Troponin I and myocardial injury in the ICU

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Cardiac troponin I (cTnI) is a protein that is specific to heart muscle. Increased concentrations appear in serum after myocardial cell injury. cTnI was compared with creatinine kinase MB (CK MB), myoglobin and the 12-lead ECG for detection of myocardial injury in an unselected series of 109 medical and surgical ICU patients. Clinical observations and daily 12-lead ECG were recorded prospectively. Samples for cTnI, myoglobin and CK MB serum analysis were collected each day. Increased serum cTnI concentrations (>0.1 µg litre⁻¹) were observed in 70.6% (n=77) of the ICU group. Tachycardia, arrhythmia, hypotension and treatment with inotropic drugs were associated with higher concentrations. The standardized mortality ratio by APACHE III for the ICU sample was 0.98. All subjects in an unmatched control group of 98 medical unit emergency admissions without a primary cardiac diagnosis had serum cTnI concentrations <0.1 µg litre⁻¹. We conclude that increased serum cTnI concentrations occur frequently in the ICU suggesting that there is a high incidence of cardiac injury in these patients.

Keywords: protein, troponin I; heart, myocardial function; intensive care

Accepted for publication: September 9, 1998

The myocardium of the critically ill patient is exposed to a wide variety of physiological and pharmacological stresses during the course of an illness, resulting in an imbalance between myocardial oxygen supply and demand. Oxygen demand is increased by tachycardia, increased contractility and increased left ventricular end-diastolic pressure (LVEDP). Anaemia and hypotension can diminish supply. Furthermore, the adult ICU population has a predominance of older subjects with a high incidence of ischaemic heart disease. There is now evidence that some episodes of myocardial ischaemia lead to myocardial cell injury.

Troponin I is a component of the contractile proteins present in all muscle. The amino acid sequence of cardiac troponin I (cTnI) contains a section that is unique to cardiac muscle. The cTnI assay measures these cardio-specific components to provide a highly specific marker for cardiac muscle cell injury. It has no cross reactivity with the two skeletal muscle isoforms. cTnI is a highly sensitive and long-lasting marker of cardiac injury. Measurement of cTnI concentrations in renal failure, in myopathic states and after acute skeletal muscle injury has provided normal concentrations in the absence of cardiac injury. Two studies have demonstrated its value in the diagnosis of myocardial infarction in the postoperative patient. The use of this new assay has led some workers to conclude that myocardial injury in the ICU may be more prevalent than previously recognized.

We studied the incidence of cardiac injury in patients admitted to the ICU of the Victoria Infirmary, using daily 12-lead ECG and serum assays for measurement of cTnI, myoglobin and creatinine kinase MB (CK MB) concentrations. The purpose was to determine how frequently myocardial injury occurred, and to compare cTnI with other tests used conventionally to detect such injury. The distribution of cTnI concentrations in the ICU population was compared with that seen in a group of normal volunteers and in a cohort of medical unit emergency admissions. All ICU admissions over a 6-month period were included.

Patients and methods

The Local Medical Ethics Committee approved the study. Consent was not deemed necessary.

Serum cTnI concentrations were measured in three unmatched groups. These were: (1) 109 consecutive ICU patients; (2) 98 unselected medical unit admissions; and (3) 58 healthy staff volunteers. There were no exclusion criteria.

ICU patients were recruited from the five-bed intensive care unit of the Victoria Infirmary, which is a mixed medical and surgical ICU. Over a 6-month period, each consecutive admission was included in the study. Sixty patients were admitted to the ICU directly from theatre and the remaining 49 from other areas within the hospital. Patients in group 1 were from the following diagnostic groups: major postoperative vascular surgery (n=9); major postoperative maxillofacial/ENT surgery (n=9); elective oesophagectomy (n=9); major emergency general surgery (n=35); primary cardiac diagnoses (n=9); primary respiratory failure
(n=12); and miscellaneous (n=26). The 98 inpatients in group 2 were emergency admissions to the receiving medical unit who did not have a primary cardiac diagnosis. The 58 healthy controls in group 3 consisted of volunteer staff members. Patient characteristics of the ICU group are shown in Table 1.

**Data collection**

In the ICU group, heart rate and rhythm, systolic arterial pressure and oxygen saturation were recorded on admission and thereafter daily by the nursing staff. The type of inotropic drug and dose were noted, as were age, sex, past cardiac medical history and admission diagnosis. Clinical data and physical characteristics were collected prospectively. The admission acute physiology and chronic health evaluation score (APACHE II), standardized mortality ratio (SMR) derived from APACHE III, and ICU outcome were recorded at the end of the study.

We recorded 12-lead ECG each day which were reported prospectively by one of the authors (S. N.). ECG abnormalities were categorized into seven groups: (1) ST segment depression in two or more leads; (2) T wave inversion during admission in two or more leads; (3) T wave inversion in two or more leads from admission with no pre-admission ECG; (4) non-specific ST changes, defined as loss or flattening of T waves in two or more leads; (5) ST elevation in two or more leads; (6) development of new left bundle branch block (LBBB); and (7) normal ECG.

In the ICU group, 12-lead ECG, and CK MB, cTnI and myoglobin concentrations were recorded daily. In patients in the medical unit control group, serum cTnI concentrations were measured once, on the day of admission. In the staff volunteer group, serum cTnI concentrations were also measured once. The 12-lead ECG, CK MB and myoglobin concentrations were not performed in these latter groups. None of the serum assay results was available for patient management.

**Sample collection and analysis**

Blood samples were collected in Vacutainer serum separator tubes, centrifuged and stored at −20°C before analysis.

<table>
<thead>
<tr>
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</table>

**Table 1** Patient characteristics of the ICU population (median (interquartile range) or number). MI=Myocardial infarction, IHD=ischaemic heart disease, LVF=left ventricular failure and AF=atrial fibrillation

**Statistical analysis**

Parametric data are described as mean (SD). Median (interquartile range) was used to describe non-parametric data. Non-parametric data were analysed using the Mann–Whitney U test.

**Results**

The ICU group comprised 54 males and 55 females, median age 68 (quartiles 51–75) yr. Mean admission APACHE II score for the 109 patients was 18.9 (SD 7.9). Patients stayed in the ICU for a mean of 3.5 (SD 4.5) days. The SMR derived from APACHE III for this period of ICU activity was 0.98.

There were 41 males and 57 females in the medical inpatient group, median age 62 (quartiles 54–68) yr and 70 (56–73) yr, respectively. The healthy volunteer group comprised 12 males and 46 females, median age 40 (36–53) yr and 32 (30–35) yr, respectively.

Of the ICU patients, 70.6% (77 of 109) had cTnI concentrations greater than 0.1 µg litre⁻¹ during ICU admission. In 44% (n=48), cTnI concentrations exceeded 0.5 µg litre⁻¹. None of the 98 acute medical unit admissions...
had a cTnI concentration greater than 0.1 µg litre⁻¹ and of the 58 healthy controls, none had cTnI concentrations exceeding 0.03 µg litre⁻¹. Of the patients with cTnI concentrations greater than 0.1 µg litre⁻¹, there were ECG abnormalities in 49 of 70 patients (70%). In seven patients, the ECG could not be interpreted (three had pre-existing LBBB, one had a paced rhythm and three had no ECG). Of those with cTnI concentrations greater than 0.5 µg litre⁻¹ and suitable ECG, 36 of 44 (82%) patients had abnormalities. Abnormal cTnI concentrations occurred most frequently on days 1 or 2 after admission to the ICU (Fig. 1).

A total of 71.5% (78 of 109) of subjects had CK MB concentrations that increased by more than 5 µg litre⁻¹; 90.8% (99 of 109) of patients had myoglobin concentrations greater than 0.03 µg litre⁻¹. Of the patients with cTnI concentrations greater than 0.1 µg litre⁻¹ and 56% (61 of 98) of patients who had 12-lead ECG available developed ECG abnormalities, as defined previously.

In many of the 77 patients, serum cTnI concentrations remained increased for several days. Apart from one patient who had constantly increased concentrations for the entire 25 days of her ICU stay, duration of the first increase varied between 1 (n=28) and 8 days (n=1). Twenty-four patients had a second peak (1–8 days’ duration), nine had a third peak (1–7 days’ duration) and in six individuals there was a fourth peak (1–13 days’ duration) in serum cTnI concentrations.

The difference in median serum cTnI concentration between those patients who had received epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine and dobutamine in various combinations (n=39) and those who did not (n=70) was highly statistically significant (P<0.001) (Table 2). There was also a significant difference when cTnI concentrations of those patients with heart rates greater than 120 beat min⁻¹ (n=50) were compared with those with no tachycardia (n=57) (P<0.001). Patients with cardiac arrhythmias (n=24) had higher cTnI concentrations than those who had no recorded episodes of arrhythmia (n=75) (P<0.02) and those with recorded systolic arterial pressures of less than 100 mm Hg (n=29) had higher cTnI concentrations than those who had no hypotension (n=74) (P<0.002). We found similar associations between median CK MB concentrations and the more severe degrees of cardiovascular stress, with the exception of arrhythmia.

Patients who died had higher cTnI concentrations (median 0.65, quartiles 0.16–2.60 µg litre⁻¹) than those surviving to hospital discharge (median 0.35, quartiles 0.06–1.23 µg litre⁻¹) (P<0.04).

The relationship between the various ECG abnormalities and abnormal biochemical results is shown in Table 3. Patients with normal ECG had a median cTnI concentration of 0.12 µg litre⁻¹. Higher median cTnI concentrations were seen in those who developed ST segment depression (1.22 µg litre⁻¹) or T wave inversion (1.34 µg litre⁻¹) during the course of ICU admission. Patients with normal ECG had a median CK MB concentration of 5.4 µg litre⁻¹, while those with ST segment depression and those with non-specific ST changes had higher median CK MB concentrations of 25.4 µg litre⁻¹ and 12.9 µg litre⁻¹, respectively. There were only two patients with ST segment elevation. They had peak cTnI concentrations of 38.7 µg litre⁻¹ and 4.0 µg litre⁻¹ and peak CK MB concentrations of 105.6 µg litre⁻¹ and 20.5 µg litre⁻¹, respectively. One patient developed LBBB and had a peak cTnI concentration of 0.2 µg litre⁻¹ and a peak CK MB of 107 µg litre⁻¹.

![Fig 1 Timing of the first increase in cardiac troponin I concentrations in 77 patients with abnormal concentrations.](image)

**Table 2** Peak concentrations of cTnI and CK MB (median (first and third quartiles)) for patients with and without defined cardiovascular stresses

<table>
<thead>
<tr>
<th>Physiological/ pathological stress</th>
<th>Peak cTnI (µg litre⁻¹) in subjects with stress</th>
<th>Peak cTnI (µg litre⁻¹) in subjects without stress</th>
<th>Mann-Whitney U test for cTnI groups</th>
<th>Peak CK MB (µg litre⁻¹) in subjects with stress</th>
<th>Peak CK MB (µg litre⁻¹) in subjects without stress</th>
<th>Mann-Whitney U test for CK MB groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR &gt;120</td>
<td>0.97 (0.29–1.88)</td>
<td>0.15 (0.06–1.01)</td>
<td>0.001</td>
<td>15.3 (6.9–37.6)</td>
<td>6.8 (2.5–15.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate beat min⁻¹</td>
<td>1.4 (0.23–2.25)</td>
<td>0.29 (0.07–1.08)</td>
<td>0.02</td>
<td>16.3 (6.57–35.57)</td>
<td>7.4 (3.9–20.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1.131 (0.28–2.44)</td>
<td>0.15 (0.06–1.02)</td>
<td>0.002</td>
<td>12.8 (6.8–63.9)</td>
<td>8.3 (3.05–20.25)</td>
<td>0.009</td>
</tr>
<tr>
<td>Dopamine drugs</td>
<td>1.39 (0.31–2.26)</td>
<td>0.15 (0.05–1.00)</td>
<td>0.001</td>
<td>20.5 (9.55–60.55)</td>
<td>6.8 (2.42–13.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>SAP&lt;100</td>
<td></td>
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</tbody>
</table>
Myoglobin concentration for this patient was 3517 µg litre⁻¹, which reflected major skeletal muscle injury. Table 4 shows the distribution of abnormal results according to diagnostic group.

**Discussion**

We have demonstrated a surprisingly high proportion of patients in a general ICU with increased serum cTnI concentrations; 70% of subjects had concentrations greater than 0.1 µg litre⁻¹ and in 44% of the sample, serum cTnI concentrations exceeded 0.5 µg litre⁻¹.

The increase in cTnI occurred most frequently on days 1 and 2 of ICU admission, suggesting that the injury had been initiated by events that preceded the patient’s arrival in the unit. It is during this period immediately before ICU stabilization that patients are exposed to the dual insults of hypoxia and hypotension. Several individuals showed more than one peak in cTnI, and therefore even when intensive care had been initiated, the processes leading to injury continued.

Two American groups working in medical ICU described an incidence of myocardial injury of 15% and 15.8%, respectively. The disparity between our study and these earlier ones probably reflects differences in the casemix, population age and severity of illness scores.

The introduction of assays for cTnI and cardiac troponin T has demonstrated that the spectrum of cardiac injury is wide. This ranges from transmural infarction to increases in troponin seen in unstable angina and after cardiac surgery. Because of its specificity, the assay facilitates recognition of myocardial injury in cases of polytrauma and renal failure and its sensitivity is of proven value in the safe triage of patients presenting with chest pain.

An ECG abnormality was recorded on admission or developed later in 70% of patients with increased serum cTnI concentrations (Table 4). In the ICU, ST segment and T wave abnormalities are not specific to myocardial ischaemia and may occur in relation to drug treatment, acid–base disturbances and electrolyte imbalance. The ubiquitous nature of ECG abnormalities has been observed previously in an ICU population of trauma patients.

After cardiac injury, cTnI persists in serum for 7 days. Serum concentrations of CK MB return to normal in 72 h. CK MB is not specific to cardiac muscle and in a critical care population, no correlation between CK MB and cTnI would be anticipated and nor was it observed. Biochemical detection of myocardial injury can be problematic in patients admitted from the operating theatre. In our study, 42 of 78 (54%) patients with increased CK MB concentrations were admitted after surgery (n=40) or trauma (n=2). In the ICU where skeletal muscle damage is commonplace, it is the specificity of cTnI for myocardial injury that provides its main advantage over CK MB.

The strong association between disturbed cardiovascular physiology and increases in serum cTnI concentrations suggests that myocardial injury was precipitated by ischaemia. cTnI is not normally detectable in serum and there has been no evidence to date of an age-associated increase in serum concentrations of the protein. The extreme degrees of cardiovascular stress to which ICU patients are subjected are a much rarer occurrence among general medical emergency admissions. We believe that the few

**Table 3** Peak concentrations of cTnI and CK MB (median and first and third quartiles) associated with the five most commonly observed ECG categories for each subject

<table>
<thead>
<tr>
<th>ECG change</th>
<th>Peak cTnI (µg litre⁻¹)</th>
<th>Peak CK MB (µg litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ECG (n=37)</td>
<td>0.12 (0.04–0.5)</td>
<td>5.4 (2.3–13.85)</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>0.38 (0.07–1.13)</td>
<td>12.9 (5.0–28.35)</td>
</tr>
<tr>
<td>T inversion on admission with no</td>
<td>0.3 (0.15–0.1)</td>
<td>7.1 (4.0–13.78)</td>
</tr>
<tr>
<td>reference ECG (n=14)</td>
<td></td>
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</tr>
<tr>
<td>New T wave inversion</td>
<td>1.34 (0.38–2.55)</td>
<td>11.9 (6.7–18.5)</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>1.22 (0.27–2.44)</td>
<td>25.4 (5.9–84.2)</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>cTnI &gt;0.1 µg litre⁻¹</th>
<th>CK MB &gt;5 µg litre⁻¹</th>
<th>ECG change</th>
<th>cTnI increase and ECG</th>
<th>CK MB increase and ECG</th>
<th>CK MB and cTnI increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>7/12</td>
<td>9/12</td>
<td>7/11</td>
<td>4/11</td>
<td>6/11</td>
<td>5/12</td>
</tr>
<tr>
<td>respiratory failure</td>
<td>(58)</td>
<td>(75)</td>
<td>(53)</td>
<td>(36)</td>
<td>(55)</td>
<td>(42)</td>
</tr>
<tr>
<td>Emergency</td>
<td>28/35</td>
<td>27/35</td>
<td>23/31</td>
<td>19/31</td>
<td>20/31</td>
<td>25/35</td>
</tr>
<tr>
<td>general surgery</td>
<td>(80)</td>
<td>(77)</td>
<td>(75)</td>
<td>(61)</td>
<td>(65)</td>
<td>(71)</td>
</tr>
<tr>
<td>cardiac aetiology</td>
<td>(100)</td>
<td>(100)</td>
<td>(67)</td>
<td>(67)</td>
<td>(67)</td>
<td>(100)</td>
</tr>
<tr>
<td>ENT/maxillofacial surgery</td>
<td>3/9</td>
<td>3/9</td>
<td>1/8</td>
<td>1/9</td>
<td>0/9</td>
<td>0/9</td>
</tr>
<tr>
<td>selective surgery</td>
<td>(33)</td>
<td>(33)</td>
<td>(13)</td>
<td>(11)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>19/26</td>
<td>18/26</td>
<td>15/24</td>
<td>11/24</td>
<td>11/24</td>
<td>16/25</td>
</tr>
<tr>
<td></td>
<td>(75)</td>
<td>(69)</td>
<td>(63)</td>
<td>(46)</td>
<td>(46)</td>
<td>(62)</td>
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</table>
individuals in the medical unit cohort with detectable concentrations probably had very minor degrees of myocardial injury. The use of dobutamine to enhance oxygen delivery to tissues has been associated with excess mortality.\textsuperscript{22} Excessively high heart rates and arrhythmias shorten the diastolic phase of the cardiac cycle and can precipitate ischaemia.\textsuperscript{23} The subendocardium is particularly prone to ischaemic injury under such conditions. In this study, individuals with the ECG appearances of subendocardial ischaemia (new T wave inversion and ST segment depression) had the highest serum cTnI concentrations. None of the patients developed new Q waves during admission, suggesting that cardiac injury was not a result of transmural myocardial infarction (Table 2). That myocardial injury can result from causes other than coronary thrombosis has been recognized for many years.\textsuperscript{24} In fact, a retrospective case-note review found that myocardial infarction had been diagnosed by clinicians in only four cases.

Three to four percent of cTnI is in free cytosolic form\textsuperscript{25}; the remainder is incorporated into the myofibrils. Increases in cTnI may be a consequence of membrane leakage and not a result of damage to the myofibrillar structure or cell death. It is hypothesized that much of the tissue injury in the critically ill patient is mediated via the action of oxygen free radicals on cell membranes.\textsuperscript{26, 27} The injury observed in our study may have been a consequence of free radical damage to the myocardium. Other factors may have been cardiac contusion in two patients with fractured sternums (peak serum cTnI of 1.01 µg litre\textsuperscript{–1} and 0.12 µg litre\textsuperscript{–1}, respectively) and direct mediastinal manipulation in patients who underwent thoracic oesophagectomy (Table 4).

In this heterogeneous cohort of ICU patients, the median serum cTnI concentration of those who died was greater than that found in hospital survivors. An earlier study found that acute cardiovascular dysfunction, but not increased serum cTnI, was an independent predictor of mortality in the ICU.\textsuperscript{19} Despite this apparently high incidence of cardiac injury, the SMR by APACHE III for the ICU sample was 0.98.

This sensitive and highly specific assay for cTnI has highlighted the wide spectrum of cardiac injury. We have reported an unexpectedly high incidence of increased serum cTnI concentrations, most of which had occurred before ICU admission. This would support the case for earlier ICU referral. Nevertheless, a significant proportion of the injury occurred after initiation of intensive therapy. This was associated with conditions promoting myocardial ischaemia, such as tachycardia, hypotension, arrhythmia and the use of inotropic drugs. Further work should examine if long-term cardiovascular morbidity ensues from such injury, and how it may be prevented.

Acknowledgement

The assay kits for cTnI, CK MB and myoglobin were provided by Beckman Instruments (UK) Ltd, Oakley Court, Kingsmead Business Park, London Road, High Wycombe, Bucks, HP11 1JU.

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