Plasma Ultrasensitive Cardiac Troponin During Long-Term Follow-up of Heart Transplant Recipients

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ABSTRACT

Background: Plasma troponin is a risk factor for cardiac events in various populations. We evaluated the determinants and predictive value of plasma cardiac troponin I (cTnI) during the long-term follow-up of heart transplantation.

Methods and Results: We prospectively measured cTnI in 100 heart transplant recipients, 13.0 ± 6.0 years after transplantation, during a routine visit including echocardiography and laboratory measurements. The patients were followed for 21.3 ± 4.9 months after this troponin measurement. cTnI ≥0.006 μg/L (detection threshold) was found in 37 of these 100 patients. Plasma troponin significantly increased with the presence and severity of coronary lesions detected by means of coronary angiography and was significantly associated with age, left ventricular mass, history of post-transplantation heart failure, body mass index, and plasma creatinine. Of 37 patients with cTnI ≥0.006 μg/L, 13 had a cardiac event during follow-up compared with 2 of 63 patients with cTnI <0.006 μg/L ($P < .0001$). The relation between cTnI and cardiac events remained significant in multivariate analysis.

Conclusions: cTnI is frequently detectable during long-term follow-up after heart transplantation and is associated with chronic graft rejection and renal failure. A detectable cTnI may help identify heart transplant recipients at high risk of cardiac events. (*J Cardiac Fail 2015;21:103−107*)

Key Words: Heart transplantation, troponin, chronic rejection, prognosis.

Cardiac events are among the frequent morbidities and causes of death following heart transplantation.[1] Many markers have been previously associated with these events, such as sex, body mass index (BMI), presence of diabetes, left ventricular ejection fraction, diastolic dysfunction, plasma B-type natriuretic peptide, creatinine, cholesterol, and uric acid.[2−7] Other risk factors have been established for developing cardiac allograft vasculopathy (CAV) within 5 years of transplantation, such as OKT3 induction, azathioprine versus mycophenolate at discharge, cyclosporine versus tacrolimus at discharge, recipient history of pulmonary embolism, and acute rejection before discharge.[1] However, these risk factors have several limitations. First, in most cases the predictive value of these factors has been established only for the early prognosis after transplantation. Second, none of them has a sufficient predictive value to be recommended in routine prediction.

Plasma troponin accurately predicts cardiac events in the general population as well as in patients with stable coronary artery disease, hypertrophic cardiomyopathy, heart failure, or end-stage renal failure.[8−16] Two studies have evaluated the prognostic utility of plasma troponin early after transplantation.[17,18] Labarrere et al have shown that patients with persistently detectable levels of serum troponin I during the first year of transplantation had a high risk for developing graft failure.[17] Erbel et al have found that cardiac troponin T concentrations measured early after transplantation represent a strong and independent risk predictor of death.[18] Perioperative injury is the more plausible explanation for early troponin elevation after transplantation. In late follow-up, troponin elevation has been associated with graft rejection.[19] Outside of this context,

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little is known about plasma troponin beyond the 1st year after heart transplantation. In the present study, we prospectively evaluated the determinants and prognostic value of plasma cardiac troponin I (cTnI) levels measured during routine follow-up >3 years after heart transplantation.

Methods

Population and Study Design

This prospective study was conducted in the transplant center of La Timone hospital, Marseille, France. From June 2011 to June 2012, we recruited patients who underwent heart transplantation at our center and were of legal age at the time of the study. Exclusion criteria were hospitalization at the time of blood sampling, acute graft rejection at the time of the visit, and time since transplantation <36 months.

All patients underwent physical examination, echocardiography, and laboratory measurements. Echocardiography was performed by an experienced physician (P.A.). Measurements were performed according to the recommendations of the American Society of Echocardiography (ASE).[20] ASE cube left ventricular mass was calculated with the use of 2-dimensional targeted M-Mode. Cardiac allograft vasculopathy was defined as irregularities or stenoses at conventional coronary angiography. Cardiac events were defined as cardiac death, acute coronary syndrome, coronary revascularization, and hospitalization for cardiac cause. Informed consent was obtained from each patient.

Laboratory Procedures

After overnight fast, venous blood samples (10 mL) were collected into tubes containing heparin. The concentration of cTnI was measured in a Centaur (Siemens) apparatus with the use of 1 polyclonal and 2 monoclonal antibodies for a chemiluminescence signal. The 99th-percentile value in a healthy population given by the manufacturer was 0.04 μg/L and the detection threshold 0.006 μg/L. The coefficient of variation was <10% in the measuring range of 0.006 to 50 μg/L.

Statistical Analysis

Intergroup comparisons were done with the use of unpaired Student *t* test or chi-square analysis. For creatinine clearance, a logarithmic transformation was performed because of a skewed distribution.

The predictive value of cTnI for 1st cardiac event was determined with the use of Kaplan-Meier survival analysis and a Cox model. Survival was compared with the use of log rank test.

Results

Patient Characteristics

One hundred heart transplant recipients were included 13.0 ± 6.0 (mean ± SD) years after transplantation. Clinical and biochemical characteristics of these patients are reported in Table 1. Four patients had combined renal-heart transplantation and 5 combined heart-lung transplantation.

Determinants of cTnI

Plasma cTnI was <0.006 μg/L in 63 patients. In the 37 other patients, the range of plasma troponin was 0.006−3.0 μg/L, and 10 patients had cTnI over the 99th percentile (0.04 μg/L). The patient with cTnI = 3.0 μg/L had an elevated CK MB plasma level and no clinical or electrocardiographic signs of acute coronary syndrome. cTnI ≥0.006 μg/L was significantly associated with older age, previous angiographic evidence of CAV, high left ventricular mass, a history of post-transplantation heart failure, high BMI, and low creatinine clearance (Table 1). As shown in Figure 1, the percentage of patients with detectable cTnI increased with the severity of CAV. The association between cTnI and time since transplantation or age at transplantation was borderline significant. There was no significant association between cTnI ≥0.006 μg/L and sex, diabetes, a history of pre-transplantation coronary disease, or type of calcineurin inhibitor (Table 1).

Table 1. Baseline Characteristics According to Troponin Levels

	cTnI <0.006 μg/L	cTnI ≥0.006 μg/L	*P* Value
n	63	37	
Sex (M/F)	42/21	28/9	.5
Age (y), mean ± SD	52.1 ± 17.7	61.6 ± 15.9	.009
Age at transplantation (y), mean ± SD	40.0 ± 16.9	46.4 ± 13.8	.06
Pre-transplantation ischemic cardiopathy (%)	10 (16%)	9 (24%)	.4
Time since transplantation (y), mean ± SD	12.1 ± 5.7	14.5 ± 6.2	.05
BMI (kg/m^2), mean ± SD	23.5 ± 4.1	25.7 ± 5.7	.03
Patients with diabetes	6	7	.3
On renal dialysis	4	2	
Left ventricular mass (g), mean ± SD	189 ± 53	160 ± 46	.005
Angiographic coronary artery disease (%)	16 (25%)	22 (59%)	.001
History of post-transplantation heart failure	2	7	
On cyclosporine	43	18	.08
On tacrolimus	20	19	.08
On corticosteroids	29	6	.005
On mycophenolate	45	2	
On azathioprine	17	6	.3
On everolimus	1	1	
Creatinine clearance, (ml/min) mean ± SD	61.9 ± 30	46.3 ± 28	.008