot of APACHE III score against troponin I (Tn I) level



gral part of the assessment of patients with acute coronary syndromes thanks to its potential in predicting prognosis and aiding identification of patients who are likely to benefit most from early invasive strategies, glycoprotein IIb/IIIa antagonists and low molecular weight heparins.[9] However, since the introduction of troponin measurement, elevation of cardiac troponin has also been reported in a wide range of different clinical situations. This presents the clinician with the possibility that the aetiology of an elevated troponin is not an acute coronary syndrome as a consequence of unstable coronary artery disease but rather an alternative cause.

The various conditions that may cause elevation of troponin not related to unstable coronary artery disease are presented. The information was obtained via a literature search using Medline and Embase.

Myocarditis and pericarditis

In one study of 80 patients with clinically suspected myocarditis, troponin T predicted myocardial cell injury more sensitively than conventional determination of cardiac enzyme levels. An elevated troponin was highly predictive for immunohistologically-proven myocarditis.[10] Nevertheless, troponin was insensitive for identifying immunohistologically-proven myocarditis and a negative result could not be reliably used to rule it out. All patients with histologically proven myocarditis had an elevated troponin.[10]

Another study of similar size showed troponin I to be superior to CK-MB for detection of myocyte injury in biopsy-proven myocarditis. Troponin I elevations were substantially more common in the first month after the onset of heart failure symptoms, suggesting that the majority of myocyte necrosis occurs early and thus the window for diagnosis and treatment may be relatively brief.[11]

Two recent studies showed that troponin I elevation is frequently observed in viral or idiopathic acute pericarditis and appears to be particularly associated with young age and ST-segment elevation.[12,13] Troponin I increase is roughly related to the extent of myocardial inflammatory involvement and, unlike acute coronary syndromes, is not a negative prognostic marker.[12] Because it has a similar temporal pattern of release, elevation of troponin cannot distinguish between acute pericarditis and acute ischaemic myocardial injury.[14]

Heart failure

Even in the absence of an acute coronary syndrome, decompensated heart failure may cause elevation of cardiac troponin and, perhaps unsurprisingly, this is associated with more severe grades of heart failure and subsequently with a worse prognosis, including increased risk of death.[15,16] Mild elevation of troponin may occur in more stable patients with chronic heart failure, and indicates a highly significantly increased risk for hospitalisation and death regardless of whether the aetiology of heart failure is ischaemic or non-ischaemic.[17,18]

The detection of increased serum levels of cardiac troponin is thought to imply ongoing myocardial damage or leakage of myofibrillar components and to reflect the persistent loss of viable cardiac myocytes characteristic of progressive heart failure, due to possible underlying mechanisms such as loss of cell membrane integrity and apoptosis.[19,20] In a study of 238 patients with advanced heart failure referred for cardiac transplantation evaluation, 49% had detectable levels of troponin I. Not only did these patients have increased mortality, they were also more likely to experience progressive left ventricular dysfunction. It was suggested that they might derive particular benefit from more aggressive treatment strategies, such as heart transplantation or heart failure device therapy.[21]

Other cardiac causes

One Italian study found that troponin I was elevated in a significant proportion of patients with hypertension and left ventricular hypertrophy compared to hypertensive patients without left ventricular hypertrophy and normal controls.[22] A further study, mainly of hospital in-patients, showed that slight elevations of troponin were associated with increased left ventricular mass index.[23] There is also some evidence of persistent troponin elevation in patients with hypertrophic cardiomyopathy, which may predict clinical and echocardiographic deterioration.[24]

Despite the common observation in clinical practice, no evidence was found for the association between new-onset atrial fibrillation with a fast ventricular response and elevation of troponin. One study did, however, report elevation of troponin in four patients with supraventricular tachycardia.[25] A study of 57 patients assessed the effects of elective electrical cardioversion of atrial fibrillation or flutter: it found no elevation of troponin in any patient, compared to frequent elevation of traditional cardiac enzymes.[26] Another study of 35 patients demonstrated that minimal elevation of troponin following elective electrical cardioversion of atrial fibrillation or flutter may occur but is uncommon.[27] In addition, one study found that troponin was not elevated either before or after electrical cardioversion for ventricular arrhythmias in 27 patients with coronary artery disease.[28] This implies that common elevations of 'traditional' cardiac enzymes following transthoracic cardioversion are likely to be related to simultaneous skeletal muscle damage and that elevation of troponin in a stable patient with an atrial or ventricular arrhythmia may suggest an ischaemic precipitant.

A recent study has identified a slight rise in troponin following exercise testing in patients with chronic heart failure.[29] An elevation of troponin was also found in a small proportion of 100 patients with chronic stable angina following an exercise test, and it was suggested as a potential aid to predict three vessel coronary artery disease even if the exercise test is negative.[30]

Troponin may be elevated after cardiac surgery and can be used to predict morbidity and mortality by measurement preoperatively[31] or post-operatively.[32] Similar prognostic information regarding death and adverse events can also be obtained by measurement of troponin either before or after percutaneous coronary intervention.[33]

Other possible cardiovascular causes of a raised troponin are coronary vasospasm,[34] cardiac contusion,[35] cardiac amyloidosis,[36] atrial septal defect closure[37] and radiofrequency ablation.[38]

Respiratory disease

Troponin elevation is now well recognised in acute pulmonary embolism and can independently predict in-hospital mortality.[39] Increased right ventricular wall stress and low cardiac output with low coronary perfusion pressure in combination are recognised pathophysiological changes that occur with a significant pulmonary embolism,[40] and are likely to contribute to the elevation of troponin. Given that troponin elevation can perform as a surrogate marker of right ventricular dysfunction and identify patients with the highest risk of death, future studies are likely to investigate whether troponin levels can accurately aid the identification of patients who are likely to benefit most from more aggressive medical and surgical treatment strategies such as the early use of thrombolytic therapy or mechanical embolectomy.[41]

A study of 71 consecutive patients with a severe exacerbation of chronic obstructive pulmonary disease who were considered on admission to be at risk for requiring ventilatory support, showed that elevation of troponin I was present in 18% of cases and was a strong independent risk factor for in-hospital death; this occurred in more than half if the test was positive.[42] There are also case reports of a rise in troponin T in two patients with lobar pneumonia without any evidence of acute coronary syndrome or renal failure.[43] A paediatric pilot study of 25 patients found that troponin I may be elevated in children hospitalised with respiratory syncytial virus (RSV).[44]

Renal disease

First-generation troponin T assays were limited by the fact that they detected troponin T isoforms expressed in human skeletal muscle in response to chronic renal disease and therefore could not determine if measured troponin T was of cardiac origin.[45] The second- and third-generation troponin T assays still demonstrate elevated troponin T concentrations in patients with renal failure – this is thought to be due to accumulation of troponin T fragments that can not be cleared by the diseased kidney.[46]

Whilst troponin T is found fairly frequently in patients with renal failure, troponin I is found less commonly and the result may depend on the assay used.[47,48] Elevation of troponin I is also likely to be related to reduced elimination.[49] The largest and most useful analysis of troponin in renal failure was a study looking at 733 patients with end-stage renal disease, which calculated the percentage of patients with increased troponin T versus troponin I at each cut-off, as follows: 99th percentile, 82% versus 6%; 10% coefficient of variation (the lowest troponin concentration that demonstrates a 10% total precision), 53% versus 1.0%; and ROC (receiver operator characteristic, optimised for sensitivity and specificity for detection of myocardial infarction), 20% versus 0.4%. After adjustment for other risk factors, elevated troponin T was predictive of increased mortality using all cut-offs but only above the 99th percentile for troponin I (almost certainly because too few patients had elevated troponin I above the 10% co-efficient of variation cut-off).[50] Importantly, despite the relatively common elevation of troponin T in patients with renal failure, they are still able to predict short-term prognosis in patients with acute coronary syndromes, regardless of their level of creatinine clearance.[51]

ICU patients

Elevation of troponin I in patients with sepsis, septic shock and systemic inflammatory response syndrome (SIRS) is common and one study showed a possible link with *Streptococcus pneumoniae* infection.[52] Elevation of troponin T has been reported as a poor prognostic marker in ICU patients with early sepsis without clinical evidence of myocardial ischaemia;[2] elevation of troponin I has been shown to represent unrecognised cardiac injury in association with increased morbidity and mortality in critically ill ICU patients.[3] In another study involving medical ICU patients, elevated troponin I was associated with increased length of hospital stay and multiorgan dysfunction but was not an independent determinant of hospital mortality.[4]

Other uncommon causes

Troponin I may also become raised in patients after high-dose chemotherapy and may be used to predict development of left ventricular dysfunction following treatment.[53] Elevation of troponin I has also been reported following extreme physical endurance activities.[54] Subarachnoid haemorrhage has been reported to cause elevation of troponin I in a patient with normal coronary arteries, the proposed mechanism being raised catecholamine concentrations and metabolic abnormalities leading to reversible cardiac dysfunction.[55]

Assay interference

It is possible that heterophilic antibodies, present in the serum of some patients, may interfere with the troponin assay to produce a false positive result. As assays become more technically advanced, it would be hoped that such interference will become a rare cause of falsely elevated troponin. One recent study determined that the incidence of falsely increased troponin I results attributable to heterophilic antibodies that were consistent with the receiver operator characteristic (ROC) cut-off for acute myocardial infarction on an original assay was 0.17% of all patients with submitted troponin I samples and 1.6% of all troponin I samples with values > 1.4 µg/L (above the upper limit of ROC cut-off). Use of a revised assay considerably improved the accuracy of the test in the majority of cases.[56] Similarly, rheumatoid factor may interfere with the

Table 3. Definition of myocardial infarction from The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction

Criteria for acute, evolving or recent MI

Either of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   - ischaemic symptoms
   - development of pathologic Q waves on the ECG
   - ECG changes indicative of ischaemia (ST segment elevation or depression); or
   - coronary artery intervention (e.g. coronary angioplasty)

2) Pathologic findings of an acute MI

Key: MI = myocardial infarction; CK-MB = creatine kinase MB; ECG = electrocardiogram

assay to produce falsely elevated results and this may vary according to the nature of the immunoassay used.[57] Accordingly, clinicians should be aware of the possibility of a technical error, particularly in the context of a totally unexpected result, and should discuss the situation with the local biochemistry laboratory staff.

Conclusion

From the available evidence, there is now a myriad of causes of a raised cardiac troponin. There is little doubt that future studies will show elevation of troponin related to many other medical and surgical conditions. The pilot study in this article demonstrates elevation of troponin in medical ward patients with a significant degree of medical illness but with no direct clinical evidence of myocardial ischaemia.

It is now well recognised that both troponin I and troponin T are highly sensitive and specific biomarkers of cardiac injury. Their detection may be a consequence of clinically obvious acute ischaemic or inflammatory myocardial insult. At other times it may indicate subclinical ischaemia potentially due to physiological or haemodynamic compromise. Further studies are required to investigate whether this represents a greater risk of underlying coronary artery disease and whether current secondary prevention measures are beneficial. It seems likely that such events simply represent an imbalance of myocardial oxygen supply and demand. It is possible, however, that the presence of a systemic inflammatory syndrome could unmask coronary artery disease by adverse effects on coronary plaque stability and thrombogenicity. Otherwise, elevation of troponin may relate to ongoing chronic cardiac myocyte loss in conditions such as severe heart failure or reduced renal clearance.

Aside from patients with renal failure, there should be no differences in interpretation between troponin I and troponin T results. In order to clarify the place of cardiac troponin in the diagnosis of acute myocardial infarction, a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee has recently redefined the diagnostic criteria (see table 3). Since different troponin I assays are not directly comparable (there is only one troponin T assay available due to patent reasons), the consensus document recommends that each laboratory should determine its cut-offs individually at the 99th percentile of a reference control group, with a < 10% variance.[8] More recently, a British Cardiac Society Working Group suggested using a slightly higher cut-off in order to differentiate between an acute coronary syndrome with associated minor myocardial necrosis and a clinical myocardial infarction.[58] Importantly, however, it is becoming clear that elevation of cardiac troponin in many clinical scenarios is likely to represent irreversible myocardial injury and will indicate a poorer prognosis regardless of the aetiology.

Key messages

- The pilot study demonstrated that 40% of patients with significant medical illness but no clinical evidence of myocardial ischaemia had raised troponin levels
- Accurate diagnosis of myocardial infarction should not rely solely on elevation of troponin
- Other cardiac causes of raised troponins include myocarditis, pericarditis, heart failure and left ventricular hypertrophy
- Non-cardiac causes of raised troponins include acute pulmonary embolism, renal failure and sepsis

Conflict of interest

None declared.

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