Cardiac-Specific Troponin I Levels and Risk of Coronary Artery Disease and Graft Failure Following Heart Transplantation

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The cardiac isoforms of troponins T and I have been used to evaluate myocardial cell damage associated with unstable angina and myocardial infarction or following cardiac surgery.1-6 Measurements of the cardiac-specific contractile proteins troponins T and I are superior to conventional measurement of other enzymes, such as creatine kinase MB, for detecting minor myocardial injury7,8 and are valid predictors of adverse events in patients with acute coronary syndromes.2,9-14 Investigations of the importance of cardiac troponins T and I in heart transplantation have been mainly focused on acute allograft rejection.15-19 It has been proposed that rejection episodes should lead to elevated serum troponin T concentrations following myocyte necrosis.15 However, data regarding this issue are controversial. Although some investigators have found a relationship between elevated serum troponin levels and acute allograft rejection, this has not been confirmed by others.15-19

The involvement of early microvascular events in the subsequent development of transplant coronary artery disease (CAD) and allograft failure in heart transplantation has also been established.20-23 Recipients who eventually develop transplant CAD or allograft failure show a prothrombogenic microvasculature and the presence of myocardial cell damage during the early months after transplantation.20,22,23

Context Previous studies have yielded conflicting data regarding whether a relationship exists between elevated cardiac troponin levels and acute allograft rejection in patients who have received heart transplants.

Objective To determine whether cardiac troponin I levels after heart transplantation were associated with a procoagulant microvasculature and long-term allograft outcome.

Design Prospective cohort study with a mean (SE) follow-up of 45.1 (2.5) months. Serum troponin I levels were measured 9.9 (0.2) times per patient during the first 12 months after heart transplantation.

Setting Heart transplant center in the United States.

Patients A total of 110 consecutive patients who received a heart transplant between 1989 and 1997 and survived at least 1 year after transplantation.

Main Outcome Measures Histological and immunohistochemical biopsy findings, development of coronary artery disease (CAD), and graft failure in patients with vs without elevated serum cardiac troponin I levels.

Results All recipients had elevated troponin I levels during the first month after transplantation. Troponin I levels remained persistently elevated during the first 12 months in 56 patients (51%) and became undetectable in 54 patients (49%). Persistently elevated troponin I levels were associated with increasing fibrin deposits in microvasculature and cardiomyocytes (P<.001). Patients with persistently elevated levels of troponin I had significantly increased risk for subsequent development of CAD (odds ratio [OR], 4.3; 95% confidence interval [CI], 1.8-10.1; P<.001) and graft failure (OR, 3.4; 95% CI, 1.2-9.7; P=.02), and also developed more severe CAD (OR, 4.2; 95% CI, 1.9-9.3; P<.001) and showed more disease progression (OR, 3.7; 95% CI, 1.3-10.4; P=.009).

Conclusion In this study, elevated cardiac troponin I levels, which are considered to be a noninvasive surrogate marker of a procoagulant microvasculature, identified a subgroup of patients with high risk for developing CAD and graft failure after cardiac transplantation.
This study was designed to determine whether patients with myocardial cell damage following transplantation could be identified using serum cardiac troponin I levels; to evaluate whether microvascular thrombosis and myocardial cell damage are persistent events after heart transplantation; and to examine whether the presence of persistent myocyte necrosis may be a useful prognostic indicator for long-term cardiac allograft outcome.

**METHODS**

**Patients**

We prospectively studied 110 consecutive adult cardiac allograft recipients who received a heart transplant at Methodist Hospital of Indiana between 1989 and 1997 and who were followed up for a mean (SE) of 45.1 (2.5) months after transplantation. Patients were enrolled in the study if they survived at least 1 year after their transplant, had pretransplantation and serial endomyocardial biopsy specimens obtained during the first year after transplantation for light microscopy and immunohistochemical studies, and had angiographic evaluations of coronary arteries. Coronary angiography was performed yearly with a mean (SE) of 3.6 (0.2) angiograms per patient.

Immunosuppression therapy consisted of prednisone at an initial dose of 1 mg/kg per day with the dose tapered to 0.5 mg/kg per day during the first month, to 0.2 mg/kg per day during the first 1 to 2 months, and to 0.1 mg/kg per day during months 3 through 12 after transplantation. Patients took this dose unless they developed complications attributed to steroid use. Azathioprine was administered at a dose of 1.5 to 2.0 mg/kg per day and cyclosporine at an initial dose of 7 to 10 mg/kg per day with the dose tapered to 3 to 5 mg/kg per day to maintain a specific whole-blood level of 300 to 480 ng/mL during the first 3 months, 180 to 360 ng/mL at 3 to 6 months, 90 to 180 ng/mL at 6 to 12 months, and 75 to 120 ng/mL at more than 12 months after transplantation, depending on renal function. Grade 3 and grade 4 rejection episodes were treated with steroids and rabbit antithymocyte globulin or mouse monoclonal antibody OKT3 to human lymphocytes.

Ejection fractions were measured by radionuclide ventriculography. Graft failure was defined as death associated with cardiac allograft dysfunction or need for a second transplant.

A control biopsy from the right ventricle was obtained before transplantation from all donor hearts. Endomyocardial biopsies were obtained by right heart catheterization at 7 to 10 days, every 2 weeks during the first 2 months, and at 3, 4.5, 6, 9, and 12 months after transplantation. Cellular infiltrates were graded according to guidelines from the International Society for Heart Transplantation. Coronary angiitis was defined as previously described.

**Evaluation of Cardiac Troponin I**

Blood samples were drawn into tubes without preservatives and centrifuged at 3000 g for 15 minutes. Serum troponin I levels were measured after transplantation and collected at 7 to 10 days, every 2 weeks during the first 2 months, and at 3, 4.5, 6, 9, and 12 months after transplantation. Cellular infiltrates were graded according to guidelines from the International Society for Heart Transplantation. Coronary angiography was performed yearly with a mean (SE) of 3.6 (0.2) angiograms per patient.

Heart transplant episodes were treated with steroids and rabbit antithymocyte globulin or mouse monoclonal antibody OKT3 to human lymphocytes.

Revised consensus definitions 

**Criteria for Diagnosis of CAD**

Coronary angiography was performed yearly with a mean (SE) of 3.6 (0.2) angiograms per patient.

Cardiac troponin I levels were measured with the OPUS immunoassay system (OPUS Plus Analyzer, Dade Behring, Newark, Del), which uses 2 goat polyclonal antibodies directed against different protein segments unique to the human cardiac isoform of troponin I. The immunoassay shows no detectable cross-reactivity with human skeletal-muscle troponin I and measures cardiac troponin I in serum up to 150 ng/mL. Because cardiac troponin I is undetectable in healthy volunteers, any level more than 0.5 ng/mL, which is the minimal concentration detectable by the assay, was considered abnormal.
comparing serial angiograms side-by-side with the baseline angiogram obtained the first year following transplantation. To reduce the possibility of donor-transmitted CAD, recipients having a normal angiogram during the first year after transplantation were studied during subsequent follow-up, and the first annual angiogram was considered to be the baseline angiogram.

**Immunohistochemistry**

Biopsies were embedded in optimum cutting temperature compound (Miles, Elkhart, Ind), snap frozen in liquid nitrogen, and stored at −20°C. Cryostat sections (4 µm) were air dried overnight without chemical fixation and reacted with monoclonal antibody 350 to fibrin (American Diagnostica, Greenwich, Conn). Antibody and control experiments were performed as described.20-22

The precise vascular localization of fibrin reactivity was performed using double and triple antibody experiments as described.20-22 Myocardial fibrin was evaluated semiquantitatively (scores 1-4) by 2 investigators unaware of the clinical or serological data as follows: score of 1 for no fibrin, score of 2 for fibrin in microvessels, score of 3 for fibrin in microvessels and around cardiomyocytes, and score of 4 for fibrin in microvessels and within cardiomyocytes.

**Statistical Methods**

All statistical tests used troponin I as a continuous variable (using base 10 logarithms) and excluded troponin I levels obtained during the first month after transplantation. The relationship between fibrin in serial biopsies and serial troponin I level measures was assessed with repeated measures analysis of variance. Subsequent analyses used each patient’s mean log troponin I level calculated from data obtained after the first month after transplantation. Spearman correlations were used to assess the relationship of clinical and demographic variables with troponin I.

The relationship between the average troponin I level and subsequent outcome was assessed with Cox proportional hazards and logistic regression. The assumption of proportionality was tested for Cox models and Hosmer-Lemeshow goodness-of-fit tests were used to validate logistic regression. To illustrate trends, we classified patients as having at least 1 detectable troponin I level during months 1 to 12 after transplantation or not having any detectable troponin I level after the first month following transplantation. These groups were compared with Kaplan-Meier estimates of CAD and graft failure. The same tests were subsequently compared.

### Table 1. Demographic and Clinical/Laboratory Data for Patients With Detectable or Undetectable Serum Cardiac Troponin I Levels During the First Year Following Transplantation*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Serum Cardiac Troponin I Level</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable (n = 54)</td>
<td>Detectable (n = 56)</td>
</tr>
<tr>
<td>Male recipient</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>Male donor</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>Age of recipient, mean (SE), y</td>
<td>48.1 (.3)</td>
<td>48.7 (.4)</td>
</tr>
<tr>
<td>Age of donor, mean (SE), y</td>
<td>28.4 (1.6)</td>
<td>27.7 (1.4)</td>
</tr>
<tr>
<td>Smoker</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Blood pressure, mean (SE), mm Hg</td>
<td>138.0 (1.3)</td>
<td>138.6 (1.5)</td>
</tr>
<tr>
<td>Systolic</td>
<td>89.2 (1.0)</td>
<td>88.5 (1.1)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>233.9 (15.2)</td>
<td>210.6 (13.0)</td>
</tr>
<tr>
<td>Triglyceride level, mean (SE), mg/dL‡</td>
<td>217.3 (5.0)</td>
<td>224.7 (5.2)</td>
</tr>
<tr>
<td>Cholesterol level, mean (SE), mg/dL§</td>
<td>130.0 (6.0)</td>
<td>152.4 (6.9)</td>
</tr>
<tr>
<td>Reason for transplantation</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Ischemic time, mean (SE), min</td>
<td>133.0 (.5)</td>
<td>54 (1.2)</td>
</tr>
<tr>
<td>HLA antigen mismatches, mean (SE)</td>
<td>1.4 (0.1)</td>
<td>1.4 (0.1)</td>
</tr>
<tr>
<td>A and B</td>
<td>2.9 (0.1)</td>
<td>2.9 (0.1)</td>
</tr>
<tr>
<td>DR</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Cell panel-reactive antibodies</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Donor-specific cytotoxic antibodies</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cellular infiltrates grades</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>1 or 2</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>3 or 4</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, mean (SE)</td>
<td>56.2 (1.2)</td>
<td>55.6 (1.4)</td>
</tr>
</tbody>
</table>

*Values are expressed as percentages unless otherwise indicated. †P values use log-troponin I as a continuous variable.
‡To convert to mmol/L, multiply by 0.0113.
§To convert to mmol/L, multiply by 0.0259.

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used with a subgroup of only those allografts without CAD during the first year after transplantation. Summary statistics are presented as mean (SE) and calculations were performed using SAS software (Version 6.12, SAS Institute Inc, Cary, NC).

**RESULTS**

A total of 110 consecutive cardiac allograft recipients had serial determinations of serum troponin I levels that were measured a mean (SE) of 9.9 (0.2) times per patient during the first 12 months after heart transplantation. Although all recipients had high concentrations of serum cardiac troponin I during the first month after transplantation, 1 group of patients showed undetectable levels after the first month of transplantation and continued to have undetectable levels during the subsequent 11 months after transplantation. Another group of recipients with initially higher troponin I levels during the first month after transplantation continued to have persistently detectable levels during the subsequent 11 months.

Troponin I levels remained persistently elevated during the first 12 months in 56 patients (51%) and became undetectable in 54 patients (49%) (Figure 1). Even during the first month after transplantation, the group that eventually stabilized to undetectable levels also had significantly lower troponin I levels than the group that maintained detectable levels (P = .003). No demographic or other clinical/laboratory variables were correlated with troponin I levels during the first year after transplantation and no relationship was found between elevated troponin I levels and the presence of cellular infiltrates within the biopsy specimens (Table 1).

The presence of myocardial fibrin was scored as shown in Figure 2. Increasing deposits of myocardial fibrin were associated with an increased proportion of serum samples with detectable troponin I levels of more than 0.5 ng/mL (Figure 3). Increasing amounts of myocardial fibrin were associated with increasing concentrations of serum cardiac troponin I (Figure 3). The presence of fibrin within the cardiomyocytes was consistently associated with the presence of coagulative myocyte necrosis (Figure 4), suggesting that fibrin in cardiomyocytes represents evidence of myocardial cell damage. When the deposition of myocardial fibrin was evaluated in serial biopsies of both study groups, significantly more myocardial fibrin (P < .001) was persistently found in the group with sustained detectable troponin I levels compared with the group showing undetectable levels following the first month after transplantation (Figure 5). This difference appeared immediately after transplantation and persisted throughout the first year.

Recipients who showed persistently detectable levels of serum troponin I during the first year after transplantation developed significantly more CAD and more graft failure than recipients with persistently undetectable levels following the first month of transplantation (Table 2). Kaplan-Meier estimates (Figure 6) indicated that CAD and graft failure rates at 5 years after transplantation among recipients with persistently detectable troponin I levels during the first year after transplantation were significantly higher (79.3% and 35.5%, respectively) when compared with recipients with persistently undetectable troponin I levels following the first month after transplantation (35.7% and 11.6%, respectively).
Recipients with persistently high levels of serum cardiac troponin I during the first year after transplantation developed more severe CAD, showed more disease progression, developed the disease earlier, and developed graft failure earlier than recipients with persistently undetectable troponin I levels after the first month following transplantation (Table 2).

Recipients with persistently detectable troponin I levels during the first year after transplantation were at significantly greater risks of CAD (hazard ratio [HR], 3.4; 95% confidence interval [CI], 1.9-6.2; \( P < .001 \)) and graft failure (HR, 3.1; 95% CI, 1.2-7.9; \( P = .02 \)) than recipients with persistently undetectable serum cardiac troponin I levels after the first month following transplantation.

To reduce the possibility of donor-transmitted disease, we evaluated allograft recipients who had a normal angiogram the first year after transplantation (\( n = 91 \)) and followed up this subgroup of patients during a period of 34.7 (2.9) months after their first angiogram. Allograft recipients who showed persistently detectable levels of serum troponin I during the first year after transplantation (\( n = 41 \)) developed significantly more CAD (odds ratio [OR], 3.9; 95% CI, 1.4-10.6; \( P = .008 \)) and more severe disease (OR, 3.7; 95% CI, 1.4-9.5; \( P = .007 \)) than allograft recipients with persistently undetectable troponin I levels following the first month after transplantation (\( n = 50 \)).

**COMMENT**

Microvascular thrombus formation often occurs in conjunction with myocardial cell damage in cardiac transplantation and is identified during the peritransplant period. A significant proportion of allografts show the presence of fibrin within the microvasculature and myocardial cells, indicating myocardial cell damage. It is therefore important to identify whether recipients with those myocardial changes show elevated levels of serum markers of cardiac necrosis, whether these changes persist during the period after transplantation, and whether the presence of sustained myocardial necrosis per se is a risk factor for subsequent transplant CAD or cardiac graft failure. Our study indicates that the detection of the highly specific marker cardiac troponin I in blood is an independent risk factor that noninvasively identifies patients who have immunohistochemical evidence of myocardial cell damage and who are at increased risk of developing CAD or graft failure.

Elevated troponin T or I levels are typical in the immediate period after transplantation, suggesting that early postoperative elevation of troponin levels is related to perioperative cardiac injury. Several factors could be associated with early myocardial injury. Although the possibility of preformed antiendothelial antibodies exists, it is difficult to assume that all recipients have preformed antibodies to the donor hearts because all recipients had elevated troponin I levels during the immediate period after transplantation. Another possibility is that myocardial cell damage is caused by acute cellular rejection. However, we did not find any association between the presence of cellular rejection episodes and increased serum troponin I. Indeed, recipients with increased serum cardiac troponin I levels did not have more episodes of rejection in matching endomyocardial biopsy specimens. The finding of elevated troponin I levels during the immediate period after transplantation in all cardiac transplant recipients suggests that the myocardial injury is perhaps secondary to an ischemic phenomenon. Perioperative ischemic myocyte injury is a common finding in heart transplant recipients.
Table 2. Relationship Between Serum Cardiac Troponin I Levels During the First Year Following Cardiac Transplantation and Development of Transplant Coronary Artery Disease and Graft Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Patients With Serum Cardiac Troponin I Level</th>
<th>Ratio (95% Confidence Interval)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable (n = 54)</td>
<td>Detectable (n = 56)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cases</td>
<td>16 (30)</td>
<td>35 (63)</td>
<td>4.3 (1.8-10.1)†</td>
</tr>
<tr>
<td>Cases with disease progression</td>
<td>7 (13)</td>
<td>18 (32)</td>
<td>3.7 (1.3-10.4)†</td>
</tr>
<tr>
<td>Cases by severity level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>38 (70)</td>
<td>21 (38)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7 (13)</td>
<td>14 (25)</td>
<td>4.2 (1.9-9.3)†</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (9)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (7)</td>
<td>17 (30)</td>
<td></td>
</tr>
<tr>
<td>Months without disease†</td>
<td>42.4 (3.5)</td>
<td>28.3 (2.6)</td>
<td>3.4 (1.9-6.2)§</td>
</tr>
<tr>
<td>Graft failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cases</td>
<td>6 (11)</td>
<td>16 (29)</td>
<td>3.4 (1.2-9.7)†</td>
</tr>
<tr>
<td>Progression to failure, mo‡</td>
<td>49.2 (3.9)</td>
<td>43.6 (3.3)</td>
<td>3.4 (1.2-7.9)§</td>
</tr>
</tbody>
</table>

*P values use log-troponin I as a continuous risk factor.†Indicates odds ratio (95% confidence interval), adjusted for time since transplantation.‡Indicates hazard ratio (95% confidence interval).

Figure 6. Coronary Artery Disease or Graft Failure in Recipients With Detectable or Undetectable Troponin I Levels

A, Kaplan-Meier estimates of the percentage of patients free of coronary artery disease and B, Kaplan-Meier estimates of the percentage of patients free of graft failure in recipients of cardiac allografts with undetectable troponin I levels after the first month following transplantation vs recipients with persistent detectable troponin I levels during the first year following transplantation.

During the immediate period after transplantation, these lesions, characterized by the presence of coagulative myocyte necrosis and infiltration of neutrophils and macrophages, are perhaps the same lesions recently described immunohistochemically by the presence of myocardial fibrin with neutrophil and macrophage infiltration and are probably the hallmark of ischemia and reperfusion.

The identification of a group of allografts with continuous deposition of fibrin and persistent elevation of cardiac troponin I levels suggests that these allografts for some reason remain in a sustained prothrombogenic status. One possible cause of such prothrombogenicity within the allograft microvasculature is related to the activation of endothelium. The recent finding of an association between the presence of myocardial cell damage, as evidenced by increasing concentrations of cardiac troponin T, with a prothrombogenic microvasculature and up-regulation of endothelial activation markers confirms this possibility. These changes in the allograft myocardium associated with the findings of elevated troponin I concentrations immediately following transplantation could be related to ischemia and reperfusion. It has been shown that tissue hypoxia can enhance induction of endothelial activation markers such as intercellular adhesion molecule 1 in human endothelial cells, and this can be inhibited by using antibodies to intercellular adhesion molecule 1 or antisense oligodeoxynucleotides. Ischemia and reperfusion increase both endothelial cell surface and soluble adhesion molecules, and blocking expression of those molecules significantly improves allograft outcome.

An important component of the activation of endothelial cells is the up-regulation of tissue factor, which promotes thrombogenicity. A prothrombogenic microvasculature facilitates the continuous deposition of fibrin, which is characteristic of a group of allografts in the present study. Persistent thrombus formation could explain recurrent myocardial cell damage with concomitant elevation of cardiac troponins. The prothrombogenicity within the allograft microvasculature sustains the cycle, promoting further endothelial activation and deposition of fibrin.

Two recent studies demonstrated that the use of glycoprotein IIb/IIIa-receptor antagonists in troponin I- and troponin T–positive patients with acute coronary syndromes significantly improves outcome. These data suggest that a single treatment or periodic brief treatments with glycoprotein IIb/IIIa-receptor inhibitors may be a possible approach to breaking this cycle in heart transplant patients. It has also recently been demonstrated that the presence of microvascular fibrin is associated with depletion of vascular tissue plasminogen activator and the presence of tissue plasminogen activator complexed to plasminogen activator inhibitor 1, suggesting that tissue plasminogen activator inhibitor 1 could favor a persistent depletion of vascular tissue plasminogen activator and subsequent increased risk of vascular disease in cardiac allografts.

The association of elevated cardiac troponin I in allografts with increased...
risk of developing transplant CAD or graft failure is of particular relevance. First, serum cardiac troponin I levels could be used as a predictor of subsequent outcomes in cardiac transplantation. The identification of noninvasive (and immunologic) predictors of transplant CAD and graft failure is essential since the use of a noninvasive technique is less costly and less inconvenient for the patient and involves significantly less risk. Second, the relationship between microvascular perturbations and myocardial cell damage with arterial epicardial disease supports a vascular compromise in the allografts. The involvement of arteries, arterioles, capillaries, and veins in transplant CAD has been demonstrated by several investigators and suggests that changes that occur in large vessels are concomitantly occurring in the small microvessels. Third, all these changes promote vascular occlusion with ischemia and myocardial cell damage, which if not corrected, ultimately will end in cardiac graft failure.

The potential limitations of this study need to be considered. First, basal determinations for donors' cardiac troponin I levels were not available to evaluate the presence of myocardial damage in donor hearts before transplantation. However, the absence of myocardial fibroin detected immunohistochemically in endomyocardial biopsies obtained before transplantation suggests there is probably no significant myocardial cell death in donor hearts before transplantation. Second, because samples were stored at −75°C for up to 10 years, we cannot exclude the possibility of protein degradation. However, we found no negative correlation between specimen age and the presence of serum samples with elevated troponin I levels. Third, the unavailability of a continuous evaluation of the status of the coronary arteries since the time of transplantation precludes precise determination of the time course for the association between cardiac troponin I levels and development of CAD. However, the finding of high cardiac troponin I levels 7 to 10 days after transplantation in all recipients who subsequently developed transplant CAD suggests that elevated cardiac troponin I levels precede the development of the disease. Fourth, the use of coronary angiography and the lack of intracoronary ultrasonographic studies could be another limiting factor. However, although intravascular ultrasonography is more sensitive for detecting CAD in epicardial arteries, it lacks accessibility to more peripheral arteries, which can be assessed using coronary angiography. Irrespective of the technique used to evaluate the status of the coronary arteries, the measurement error using each particular technique would be similar in all recipients.

In summary, our findings suggest that serum cardiac troponin I levels can be used as a surrogate marker to identify heart transplant recipients at risk of developing CAD or graft failure but not to identify the presence of cellular rejection. A strong association between immunohistochemical evidence of thrombus formation and myocardial cell damage within the allografts with the presence of elevated serum cardiac troponin I levels and subsequent outcome indicates that the status of the microvasculature is essential for the survival of the allografts. The presence of elevated cardiac troponin I levels immediately after transplantation in cardiac transplant recipients suggests the need for intervention before transplantation to protect the microvasculature within the donor hearts, perhaps by improving the preservation of the donor organs or preparing the recipient in advance to prevent damage during the reperfusion period.

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REFERENCES


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TROPONIN I LEVELS AFTER HEART TRANSPLANTATION


34. Labarrere CA. Relationship of fibrin deposition in microvascularity to outcomes in cardiac transplantation. *Curr Opin Cardiol*. 1999;14:133-139.


Science, like art, music and poetry, tries to reduce chaos to the clarity and order of pure beauty.
—Detlev W. Bronk (1897-1975)