

Troponin T release after heart transplantation

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Abstract

Background—For the diagnosis of myocardial cell damage the measurement of the serum concentrations of myofibrillar antigens has several potential advantages over the assessment of traditional serological markers. These include the expression of myofibrillar antigens as cardiospecific isoforms and their high intracellular concentrations. Recently a sensitive and specific enzyme immunoassay for cardiac troponin T has been developed that shows little cross-reactivity with skeletal isoforms.

Objective—To characterise myocardial cell damage after orthotopic heart transplantation, concentrations of circulating troponin T were measured prospectively in serial blood samples from 19 consecutive patients taken during the first three months after transplantation.

Results—Mean (SD) serum concentrations of cardiac troponin T reached a maximum of 3.6 (1.8) $\mu\text{g/l}$ at 7.1 (4.2) days after transplantation and remained higher than 0.5 $\mu\text{g/l}$ (twice the detection limit of the assay) in all patients for at least 43 days (mean (SD) 59 (20) days). There was considerable variation in cumulative troponin T release (area under the concentration curve) between the patients (ranging from 27 to 150 $\mu\text{g} \times \text{days/l}$) that was not related to the total ischaemic time before transplantation or to the patient's renal or hepatic function, preoperative cardiac diseases, major histocompatibility complex matching or the number of complications related to rejection.

Conclusions—Because the half life of cardiac troponin T in serum is 2 h the current data show that antigen continued to be released from implanted hearts during the first postoperative months in quantities similar to minor Q wave myocardial infarction. Troponin T release after transplantation continued for much longer than after myocardial infarction or other cardiac surgery. Processes other than perioperative ischaemic damage must be responsible for the considerable individual differences in the release of cardiac troponin T.

(Br Heart J 1993;69:395-398)

For the diagnosis of myocardial cell damage the measurement of serum concentrations of

myofibrillar proteins (such as actin, myosin, tropomyosin, and the troponin complex) has several potential advantages over the measurement of traditional serological markers. These include the expression of myofibrillar proteins as cardio-specific isoforms and their high intracellular concentrations.¹

A sensitive and specific enzyme immunoassay has been developed for cardiac troponin T which shows little cross-reactivity with the skeletal troponin T isoforms.^{2,3} As shown in previous studies, circulating troponin T is not detectable in the absence of cardiac muscle damage; serum concentrations increase only when troponin T is released from damaged myocytes during severe ischaemia^{4,5} or myocardial infarction.⁶ These studies showed that the diagnostic efficiency of troponin T measurements was better than that of total creatine kinase (CK) or CK-MB to CK ratios.

In the present study we attempted to evaluate myocardial cell damage after orthotopic heart transplantation by serial measurements of troponin T.

Patients and methods

PATIENTS

We studied 19 consecutive patients (mean (SD) age 52 (6) years, two women) who underwent orthotopic heart transplantation at the Department of Cardiac Surgery, University of Heidelberg, Germany, between November 1989 and March 1991. Blood samples (4 ml) were obtained routinely in the first three months after surgery: every 1-2 days during the first two postoperative weeks and every 2-7 days thereafter.

IMMUNOSUPPRESSIVE REGIMEN

All patients were treated with a standard regimen of cyclosporin, corticosteroids, and azathioprine. All patients were given antithymocyte globulin (ATG) after operation until therapeutic concentrations of cyclosporin were reached (mean 6 days). During the study period the target concentration of cyclosporin in whole blood was 250-400 $\mu\text{g/l}$ as assessed by radioimmunoassay with a monoclonal antibody. Administration of azathioprine was stopped when there were fewer than 4.0/nl blood leucocytes. Acute rejection episodes, diagnosed by endomyocardial biopsy, were initially treated with intravenous methylprednisolone (1 g daily for three days). One of the study patients received monoclonal

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Accepted for publication
21 December 1992

anti-T3-receptor antibodies (OKT3) for 10 days because of ongoing acute rejection despite two courses of intravenous methylprednisolone and one course of ATG.

TROPONIN T SERUM CONCENTRATIONS

Concentrations of circulating troponin T were measured by a one-step enzyme immunoassay with two specific monoclonal antibodies and streptavidin coated tubes as the solid phase.²⁵ The capture antibody was labelled with biotin, the second antibody was conjugated to horseradish peroxidase. We performed the assays within 90 minutes at room temperature using the Enzymun-Test system (Boehringer Mannheim GmbH, Germany) (range 0.20–15 $\mu\text{g/l}$).

STATISTICAL ANALYSIS

Student's *t* test or the analysis of variance was used as appropriate. Correlations between variables were tested by the (univariate or multivariate) least-squares linear regression analysis and the SAS statistical package (SAS Institute, Cary, Illinois).

Cumulative troponin T release was defined as the area under the troponin T serum concentration curve within the time interval of the study period (that is, 3 months after transplantation) and was calculated by the trapezoidal rule.

Continuous data are given as mean and SD.

Results

Figure 1 shows a typical time course for serum troponin T concentrations after heart transplantation. The troponin T concentration was 3.0 $\mu\text{g/l}$ on the first postoperative day, increased to a maximum of 3.6 $\mu\text{g/l}$ on day 5, and then decreased exponentially. The half time was approximately 10 days.

All 19 patients showed similar time courses of postoperative troponin T serum concentra-

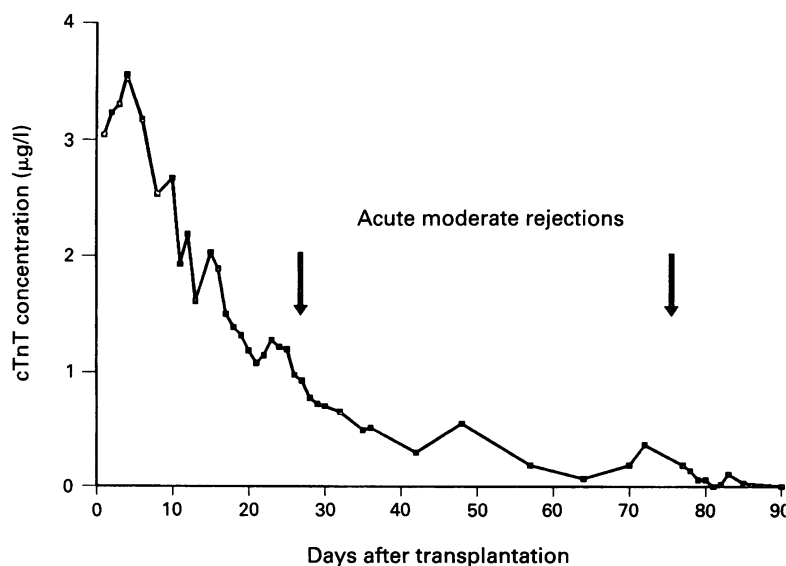


Figure 1 Serum concentrations of circulating cardiac troponin T (cTnT) in a 62 year old patient during the first 90 days after heart transplantation. Two episodes of moderate rejection (arrows) were preceded by a transient increase in troponin T serum concentrations.

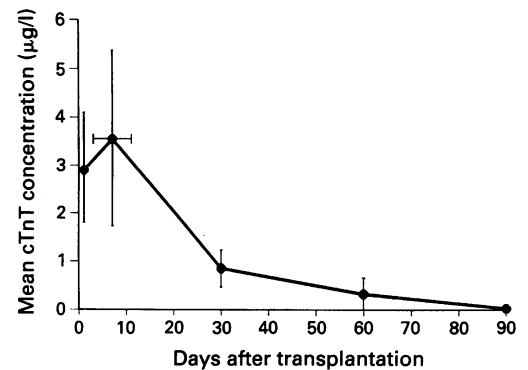


Figure 2 Mean (SD) serum concentrations of cardiac troponin T (cTnT) on the first postoperative day; at the time of peak troponin T release; and at 30, 60, and 90 days after heart transplantation in the 19 study patients.

tion. Mean serum troponin T concentrations (fig 2) reached a maximum of 3.6 (1.8) $\mu\text{g/l}$ at 7.1 (4.2) days after transplantation and remained higher than 0.5 $\mu\text{g/l}$ (that is, twice the detection limit of the assay) in all patients for at least 29 days (mean (SD) 59.1 (20.0) days). In most patients the pattern of troponin T release was unchanged during moderate and severe acute rejection episodes (fig 3). But as fig 1 shows, in some patients the rejection episode was preceded by a slight transient increase in troponin T release.

Cumulative troponin T release in individual patients ranged from 27 to 150 $\mu\text{g} \times \text{days/l}$ (mean, 71 (30) $\mu\text{g} \times \text{days/l}$). Cumulative troponin T release was not related to total ischaemic time before transplantation (fig 4), to the patient's renal or hepatic function, to preoperative cardiac diseases, or to matching for the major histocompatibility complex (MHC). Cumulative troponin T release was also similar in patients without acute rejection episodes during the first postoperative year (69 (18) $\mu\text{g} \times \text{days/l}$, $n = 4$) and in patients with one episode (76 (4) $\mu\text{g} \times \text{days/l}$, $n = 4$), two (80 (18) $\mu\text{g} \times \text{days/l}$, $n = 3$), and more than two episodes of acute rejection (67 (31) $\mu\text{g} \times \text{days/l}$, $n = 8$).

Cardiac catheterisation was routinely performed one year after transplantation. In all patients the epicardial coronary arteries did not show important narrowing and left ventricular function was normal.

Discussion

Because the serum half life of troponin T is only 120 minutes our data show that antigen release from disintegrating myofibres of implanted hearts must continue in the first months after heart transplantation. Cumulative troponin T release (fig 5) resembles that found in patients with minor Q wave myocardial infarction.² Troponin T release lasts longer after transplantation than after acute myocardial infarction,⁶ or coronary artery bypass grafting or valve replacement,⁷ (fig 5).

In patients with acute myocardial infarc-

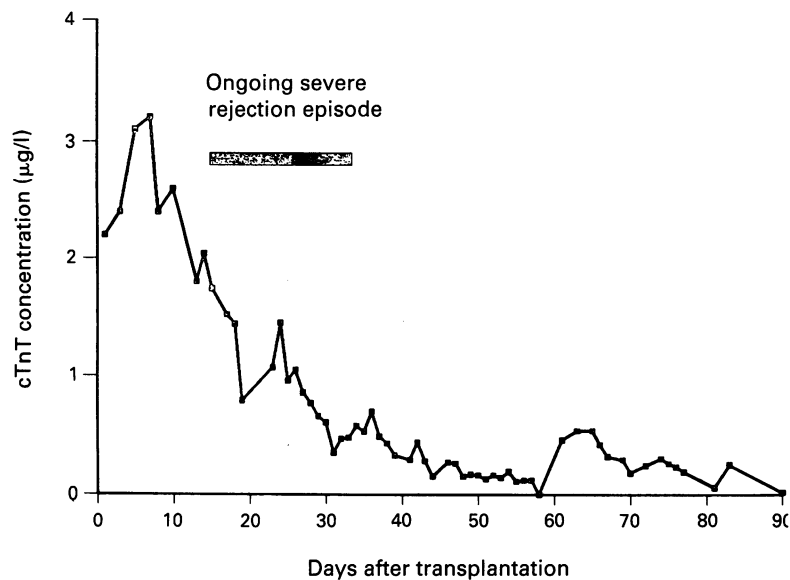


Figure 3 Time course of postoperative serum concentrations of cardiac troponin T (cTnT) in a 43 year old patient. A severe acute rejection occurred on day 14 after transplantation and was treated with two courses of intravenous methylprednisolone, one course of ATG, and a final course of OKT3. During the ongoing acute rejection episode, troponin T release seemed to be unaffected.

tion, troponin T appears in the circulation within 3-5 hours after onset of chest pain, and troponin T concentrations remain increased for at least six days but no longer than 21 days.⁴ Smaller amounts of circulating troponin T were also detectable after coronary artery bypass grafting or valve replacement; troponin T release and the length of time that troponin T appeared in the circulation were significantly related to the aortic cross clamp time during operation.⁶

Our results in patients with heart transplants differ from these earlier studies in several ways. First, troponin T release in our patients was not related to total ischaemic time before transplantation (fig 4). Secondly, the time course of troponin T release was different: concentrations of circulating troponin T increased during the first 5-10 days and were still detectable for a mean of 59 days after surgery (fig 5). Furthermore, there was considerable variation in cumulative troponin T release among the patients (range 27-150 $\mu\text{g} \times \text{days/l}$) and release was not associated with any of the clinical variables studied.

These observations are consistent with

Figure 4 No significant relation was seen between cumulative cardiac troponin T (cTnT) release and total ischaemic time before transplantation.

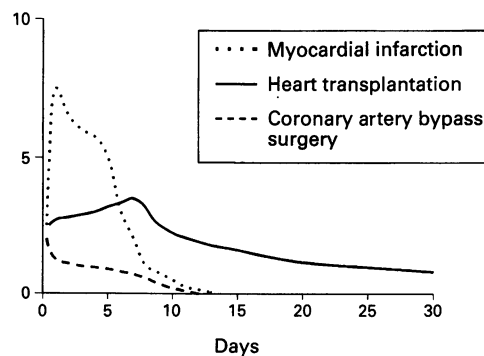
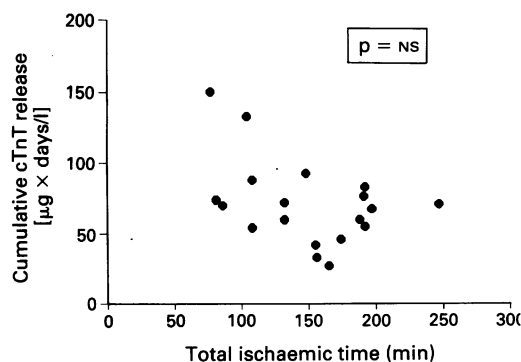


Figure 5 Time course of cardiac troponin T (cTnT) serum concentrations after minor Q wave myocardial infarction,⁶ heart transplantation (current data), and coronary artery bypass surgery⁷ during the first 30 postoperative days.

immunologically mediated changes rather than ischaemic damage being the underlying mechanism for troponin T release after heart transplantation. Such processes could be humoral (for example, preformed antibodies towards minor transplantation loci) or cellular, which remain active until immunosuppressive therapy and adaptation of the host immune system have taken full effect.

Scintigraphic investigations performed with indium-111 labelled antimyosin found evidence of prolonged sarcolemmal damage after heart transplantation.^{8,9} These studies showed considerable myocardial antimyosin uptake soon after transplantation with gradual reduction during the subsequent months. In some patients, however, cardiac uptake of antimyosin antibody continued for more than one year after heart transplantation and rejection related complications were more common in such patients. In our study, however, serum troponin T concentrations decreased below the detection limit of the assay within three months of transplantation in *all* patients (fig 2). The reason for the discrepancy between labelled antimyosin and troponin T, both markers of severe myocardial cell damage, remains unclear.

In five of the 19 current study patients episodes of acute rejection were preceded by a transient increase in troponin T release (fig 1). Because this was not a consistent finding (fig 3), these preliminary data indicate that troponin T measurements might not be sufficiently sensitive to detect acute rejection episodes soon after heart transplantation.

Measurement of concentrations of circulating troponin T in several serum samples showed continuing antigen release during the first three months after heart transplantation in quantities similar to minor Q wave myocardial infarction. Troponin T is released for considerably longer after transplantation than after myocardial infarction or other cardiac surgery. Furthermore, the amount of troponin T release varies considerably among the patients but is not related to clinical variables, such as total ischaemic time before transplantation or the number of acute rejec-

tion episodes after transplantation. These findings may be explained by prolonged leakage of cytosolic troponin T (from viable myocytes) as well as prolonged disintegration of myofibres (from irreversibly damaged myocytes) during the first months after heart transplantation.

This work was supported by a grant from the Deutsche Forschungsgemeinschaft/Bonn within the SFB 320 "Herzfunktion und ihre Regulation", Ruprecht-Karls-Universität, Heidelberg, Germany.

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