Prognostic Significance of Raised Cardiac Troponin T in Patients Presenting with Acute Limb Ischaemia

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Objective. To study the relation between serum cardiac troponin T (cTnT) and mortality in patients presenting with acute limb ischaemia secondary to an embolism.

Material and methods. A two years prospective study of all patients admitted to the vascular unit with a diagnosis of acute limb ischaemia secondary to an embolism. On admission all patients had an ECG. A blood sample was taken for measurement of cTnT, CRP, serum biochemistry, full blood count and clotting. All embolectomies were performed under local anaesthesia. Patients were followed until discharge from hospital and up to twelve months after surgery.

Results. There were 37 patients with lower limb and 2 patients with upper limb ischaemia. Twenty four patients were female and fifteen were male, with the mean age of 76 years (50–95) for women and 84 years (77–90) for men. Seventeen patients (44%) had a raised cTnT. The patients with raised cTnT were older than those with normal cTnT [86y (77–92) vs 77y (51–95), p = 0.01, t test]. Only two patients with raised cTnT gave a history of chest pains. All of the patients with an elevated cTnT had also raised CRP. There was no significant difference in the serum creatinine in the group of patients with elevated cTnT compared to those with normal cTnT [112 μmol/L (range 98–159) vs 119 μmol/L (range: 47–177), p = ns]. The cumulative survival for cTnT+ patients at 7 days was 53% and that of cTnT− patients was 100%. The cumulative survival for cTnT+ and cTnT− patients was statistically different (p = 0.0000, χ² = 13.1, Log Rank test). Using regression analysis, an elevated cTnT was found to be an independent predictor of outcome.

Conclusion. A significant proportion of patients presenting with an acutely ischaemic limb have an elevated cTnT. An elevated cTnT may be an early marker of overall disease severity and a predictor of outcome.

Keywords: Cardiac Troponin T; Prognostic significance; Acute limb ischaemia.

Background

Several studies have demonstrated that minor elevations in perioperative serum troponin (cTnT) concentrations are associated with significantly lower long term survival after vascular surgery.1,2 In these patients underlying heart disease is often unrecognised due to decreased exercise tolerance from peripheral vascular disease. The most common aetiological factor for an acutely ischaemic leg is an embolus of cardiac origin. Less common factors include in situ thrombosis or a thrombosed popliteal aneurysm. Patients presenting with an acutely ischaemic leg are often elderly and with co-morbid factors that may not be apparent on admission to hospital. Mortality following successful embolectomy is not insignificant. Early identification of patients at risk may lower both, morbidity and mortality, and improve the postoperative outcome. We studied prospectively, the relation between cTnT and mortality in patients presenting with acute limb ischaemia secondary to an embolism.

Material and Method

We studied patients who were referred to a vascular unit with acute limb ischaemia over the period of 24 months (October 2002 to October 2004). On admission every patients were assessed a specialist registrar and a consultant vascular surgeon. All patients
underwent a full cardiovascular examination, followed by a 12 lead ECG and a Colour Flow Duplex scan of the ischaemic limb and the abdominal aorta. The ankle brachial pressure index (ABPI) was also measured whenever possible. But this was not possible in the majority of patients and had to be abandoned. Blood samples were taken for a full blood count, urea and electrolytes, Troponin T (cTnT) and C reactive protein (CRP). The blood test and the ECG were repeated twelve hours after admission. For patent reasons cTnT assay has a single manufacturer (Roche Diagnostics). The current version uses a third generation troponin T (Elecsys Troponin T; Modular Analytics E170). The assay uses two monoclonal antibodies specifically directed against human cardiac troponin T. It has a lower limit of detection of 0.01 ug/L and an upper limit of the reference interval (99th percentile of a healthy population) of <0.01 μg/L. The serum concentration of cTnT at which the coefficient of variation is 10% is 0.03 μg/L. According to the manufacturer (information obtained from the package insert), the monoclonal antibodies used in the assay have negligible (0.001%) cross-reactivity with human skeletal muscle troponin T.

All embolectomies were performed under local anaesthesia using 1% plain lignocaine (max dose: 5 mg/kg). A completion angiogram was performed to establish complete clearance of the vessel. The arteriotomy was repaired with a vein patch using 6-0 polypropylene. All patients were subsequently commenced on an intravenous heparin infusion to maintain an APTT ratio of 2.0, pending anticoagulation with warfarin with a target INR of 2.0. All patients had an APTT ratio of 2.0, pending anticoagulation with warfarin with a target INR of 2.0.

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Results

Of the 119 patients admitted to the vascular unit with limb related complaints 39 had an acutely ischaemic limb. The demographic data is displayed in Table 1. There were 37 patients with lower limb and 2 patients with upper limb ischaemia. Twenty four patients were female and fifteen were male, with the mean age of 76 years (50–95) for women and 84 years (77–90) for men. Eighteen patients had a history of ischaemic heart disease and two gave a history of chest pain or recent myocardial infarct. Eleven patients had a history of hypertension, seven of diabetes and twenty four of atrial fibrillation. Seventeen patients (44%) had a raised cTnT. The patients with raised cTnT were older than those with normal cTnT [86y (77–92) vs 77y (51–95), p = 0.01, t test]. The mean cTnT was 0.20 μg/L (range: 0.11–0.27). Only four patients had electrocardiographic evidence of myocardial injury on admission. The mean cTnT in this group of patients was 0.17 μg/L (range: 0.11–0.24). Two of the patients with ECG changes felt generally unwell and had chest pains. The other patients with raised cTnT all denied chest pain and their ECGs showed no evidence of ischaemia. This finding may suggest silent myocardial cell damage. None of the echocardiograms showed any evidence of mural thrombus, vegetation or septal defects.

All of the patients with an elevated cTnT had also raised CRP. There was a strong correlation between a raised cTnT and the CRP (Pearson correlation = 0.5, p = 0.001, Fig. 1). There was no significant difference in the serum creatinine in the group of patients with elevated cTnT compared to those with normal cTnT [112 μmol/L (range 98–159) vs 119 μmol/L (range: 47–177), p = ns].

No patients underwent an amputation. All patients who died within 28 days of hospitalisation had raised cTnT levels. Patients were stratified as to whether or not their cTnT was elevated. The Kaplan Meier survival curves for the group of patients with raised troponin (cTnT+), and those with normal troponin (cTnT−) is shown in Fig. 2. The cumulative survival

Statistical

Categorial data were analysed using the Chi-square test. The Pearson test was used to determine the correlation between cTnT and CRP. Survival was determined using Kaplan Meier’s lifetime table method. Regression analysis was used to determine the most significant factor affecting survival. To avoid collinearity, the predictors entered into the model were age, sex, cTnT, CRP, ischaemic heart disease (IHD) and aspirin therapy.

| Table 1. Demographic data of patients studied |
|-------------------------------|--------|--------|--------|--------|
|                             | cTnT +ve | cTnT –ve | p value |
| Male                        |        |        | 0.003  |
| Female                      | 11     | 4      |        |
| Age (range)/year            | 86 (77–92) | 77 (51–95) | 0.01  |
| Hypertension                | 3      | 8      | ns     |
| Ischaemic heart disease     | 11     | 7      | 0.04   |
| Aspirin therapy             | 4      | 10     | ns     |
| Diabetes                    | 3      | 4      | ns     |
| Atrial fibrillation         | 8      | 16     | ns     |

Eur J Vasc Endovasc Surg Vol 32, November 2006
for cTnT+ patients at 7 days was 53%. The cumulative survival for cTnT+ and cTnT− patients was statistically different ($p = 0.0000$, $\chi^2 = 13.1$, Log Rank test). During the follow up period no further mortality was noted at one year in all the patients studied.

Using logistic regression analysis, age ($z = -1.00$, $p = 0.3$), sex ($z = 1.64$, $p = 0.1$), CRP ($z = -0.68$, $p = 0.5$), IHD ($z = -1.74$, $p = 0.08$), and aspirin therapy ($z = 1.88$, $p = 0.06$) were all not associated with outcome. However, an elevated cTnT ($z = 2.64$, $p = 0.008$) was found to be of predictor of mortality.

**Discussion**

One of the important findings of this study is the observation that up to 44% of patients presenting as an emergency with an acutely ischaemic limb show evidence of raised cTnT. We also found that an elevated cTnT on admission in these patients is associated with an increase in 28-day mortality. Elevated cTnT however does not seem to affect mortality in the medium term. Troponin T and I are the most sensitive markers of myocardial cell damage and may be elevated in conditions other than acute coronary syndrome. Cardiac troponins are also elevated, and have been shown to be of prognostic significance in many conditions associated with secondary ischaemic injury such as coronary angioplasty and arrhythmias, pulmonary embolism, heart failure and in conditions causing non-ischaemic myocardial injury such as pericarditis, septicaemia, renal failure and stroke. Elevated troponin levels correlate with a decrease in left ventricular function in both cardiac and non-cardiac patients. Ammann et al. showed independent predictive value of raised troponin in critically ill patients. In the current study, the correlation between cTnT on admission and mortality was strong. A raised troponin was also found to be an independent risk factor for mortality suggesting that the mortality may be cardiac related. However as we did not perform myocardial perfusion scan or coronary angiogram in these patients, the correlation between raised cTnT on admission and reversible cardiac dysfunction remains deductive.

The absence of chest pain and ischaemic changes on ECG in most patients may reflect silent myocardial cell damage. It is difficult to know from this study whether the elevated cTnT is a primary event of cardiac origin or a secondary event on the myocardium by an inflammatory response triggered as a result the acute ischaemic event in the limb. Given that arrhythmias can cause an elevation of troponin and that myocardial cell necrosis can cause arrhythmias which in turn can cause embolism, it is difficult to know whether all patients presenting with acute limb ischaemia and raised troponin should undergo risk stratification investigations. These issues are pertinent when one considers the mortality in this group of patients. However, we acknowledge that this is a small study and interpretation of results is therefore limited. Whether risk stratification using cTnT, and early risk reduction strategies will translate into improved clinical outcome remains to be seen.

In conclusion, we found that a significant proportion of patients presenting with an acutely ischaemic limb have an elevated cTnT. We also found that an elevated cTnT might be an early marker of overall disease severity and a predictor of outcome.

**Acknowledgements**

We thank the Consultant Vascular Surgeons at Selly Oak Hospital, University Hospital Birmingham NHS Foundation Trust, for allowing us to study the patients treated under their care.
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Accepted 6 April 2006
Available online 23 May 2006