TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

High-sensitive Troponin T measurements early after heart transplantation predict short- and long-term survival

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Keywords
heart transplantation, prognosis, survival, Troponin T.

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Conflicts of Interest
The authors have declared no conflict of interest.

Received: 11 April 2012
Revision requested: 15 May 2012
Accepted: 30 October 2012
Published online: 17 December 2012

doi:10.1111/tri.12024

Summary

Following heart transplantation, cardiac biomarkers remain elevated for several weeks eventually as a result of membrane leakage of the donor organ. We now test the predictive power of blood levels of troponin T (TNT) measured by the new hsTNT assay (Roche Diagnostics, Roche Diagnostics, Mannheim, Germany) early after heart transplantation. TNT was determined in 141 cardiac allograft recipients and 40 controls. Our findings demonstrate that patients who died within the first year after transplantation had significantly higher median hsTNT serum levels 6 weeks after transplantation (156 ng/l ± 203 vs. 29 ng/l ± 21, $P = 0.0002$). Using ROC analysis, a serum hsTNT concentration of 33.55 ng/l 6 weeks after transplantation was found to be the best cutoff to predict death at 1 year (HR 0.16, 95%CI:0.05–0.46, $P = 0.001$) with a sensitivity of 90.91% and a specificity of 70.97%. In addition, survival at 5 years (HR 0.15, 95% CI 0.06–0.35, $P < 0.0001$) was significantly better among patients below that cutoff value. In multivariate analysis, hsTNT serum level 6 weeks after transplantation emerged as an independent predictor for first-year mortality (hsTNT–HR 0.90, 95% CI: 0.81–1.00, $P = 0.03$). Cardiac troponin T concentrations early after transplantation as measured with a highly sensitive assay represent a strong and independent risk predictor of death after heart transplantation.

Introduction

Heart transplantation (HTX) is an established treatment for end-stage heart failure of any cause including congenital heart disease and cardiomyopathy. Overall, 1-year survival is up to 85% [1,2]. Graft failure, acute rejections, and infections are the leading causes of death during the first year; thereafter, cardiac allograft vasculopathy and malignancy are the major causes of death [1,2].

Cardiac troponin T (TNT) and troponin I are the most specific and sensitive laboratory markers of myocardial cell injury and therefore have replaced creatine kinase MB as the gold standard [3,4]. As TNT is expressed only in myocytes, other conditions than myocardial ischemia including acute pulmonary embolism (PE), myocarditis, heart failure, sepsis, and end-stage renal disease account for elevated TNT values, too [5]. These combinations are associated with an adverse prognosis and should be sought after actively [6]. In cardiac allograft recipients, a described continued release of TNT over 2–3 months after heart transplantation has been reported [7]; however, the underlying reasons still remain unclear. In some cases, episodes of early postoperative rejection seemed to be accompanied by mild rises in TNT serum levels, masked mainly, however, by the high troponin T background concentrations [8]. In addition, we and other showed that elevated TNT serum levels are related to severe histological acute rejection [7,9]. Consistently, Labarrere *et al.* reported that elevated serum levels of TNT seem to be associated with transplant vasculopathy development within the first year [10,11]. However, the

usually used conventional technique for troponin determination is limited by low sensitivity and positive prediction.

Recently, a new highly sensitive cardiac troponin T (hsTNT) assay was developed, decreasing the diagnostic threshold to the 99th percentile value, thus measurement of TNT concentrations that are lower by a factor of 10 than those detectable with conventional assays [12]. The objective of this study was to evaluate if the hsTnT assay represents a good tool to differentiate between patients with a high or low risk for major complications after heart transplantation.

Materials and methods

Heart-transplant patients

We studied 141 nonconsecutive heart-transplant patients who had received heart transplant at the Heidelberg Heart Transplant Center from January 1997 to January 2008 and received regular routine follow-ups. Data were retrieved from our institutional database (MS Access, Microsoft, Seattle, WA, USA). All serum samples were stored at −80 °C until use. In addition, we collected 40 serum samples from apparently healthy subjects. Control subjects were apparently healthy probands. For this study, they were checked for heart problems using ECG, echocardiography and (if necessary) stress testing. Only subjects with inconspicuous examination results were included in this study as controls. Patients with severe renal failure (creatinine above 2 mg/dl) within the first 6 months were not included in the study. In addition, acute cellular and humoral rejection, diagnosed by endomyocardial biopsy, infection (viral/bacterial), or myocarditis were excluded if it was within 4 weeks before and/or after the time of blood sampling. Of the 141 patients, 14 subjects died within the first year, another 12 between the second and the fifth year after transplantation. The causes of death within the first year were infections in 72% ($n = 10$), myocardial infarctions in 7% ($n = 1$), and acute rejections, diagnosed by endomyocardial biopsies, in 21% ($n = 3$). The causes of death within the second and fifth year were infections in 58% ($n = 7$), myocardial infarctions in 25% ($n = 3$), and cancer in 17% ($n = 2$). Detailed baseline characteristics for all patients are shown in Table 1 and for control subjects in Table 1 of supplemental material. Patients gave written consent, and the study was approved by the local institutional ethics committee. The presence of transplant vasculopathy was diagnosed by coronary angiography and by strain-encoded cardiac magnetic resonance [13].

Determination of plasma lipid concentration, plasma cell composition

Total serum cholesterol, triglycerides, leukocytes, C-reactive protein (CRP), and creatinine were analyzed using a standard method by the department of clinical chemistry of the chemistry of Heidelberg.

Troponin measurements

Peripheral venous blood was collected, centrifuged at 3000 ***g*** for 10 min; serum was separated and stored in aliquots at −80 °C until further analysis as described previously [14]. We used the Elecsys®/cobas TNT fourth-generation assay (Roche Diagnostics), analyzed by Elecsys 2010/cobas e411 and Modular® Analytics E170/cobas e601 immunoanalyzers (Roche Diagnostics) as described previously [12]. The assay uses fragment antigen-binding (FAB) fragments of 2 TNT specific mouse monoclonal antibodies in a sandwich format [12]. Epitopes located in the central part of the TNT molecule (amino acid positions 125–131 and 135–147, respectively) will be recognized by antibodies [12]. Detection is based on an electrochemiluminescence immunoassay (ECLIA), using a Tris(bipyridyl)-ruthenium(II) complex as label [12].

Statistical analysis

Quantitative values are expressed as mean (±SD) and qualitative values as percentages. Analysis was performed using Graph Pad Prism 5.0 software (GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA USA). We compared the characteristics of patients who died within the first year and long-term survivors by chi-squared test. We grouped the patients according to first-year mortality and compared the groups by Mann–Whitney test. The hsTNT serum levels 6 weeks after surgery were further analyzed by receiver operating characteristic (ROC). Survival curves were estimated using the Kaplan–Meier method and compared by the log-rank (Mantel-Cox) test. Values of $P < 0.05$ were considered statistically significant. In addition to a multivariate analysis using the logistic regression model, we adjusted the relation between hsTNT serum levels 6 weeks postprocedural and variables known to influence the first-year mortality.

Results

Patients' characteristics

A total of 181 serum samples from 141 heart-transplant patients and 40 healthy subjects with complete follow-up were collected at the Heidelberg Heart Transplant Center from January 1997 to January 2008. Baseline characteristics are shown in Table 1. No differences were seen according to the immunosuppressive therapy between the groups (not shown).

hsTNT serum levels in heart-transplanted patients

With the highly sensitive assay, concentrations of cardiac troponin T were at or above the limit of detection (1 ng/l)

Table 1. Patient demographic and clinical characteristics at baseline.

Parameter	Value	hsTNT > 33.55 ng/l	hsTNT < 33.55 ng/l	*P*-value
Demographics, *n* ± SD				
No. Patients, *n* (%)	141	46 (39)	95 (61)	
Gender – male, *n* (%)	101 (72)	33 (72)	68 (72)	NS
Side diagnosis, *n* (%)				
Hypertension	92 (65)	24 (52)	68 (72)	NS
Hypercholesteremia (>200 mg/dl)	65 (46)	25 (54)	40 (42)	NS
Hypertriglyceridemia (>150 mg/dl)	82 (58)	39 (84)	43 (45)	0.02
Diabetes Mellitus	50 (36)	17 (37)	33 (35)	NS
Transplant vasculopathy, *n* (%)	67 (47)	33 (71)	34 (36)	0.02
Tumor, *n* (%)	12 (8)	6 (13)	6 (18)	NS
Reduced LVEF (<55%), *n* (%)	17 (15)	8 (17)	9 (10)	NS
Etiology for HTx, *n* (%)				
Cardiomyopathy	85 (60)	28 (60)	57 (60)	NS
Ischemic heart disease	47 (33)	17 (39)	30 (32)	NS
Amyloidosis	7 (5)	1 (1)	6 (6)	NS
Other	2 (1)	0 (0)	2 (2)	NS
Baseline immunosuppressive therapy				
Cyclosporin, ng/ml ± SD (*n* = 36)	108.8 ± 12	106.7 ± 13	110.3 ± 12	NS
Tacrolimus, g/ml ± SD (*n* = 83)	10.5 ± 2,3	10.4 ± 1.9	10.5 ± 2.5	NS
MMF, g ± SD (*n* = 120)	2.2 ± 0.7	2.3 ± 0.6	2.1 ± 0.9	NS
Everolimus, mg ± SD (*n* = 11)	3.3 ± 1.1	3.6 ± 1.5	3.0 ± 0.8	NS
Sirolimus, μg/l ± SD (*n* = 11)	9.3 ± 1.4	8.9 ± 1.5	8.9 ± 3.2	NS
Steroid dose*, mg ± SD	8.0 ± 4.4	8.3 ± 4.7	7.8 ± 4.2	NS
Laboratory values				
Hemoglobin (g/dl) ± SD	11.8 ± 1.9	11.6 ± 1.8	11.9 ± 1.9	NS
NT_BNP, mg/dl ± SD	1086 ± 1678	1241 ± 1786	936 ± 1579	0.02
Leukocytes, /nl ± SD	6.3 ± 1.5	6.4 ± 1.5	6.2 ± 1.5	NS
CRP, mg/l ± SD	7.3 ± 5.8	8.1 ± 6.8	6.0 ± 3.9	NS
Creatinine, mg/dl ± SD	1.39 ± 0.5	1.43 ± 0.6	1.35 ± 0.3	NS
Acute rejections (ISHLT classification)				
No. rejections per patient	8.7	8.5	8.9	NS

LVEF, left ventricle ejection fraction; MMF, mycophenolate; NT_BNP, N-terminal brain natriuretic peptide; CRP, C-reactive protein.
P-value – hsTNT > 33.55 ng/l vs. hsTNT < 33.55 ng/l.
*Prednisolone.

in 121 transplanted patients (94%) and at or above the 99th percentile for apparently healthy subjects ($\geq$ 14 ng/l) in 84 cardiac allograft recipients (66%) 6 weeks after transplantation. In addition, serum hsTNT levels 6 weeks after transplantation were significantly higher in cardiac allograft recipients compared with apparently healthy subjects ($P < 0.0001$, Table 2). This study underlined the results of hsTNT serum levels in control subjects showing that the median hsTNT serum level was 3.5 ng/l ± 1.7, thus below 14 ng/l, the 99th percentile for apparently healthy subjects ($n = 40$, Table 2) [15]. Notably, there was no correlation found between creatinine and hsTNT serum levels ($r = 0.11$, *P*-value 0.78).

Table 2. hsTNT serum levels in cardiac allograft recipients 6 weeks after heart transplantation and healthy controls. The transplanted patients were grouped according to the first-year mortality.

	hsTNT, ng/l	
	Median	SD
Healthy subjects ($n = 40$)	3.5	1.7
Cardiac allograft recipients ($n = 141$)	65	120
P-value	<0.0001	
Patient who died within the first year ($n = 14$)	155.8	203
Patient who survived the first year ($n = 127$)	29.0	21
P-value	0.0002	

hsTNT predicts outcome in patients after heart transplantation

To examine a predictive value of hsTNT for the risk of lethal complications within the first year after transplantation, we measured hsTNT levels 6 weeks after transplantation in 141 heart-transplant recipients who died within the first year ($n = 14$) as compared with survivors ($n = 126$). The study demonstrated that using univariate analysis 6 weeks after transplantation, hsTNT serum levels were considerably higher in cardiac allograft recipients who died within the

first year after transplantation compared with patients who survived the first year (155.8 ± 203 ng/l vs. 29 ng/l ± 21, $P = 0.0002$, Table 2).

To determine the diagnostic efficacy of hsTNT concentrations in predicting cardiac allograft recipients with a high risk to die within the first year, we used the ROC analysis. A serum hsTNT concentration of 33.55 ng/l was found to be the best cutoff value to predict death within 1 year with a diagnostic sensitivity of 90.91% (AUC 0.88, 95%CI: 0.77–0.98, $P = 0.0002$, Fig. 1) with a negative predictive value of 86.1%. The diagnostic specificity was lower, yielding a specificity of 70.97% with a positive predictive value of 56.2%.

Using the ROC-based hsTNT, cutoff survival was significantly better (Fig. 2) among heart-transplant recipients with hsTNT concentrations below cutoff (HR 0.16, 95% CI: 0.05–0.46).

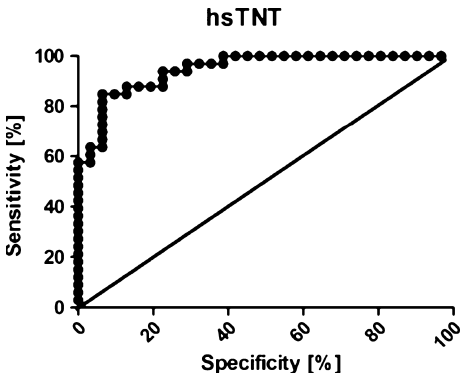

Figure 1 ROC analysis of hsTNT serum levels for first-year mortality. ROC analysis of the prognostic value of hsTNT for first-year mortality 6 weeks after transplantation. Designed by ROC analysis, a cutoff hsTNT serum level of 33.55 ng/l 6 weeks after surgery was found to be the best cutoff value to classify patients with a high risk to die within 1 year.

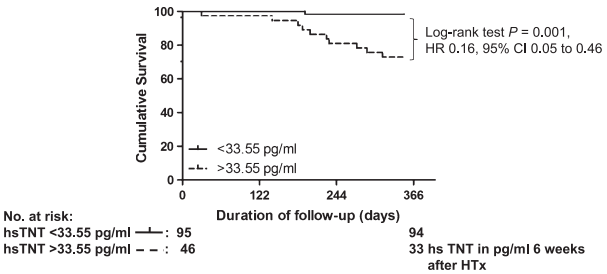

Figure 2 Prognostic value of hsTNT for first-year mortality. Serum hsTNT levels were measured 6 weeks after heart transplantation in 141 cardiac allograft recipients. The patients were grouped according to hsTNT serum levels above or below the cutoff of 33.55 ng/l designed by ROC analysis, shown in a Kaplan–Meier curve and analyzed by log-rank test.

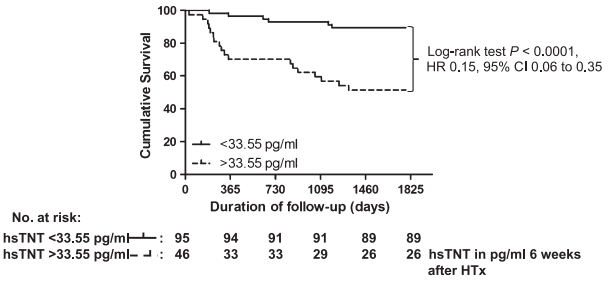

Figure 3 Prognostic value of hsTNT for 5-year survival. Serum hsTNT levels were measured 6 weeks after heart transplantation in 141 cardiac allograft recipients. The patients were grouped according to hsTNT serum levels above or below the cutoff of 33.55 ng/l designed by ROC analysis, shown in a Kaplan–Meier curve and analyzed by log-rank test.

Table 3. Multivariate analysis for 1-year death rate in relation to other known risk factors and creatinine.

	Mean value				
Confounder	>33.55 ng/l	<33.55 ng/l	OR	95% CI	*P*-value
hsTNT	1 155.8	29.0	0.90	0.81–1.00	0.03
Pulmonary artery pressure	1 33.5	25.8	1.13	0.96–1.32	0.11
Pulmonary artery resistance	1 214	172	0.99	0.97–1.00	0.27
Ischemic time	1 207	191	0.91	0.83–1.00	0.06
Age of donor heart	1 41.8	42.3	0.94	0.85–1.64	0.73
Creatinine	1 1.38	1.40	0.98	0.80–2.25	0.78
No. acute rejection	1 9.2	8.4	1.09	0.98–1.81	0.53

To evaluate whether the significant difference between the groups according to the cutoff persist over time, we analyzed 5-year follow-up of the patients included in this study. Indeed, we found that the difference in the outcome between both groups persists over an observation period of 5 years. Cardiac allograft recipients with a serum level of hsTNT below the cutoff of 33.55 ng/l 6 weeks after transplantation had a highly significant better 5-year survival rate than patients with a hsTNT serum level above the cutoff (HR 0.15, 95% CI 0.06–0.35, $P < 0.0001$, Fig. 3).

We added a multivariate analysis adjusting for potential confounding variables including pulmonary artery pressure and pulmonary artery resistance, both diagnosed within 1 week before transplantation, ischemic time, age of donor heart, creatinine and number of acute rejections, diagnosed by endomyocardial biopsy. In a multivariate analysis, hsTNT serum levels remained an independent risk predictor of lethal complications within the first year (hsTNT–HR 0.90, 95% CI: 0.81–1.00, $P = 0.03$, Table 3).

Discussion

Heart transplantation is a therapy for end-stage heart failure of any cause. However, graft failure, infection, and acute rejection still limits first-year survival after heart transplantation. Most of these acute sequelae are associated with myocyte death, which renders cardiac troponin an ideal tool to monitor heart transplant recipients and predict adverse prognosis.

This study findings demonstrate that circulating levels of TNT are now detectable in the great majority of cardiac allograft recipients using a more sensitive TNT assay. Troponin concentrations at 6 weeks post-heart transplant are significantly higher among patients who died within the first year as compared with survivors ($P = 0.0002$), and hsTNT serum levels above 33.55 ng/l provide a strong predictive value for death of any cause within the first year. In multivariate analysis adjusting for potential confounders, hsTNT persisted as a strong and independent prognosticator (HR 0.90, 95% CI: 0.81–1.00, $P = 0.03$).

With the use of conventional assays, the prevalence of detectable concentrations of TNT in the general population is approximately 0.7% [16]. Data of our group showed that in heart-transplanted patients without graft rejection or infection, the proportion of positive troponin T tests was 25.7% [7]. According to hsTNT, a multicenter study established the 99th percentile value of hsTNT at 14 ng/l. We recently demonstrated that the 99th percentile of the distribution of hsTNT values in apparently healthy subjects was determined at 14 ng/l [12]. This study shows that in the majority of cardiac allograft recipients, hsTNT serum levels are detectable, which is in line with a recently published study [17]. Applying this cut point of 14 ng/l to this study, two-third of cardiac allograft recipients showed hsTNT serum levels above the cutoff. Elevated hsTNT may be attributable to acute or chronic myocardial damage, such as acute or chronic heart failure, myocarditis, acute pulmonary embolism, or chronic pulmonary hypertension, but also associated with extracardiac disease such as end-stage renal failure or severe sepsis. Regardless of the exact reason, elevated TNT concentrations indicate adverse prognosis [15]. The underlying mechanisms responsible for the release of low levels of cardiac troponin T in cardiac allograft recipients is not fully understood, but may include clinically silent ischemic episodes and small vessel occlusions caused by transplant vasculopathy, inflammatory processes such as an acute or chronic rejection or cardiac infection (viral/bacterial), cardiomyocyte apoptosis, pulmonary arterial hypertension, reduced renal clearance, at least in parts based on immunosuppressive therapy, and increased myocardial strain owing to pressure or volume overload. However, by excluding acute cellular and humoral rejection, diagnosed by endomyocardial biopsy, infection (viral/bacterial) or myocarditis, these possible mechanisms could be excluded as an underlying cause of elevated hsTNT levels. But transplant vasculopathy was significantly more frequent in patients with elevated hsTNT. In addition, there was a trend for an association with pulmonary hypertension and ischemic time. Thus, it might be more likely that detectable hsTNT serum levels in cardiac allograft recipients may represent a combination of different physiological and pathological episodes. The exact underlying reasons of the release of hsTNT will need to be studied in experimental models.

A previous study showed that elevated levels of cardiac troponin T concentrations as measured with a highly sensitive assay are related to incidence of cardiovascular death in patients with coronary artery disease [15]. In addition, TnT elevation has also linked to an adverse outcome and/or increase in all-cause mortality in patients without acute coronary syndrome such as renal dysfunction or acute pulmonary embolism [18,19]. This study demonstrates that hsTNT elevation has a predictive value for the first-year mortality. In line with the results is the finding of this study that using the cutoff of 33.55 ng/l, designed by ROC analysis, cardiac allograft recipients with a serum level of hsTNT below the cutoff have highly significant better outcome for 5-year survival rate. By multivariate analysis, we found that hsTNT early after surgery represents an independent risk factor for first-year mortality. Thus, this study may help to further stratify cardiac allograft recipients after surgery to identify patients with a high risk for a poor intermediate and long-term outcome. These patients may be checked and if necessary treated more intensively to further improve the survival after transplantation. Nevertheless, data from further heart-transplanted patient studies will be needed to confirm this hypothesis and to further evaluate the underlying reasons.

Limitations of this study include that the study population was predominantly the gender men. Therefore, extrapolation of our results to women should be done with caution. hsTNT levels in humoral rejection and the potential confounding influence of cytomegalovirus myocarditis cannot be addressed on the basis of the present data, as they were excluded from analysis. We cannot comment on the accuracy among patients with terminal kidney failure requiring dialysis, because such patients with a severe or terminal kidney failure requiring dialysis or a significant renal dysfunction as identified by a creatinine level of ≥ 2 mg/dl were excluded.

In conclusion, the study provides the observation that hsTNT was detectable in almost all our patients. The hsTNT assay represents a good discriminator to separate troponin elevation within the first 3 months after heart transplantation. The assay provides a strong and independent prognostic information for death of any cause within the

first year after heart transplantation. Even more important, the difference between the groups persists over a 5-year follow-up. Prospective studies are needed to further evaluate the impact of the predictive value of hsTNT serum level early after heart transplantation.

Authorship

CE: participated in writing the paper, in data analysis and research design. RT, AD and AR: participated in research design. TJD and SW: participated in data analysis. MA: contributed important reagents. EG: contributed analytic tools, participated in writing the paper. HAK: participated in the study. CG: participated in research design, participated in writing the paper.

Funding

This study was supported by Novartis.

Acknowledgements

The authors greatly appreciate the expert technical assistance of Nadine Wambsganss.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Patient demographic and clinical characteristics at baseline.

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