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Post-Heart Transplant Diastolic Dysfunction Is a Risk Factor for Mortality

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Objectives The purpose of this study was to evaluate the incidence and prognostic implication of diastolic dysfunction (DD) occurring in the first year after transplant.

Background Diastolic dysfunction is a recognized complication in heart transplant recipients, but its true incidence and natural history has been poorly characterized. We studied the prognostic implication of DD, as defined by elevated filling pressures with normal systolic function, occurring in the first year after transplant.

Methods Between June 1992 and June 2002, all patients who underwent heart transplantation at a single institution were included in the study (231 at 6 weeks and 250 at 6 months and 1 year). Diastolic dysfunction was defined as right atrial pressure (RAP) ≥15 mm Hg (right ventricular [RV] DD) or pulmonary capillary wedge pressure ≥18 mm Hg (left ventricular [LV] DD) with normal systolic function by echocardiogram and without severe mitral or tricuspid insufficiency. In addition, RV DD was defined by a RAP/stroke volume (SV) ratio.

Results The incidence of DD was 22%, 8%, and 12% at 6 weeks, 6 months, and 1 year, respectively. The incidence of LV DD was more frequent than that of RV DD at any time point ($p < 0.0001$). By multivariable analysis RV DD, as manifested by an elevated RAP/SV, but not LV DD was a strong predictor of cardiac mortality at all time points.

Conclusions Diastolic dysfunction is common early after transplant, and its incidence decreases during the first year. Right ventricular DD, as measured by an elevated RAP/SV ratio, but not LV DD is a strong predictor of cardiac mortality. Further studies are needed to evaluate the functional status of patients with RV or LV DD and whether aggressive medical therapy for early DD could alter outcome. (J Am Coll Cardiol 2007;50:1064–9) © 2007 by the American College of Cardiology Foundation

Diastolic dysfunction (DD) is a well-recognized complication after heart transplantation. During the first few days to weeks after heart transplantation, the right atrial pressure (RAP) and left atrial pressure are often elevated, reflecting decreased compliance of the transplanted heart (1). However, these abnormalities tend to resolve in subsequent weeks in the majority of patients. Acute rejection might play an important role in the development of abnormal diastolic function, at least acutely (2). In contrast, the causes and implications of chronic DD of the heart allograft are less clear. Anecdotal evidence and small studies suggest that post-transplant DD is poorly tolerated and might be associated with graft loss and decreased survival (3). Therefore, the objective of this study was to evaluate the time-related incidence of post-transplant DD during the first year after transplantation and the impact of right ventricular (RV) versus left ventricular (LV) DD on subsequent survival.

Methods

Patient population. A retrospective analysis was conducted of all patients who underwent heart transplantation at the University of Alabama at Birmingham between July 1992 and June 2002. A total of 294 patients were transplanted. Of these, 273 patients survived at least 1 year and comprise the study group. If the hemodynamic or echocardiographic data were not available in a particular time point, then the patient was not included in the analysis for that time point.

Definitions. The diagnosis of DD was determined during right heart catheterization, which is a routine part of the endomyocardial biopsy protocol at our institution. The diagnosis of DD required normal RV and LV ejection fraction and the absence of at least moderate-to-severe mitral or tricuspid valve regurgitation as evaluated by

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echocardiography. Right ventricular DD was defined by 1 of 2 criteria. A RAP ≥15 mm Hg was the primary criterion for RV DD. In addition, RV DD was also defined by the relationship of RAP to stroke volume (SV) (thermodilution cardiac output divided by heart rate). In light of the variable relationship between these 2 variables, DD was examined as a continuous variable—higher values of RAP/SV indicating greater degrees of RV DD. Left ventricular DD was similarly defined as pulmonary capillary wedge pressure (PCWP) ≥18 mm Hg or as a continuous variable by higher values of PCWP/SV. Cardiac death was defined as death attributed to coronary allograft vasculopathy, graft failure, rejection, sudden cardiac death, and death due to unknown cause.

Data collection. The clinical data were collected from the Cardiac Transplant Research Database forms and included pre-transplant donor and recipient factors, perioperative factors, and typical post-transplant characteristics. The demographic variables collected on all patients included age, race, gender, height, weight, body mass index, pre-transplant heart disease, and transplant date. Clinical variables collected included detailed history of immunosuppressant and nonimmunosuppressant medications, rejection history including number of treated rejections, lipid levels, presence of diabetes mellitus, hypertension, history of tobacco use and cytomegalovirus serology, and infections. Data were collected from the right heart catheterization and echocardiograms closest to the time points of 6 weeks, 6 months, and 1 year after transplant. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham.

Analysis. Descriptive statistics were computed for each variable at baseline (% for discrete variables, mean ± standard deviation for continuous variables) and compared between groups with chi-square and *t* tests, respectively. Outcomes were assessed within groups with paired *t* testing. p values of <0.05 were considered significant. Predictors of cardiac death were examined by multivariable analysis in the hazard function domain. Variables entered into the multivariable analysis are those listed under the section "Data Collection." Patients were censored at the time of death from "noncardiac" causes. Cardiac death was examined after the first post-transplant year, and the predictive value of DD was examined at the time points of 6 weeks, 6 months, and 1 year.

Results

Study population. Two hundred seventy-three patients were included in the study. Of these, 16, 20, and 15 were excluded at 6 weeks, 6 months, and 1 year, respectively, because of depressed ejection fraction (n = 2, 7, and 4, respectively) or significant tricuspid regurgitation (n = 13, 13, and 10, respectively). In addition, there was 1 patient with both (depressed ejection fraction and tricuspid regurgitation) at 6 weeks and 1 year. None of the patients in the study had significant mitral regurgitation. The total number of patients included in the analysis was 231 at 6 weeks and 250 at 6 months and 1 year. The baseline characteristics of the population studied are summarized in Table 1. As expected, the hemodynamic parameters measured, like mean pulmonary artery, RA, and PCWP pressures, were significantly higher in the group of patients with DD, but surprisingly, the transpulmonary gradient was not statistically significant. Other important variables, like recipient height and weight and ischemic time, were only significantly different at 6 months but not at 6 weeks and 1 year.

Abbreviations and Acronyms

DD = diastolic dysfunction
LV = left ventricular
PCWP = pulmonary capillary wedge pressure
RAP = right atrial pressure
RV = right ventricular
SV = stroke volume

Incidence of DD. The incidence of any post-transplant DD was 22% (n = 50), 8% (n = 20) and 11% (n = 28) at 6 weeks, 6 months and 1 year, respectively. The incidence of LV DD (PCWP ≥18 mm Hg) was more frequent than that of RV DD (RAP ≥15 mm Hg) at any time point ($p < 0.0001$). The incidence of LV DD was 21% (n = 48), 8% (n = 20) and 10% (n = 25) at 6 weeks, 6 months, and 1 year, respectively, whereas the incidence of RV DD was 3% (n = 7), 1% (n = 2), and 3% (n = 7), respectively, at the same time points.

LV DD. By univariate analysis, the presence of early LV DD (as defined by PCWP ≥18 mm Hg) was predictive of LV DD at 1 year. Specifically, the likelihood of LV DD at 1 year was 20% when LV DD was present at 6 weeks versus 9% when not present at 6 weeks ($p = 0.02$). However, LV DD at 1 year, defined by PCWP alone or PCWP/SV, was not an independent predictor (by multivariable analysis) of subsequent mortality.

RV DD. Although RV DD (as defined by RAP ≥15 mm Hg) was much less common than LV DD, the early presence of RV DD at 6 weeks was predictive of RV DD at 1 year. The likelihood of RV DD at 1 year was 40% when present at the 6 weeks catheterization versus 2% when not present ($p < 0.0001$).

Mortality. By multivariable hazard function analysis, RV DD was a significant predictor of cardiac death. The ratio of RAP/SV was a stronger predictor than RAP alone (Table 2). Right ventricular DD at all 3 time points after transplant was predictive of subsequent mortality, but later identification (or possibly persistence) of RV DD had greater predictive value, both for RAP alone (Fig. 1) and RAP/SV (Fig. 2). Viewed from an actuarial perspective, RV DD that persisted from an earlier catheterization study was associated with particularly poor late survival (Fig. 3). None of the other characteristics analyzed, including the pre- and post-transplant baseline characteristics included in Table 1, were significant predictors of cardiac mortality.

Table 1 Baseline Characteristics of the Patients Included in the Study

	6 Weeks			6 Months			1 Yr		
Recipient Characteristics	**No DD**	**DD**	**p Value**	**No DD**	**DD**	**p Value**	**No DD**	**DD**	**p Value**
Age (yrs)	52 ± 10.7	50 ± 11.3	0.2	51 ± 11.0	52 ± 9.6	0.8	52 ± 10.5	50 ± 8.6	0.3
Gender (% male)	79%	80%	0.95	80%	88%	0.4	80%	88%	0.3
Ethnicity (% black)	11%	14%	0.65	13%	12%	0.9	11%	12%	0.95
Etiology (% ischemic)	56%	50%	0.5	54%	76%	0.07	57%	54%	0.7
History of renal insufficiency	7%	9%	0.7	9%	6%	0.7	9%	4%	0.4
Creatinine clearance at listing (geometric means)	73 ± (31.2, 21.9)	77 ± (25.1, 18.9)	0.4	73 ± (30.5, 21.5)	77 ± (25.4, 19.1)	0.5	73 ± (29.2, 20.9)	73 ± (42.6, 26.9)	1.0
Serum creatinine at transplant (geometric means)	1.2 ± (0.42, 0.31)	1.3 ± (0.41, 0.31)	0.26	1.2 ± (0.42, 0.32)	1.2 ± (0.35, 0.27)	0.5	1.2 ± (0.43, 0.32)	1.3 ± (0.25, 0.21)	0.1
Height (cm)	174 ± 8.5	175 ± 9.7	0.8	175 ± 8.8	177 ± 8.2	0.2	175 ± 9.1	177 ± 6.5	0.1
Weight (kg)	79 ± 14.8	83 ± 16.8	0.1	79 ± 15.5	87 ± 9.5	0.004	79 ± 15.1	89 ± 15.3	0.6
Donor characteristics									
Age (yrs)	26 ± 9.4	30 ± 11.3	0.02	26 ± 9.8	23 ± 8.3	0.2	26 ± 9.6	25 ± 10.3	0.8
Gender (% male)	79%	77%	0.7	78%	94%	0.14	78%	85%	0.4
Ethnicity (% black)	19%	14%	0.4	19%	12%	0.5	20%	15%	0.6
Height (cm)	177 ± 10.3	177 ± 9.3	0.9	177 ± 10.3	179 ± 3.6	0.02	177 ± 10.3	177 ± 8.2	0.9
Weight (kg)	76 ± 16.4	77 ± 15.2	0.7	76 ± 16.3	75 ± 7.7	0.8	76 ± 16.2	74 ± 10.7	0.5
Ischemic time (min)	187 ± 70.8	193 ± 60.8	0.6	182 ± 67.7	217 ± 73.8	0.04	187 ± 69.5	180 ± 57.3	0.6
Invasive characteristics (post-transplant)									
Mean RAP (mm Hg)	6 ± 2.8	10 ± 3.9	<0.0001	5 ± 2.7	12 ± 4.5	<0.0001	6 ± 2.7	13 ± 4.4	<0.0001
Mean PCWP (mm Hg)	11 ± 3.5	21 ± 3.4	<0.0001	10 ± 3.5	21 ± 3.6	<0.0001	11 ± 3.3	20 ± 3.3	<0.0001
Mean PA pressure (mm Hg)	20 ± 5.7	29 ± 5.3	<0.0001	20 ± 8.1	28 ± 4.4	<0.0001	20 ± 4.6	28 ± 4.0	<0.0001
Mean transpulmonary gradient	9 ± 3.8	8 ± 4.3	0.09	9 ± 3.3	7 ± 4.4	0.01	9 ± 3.5	8 ± 3.4	0.2

The patients are grouped on the basis of the presence or absence of diastolic dysfunction (DD) at each time point.
PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

Table 2 Risk Factors for Cardiac Mortality

	6 Weeks		6 Months		1 Yr	
Variable	RR	p Value	RR	p Value	RR	p Value
Younger recipient age	1.6*	0.001	1.6	0.003		NS
Higher % IBW	2.0†	0.02	1.9	0.04	2.0	0.05
Earlier date of transplant	2.9‡	0.03	4.1	0.01	3.75	0.05
Female recipient		NS	2.9	0.02	3.5	0.008
Higher RAP/SV	2.7§	0.02	2.5	0.003	3.6	0.002

Cardiac mortality defined as death after the specified cardiac catheterization. *Relative risk (RR) comparing age 30 to age 50. †Relative risk comparing % ideal body weight (IBW) = 125% to % IBW = 100%. ‡Relative risk comparing 5 years' difference. §Relative risk comparing mean right atrial pressure/stroke volume (RAP/SV) = 250 versus RAP/SV = 100.

Discussion

Increased filling pressures during the early post-transplant period are likely related to prolonged ischemic time, donor–recipient size mismatch, operative technique (1,4,5), and allograft rejection (6). The decreasing incidence of DD over time in the present study is consistent with prior studies, suggesting that after the first few weeks, the restrictive physiology of the non-rejecting allograft tends to subside, with normalization of the diastolic parameters (7,8). However, the presence of early DD identifies a group of patients with an important incidence of DD at 1 year and with a higher likelihood of poor outcome. The incidence of LV DD is more frequent than that of RV DD, which is not surprising given the higher volume mass and susceptibility to ischemia of the left ventricle and its greater dependence on pre-load and afterload hemodynamic changes. Interestingly, none of the usual parameters associated with DD, like age, ischemic time, donor or recipient size, or prior thoracic surgery was consistently different among the patients with and without DD.

Post-transplant DD has significant prognostic implications. A study done by Ross et al. (9) suggests that the persistence of abnormal diastolic parameters by Doppler echocardiography after the first few weeks after transplant is associated with increased late mortality, independent of other risk factors that might increase filling pressures, like rejection and allograft vasculopathy. Similarly, a recent study by Aziz et al. (10) found that the presence of DD, measured primarily by echocardiographic indexes 2 years after transplantation, was associated with symptoms of heart failure and possibly a decreased survival 2 to 5 years after transplantation. However, these studies were based on Doppler echocardiographic parameters only and not on elevated filling pressures measured by a pulmonary artery catheter or direct LV measurement. Moreover, the latter study did not exclude patients with rejection, which is known to affect the Doppler diastolic parameters (6).

Several factors were associated with mortality in our study when included in a multivariable analysis as described in Table 2. The most important finding of our study is that the presence of RV DD, but not LV DD, is a strong predictor of cardiac mortality. Interestingly, evaluating the right-sided filling pressures is part of the physical exam in post-transplant patients, and the finding of an elevated jugular

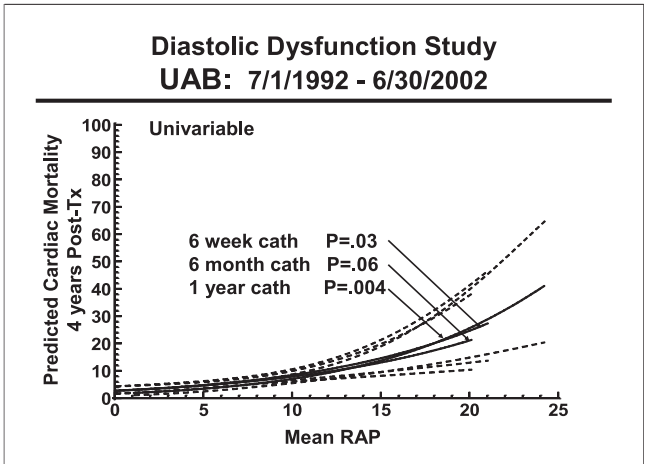

Figure 1 RAP and Cardiac Mortality

Relationship between mean right atrial pressure (RAP) and the likelihood of subsequent cardiac mortality. The lines for each time point are essentially superimposable. The **dashed lines** represent the 20% confidence limits. cath = catheterization; Tx = transplant; UAB = University of Alabama at Birmingham.

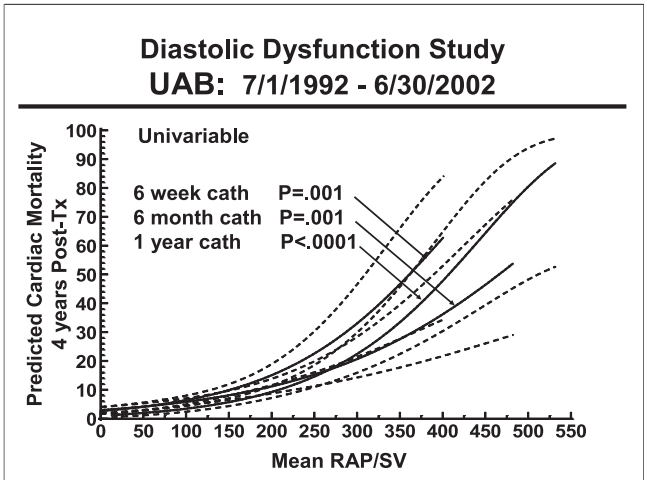

Figure 2 RAP/SV and Cardiac Mortality

Univariable depiction of the relationship between mean RAP divided by stroke volume (SV) and predicted cardiac mortality at 3 time points. Abbreviations as in Figure 1.

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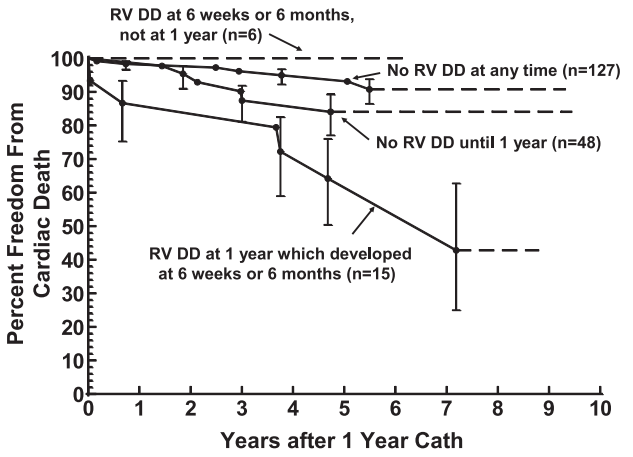

Figure 3 **RV DD and Cardiac Death**

Actuarial survival for differing categories of right ventricular (RV) diastolic dysfunction (DD). The **error bars** enclose ± 1 SE. Right ventricular DD is defined in terms of RAP/SV, and at each time point (6 weeks, 6 months, 1 year) is the value of RAP/SV at which discrimination in survival is possible at $p = 0.05$. Abbreviations as in Figures 1 and 2.

venous pressure might help identify a subgroup of patients with a worse prognosis. In addition, when the elevated right-sided filling pressures are associated with a depressed cardiac output, manifested by higher RA/SV ratio, then the association with cardiac mortality is even stronger. This altered ratio probably identifies a group of patients with higher diastolic impairment, because the higher filling pressures are no longer enough to maintain an adequate cardiac output, possibly an indirect measurement of RV stiffness. Other studies suggest that early post-transplant DD is generally benign and reversible. In our study, we used 6 weeks as the "early" time point. By 6 weeks, most of the early changes resulting from perioperative insults like ischemia have subsided, with normalization of Doppler diastolic parameters (7), but occasionally major histostructural changes can be detected (11). Interestingly, in our study, the presence of RV DD at 6 weeks defined a subgroup of patients with a higher incidence of RV DD at 1 year (40% when present at 6 weeks, vs. 2% when not), indicating that the histostructural changes that might occur early on might already be a pathological response, resulting in the subsequent development of DD. The present study is the first to systematically analyze the prognostic implications of RV DD in heart transplant recipients. Despite its hemodynamic importance, less attention has been given to the RV systolic and diastolic function in various cardiac conditions. In patients with heart failure due to LV systolic dysfunction, the presence of RV systolic failure is an important predictor of morbidity and mortality (12,13). In addition, the presence of RV DD, manifested by echocardiographic abnormalities of the tricuspid inflow pattern, is frequent and independent of increased RV afterload (14). Elevated RAP has also been found to be an independent risk factor for mortality in patients with pulmonary arterial hypertension (15). The exact mechanism of the association of RV DD in heart transplant recipients and mortality is unknown, but we can postulate that the presence of elevated RAP in post-transplant patients is the result of abnormal histostructural changes that lead to restrictive physiology of the RV in heart allografts. It might be that the mere presence of an elevated RAP, with its associated complications of peripheral edema and liver congestion, might make patients more susceptible to additional stresses on cardiac function, such as episodes of rejection or infection, especially in patients with a depressed cardiac output already. Of note, our study included data obtained during the first year after transplantation; so it remains unknown whether this phenomenon is an adverse "early" event that would later disappear or a surrogate for the subsequent development of biventricular DD.

In summary, our study suggests that DD is common early after transplant and its incidence decreases during the first year. Although uncommon, RV DD but not LV DD at 1 year is a strong and important predictor of mortality, especially if associated with a depressed cardiac output. Therefore, we postulate that the continued hemodynamic assessment of the cardiac allograft should be part of the routine evaluation of heart transplant recipients, at least during the first year. Further studies are needed to evaluate the impact of these hemodynamic derangements long-term, not only with respect to mortality but also in terms of functional status and quality of life. More intriguing is whether aggressive medical therapy for early DD could alter the likelihood of subsequent DD and its potential long-term effects on patients.

Limitations of our study result from its retrospective nature. It should be viewed as hypothesis-generating and not a definitive answer. Because of its retrospective character, further modalities to measure diastolic function were not included, such as Doppler indexes by echocardiography, nuclear ventriculography, or cardiac magnetic resonance. Moreover, our study looks at the presence of DD up to 1 year after transplant. Additional studies are needed to follow these patients over prolonged periods of time to assess the incidence and prognostic significance several years after transplant.

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