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VENTRICULAR REMODELING FOLLOWING INFANT-PEDIATRIC CARDIAC TRANSPLANTATION

DOES AGE AT TRANSPLANTATION OR SIZE DISPARITY MATTER?^{1, 2}

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Early left ventricular (LV) remodeling following pediatric cardiac transplantation has not been described. To identify patterns and determinants of change in left ventricular mass and volume posttransplant, we studied 125 consecutive children who underwent cardiac transplantation between January 1, 1989 and July 31, 1993. Two-dimensional imaging-directed M-mode echocardiograms were studied weekly until 26 weeks post-transplant. LV mass and volume (indexed to BSA^{1.5}) were measured. LV mass index increased until 3 weeks post-transplant, and then decreased. The mean decrement in LV mass index after 8 weeks post-transplant (relative to baseline) was significantly larger in patients with donor-recipient weight ratio >1.5 compared with patients with donor-recipient weight ratio ≤1.5 (−2.2 g/m³ compared with 33.4 g/m³, respectively, $P<0.01$). Multiple linear regression was performed employing donor-recipient weight ratio, time since transplantation, ischemic time, and age at transplant as prognostic variables. Donor-recipient weight ratio ($P<0.0001$), time since transplant ($P<0.01$), and age at transplant ($P=0.02$) were identified as independent predictors of change in LV mass index. Donor-recipient weight ratio ($P=0.001$) and time since transplantation ($P=0.02$) were independent predictors of change in LV volume index. There was an interaction between donor-recipient weight ratio and time since transplantation, suggesting that donor-recipient weight ratio has an independent effect as well as a time-dependent effect on change in LV mass and volume indices. LV mass and volume indices increased early posttransplant and then decreased; this pattern was temporally predictable, and dependent on donor-recipient weight ratio and age at transplant.

Advances in strategies for prolonging survival prior to transplantation (1) and innovative surgical techniques enabling transplantation for patients with complex structural cardiac abnormalities (2, 3) have expanded the candidate pool for pediatric and neonatal cardiac transplantation. As a result, the number of infant and pediatric cardiac trans-

plants performed in the United States has increased from 52 in 1985 to 276 in 1994 (United Network for Organ Sharing [UNOS], April 1995, personal communication). The ensuing shortage of "ideal-sized" donor organs has led to increasing use of "size-disparity" cardiac transplantation in infants and children (4–6).

Previous studies have demonstrated that following pediatric cardiac transplantation, cardiac chamber growth is normal over the long term (7–9). However, there is a paucity of data addressing early left ventricular remodeling following transplantation. Elucidation of changes in ventricular morphometry during this period would improve our understanding of the process of adaptation of the donor heart to the recipient circulation (10), especially following donor-recipient size disparity transplantation. In addition, definition of these changes may help in interpretation of echocardiographic algorithms that use trends in left ventricular mass and volume for diagnosis of rejection (11, 12).

Left ventricular (LV)* remodeling patterns in the early posttransplantation period may be affected by donor-to-recipient weight ratio (13, and Kertesz NJ et al., personal communication), blood pressure (14), graft ischemic time (15), time since transplantation and recipient age at the time of transplantation. The effect of these variables on LV remodeling following cardiac transplantation has not been assessed systematically in children, in whom the potential for growth poses an additional and unique challenge to the transplanted heart. This study examined the effect of these clinical variables on the early changes in LV mass and volume following infant and pediatric cardiac transplantation.

MATERIALS AND METHODS

Patients. All patients who underwent primary orthotopic cardiac transplantation at Loma Linda University Medical Center between January 1, 1989 and June 30, 1993 and fulfilled the following criteria were included: (1) age at transplantation <18 years, (2) survival for at least six months following transplantation, (3) not diagnosed with coarctation of the aorta within the first twelve months following transplantation, and (4) adequate quantitative echocardiographic data available for analysis.

Clinical data. Indications for transplantation, donor and recipient age, height and weight at time of transplantation, and cardiac ischemic time (defined as the time between cross-clamping of the donor aorta and removal of the cross-clamp following reimplanta-

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* Abbreviations: BSA, body surface area; LV, left ventricle (left ventricular).

tion) were recorded. For each patient, the dates of rejection episodes were noted. Systolic blood pressures obtained at each outpatient visit were recorded and converted to z scores using standard nomograms for purposes of age-independent statistical comparisons (16).

Echocardiographic analysis. Echocardiograms were performed with several commercially available scanners with transducer frequencies appropriate for the patient's size. Each study included two-dimensional, M-mode, pulsed Doppler, and color flow Doppler mapping. Echocardiographic measurements were obtained on a weekly basis from the first week posttransplant until 26 weeks posttransplant. If more than a single eligible measurement had been obtained on a patient during a specified week, the measurements were averaged and the mean of these measurements was used for analysis. For the purposes of this study, rejection was defined as augmentation of immunosuppression for a specified period. Echocardiographic studies that were obtained during rejection were excluded from analysis (11).

Echocardiographic measurements. Two-dimensional imaging-directed M-mode tracings were recorded on strip-chart paper at 100 mm/sec paper speed, and digitized with a Summasketch Plus digitizer (Summagraphics, Seymour, Conn.) using a modified computer-assisted measurement format (17). For the purpose of LV measurements, M-mode tracings were obtained at or just below the level of the mitral valve tips. Measurements of interventricular septal thickness, posterior wall thickness and LV end-diastolic dimension were traced on the digitizing pad for three consecutive cardiac cycles. Strings of coordinates at intervals of 6 millisecon were generated from the traces for each of the analyzed cardiac cycles. Leading edge-to-leading edge measurements were made according to the standard criteria of the American Society of Echocardiography (18).

LV end-diastolic volume and LV mass were calculated using the cube function formula. This function assumes that the LV is a prolate ellipsoid of regular configuration with a long-to-short axis length ratio of 2:1. The formula used for calculation of LV end-diastolic volume (LVEDV) is: $LVEDV = (LVID_d)^3$ (19). The formula used for calculation of LV mass (LVM) is: $LVM = 1.04[(IVS_d + LVID_d + LVPWT_d)^3 - LVID_d^3]$ (20, 21), where IVS_d = interventricular septal thickness in diastole, $LVID_d$ = LV end-diastolic minor axis dimension, and PWT_d = LV posterior wall thickness in diastole. LV mass and volume measurements were indexed to body surface area (BSA) to the 1.5 power (22, 23).

Anastomotic sites were assessed for obstruction by complete echocardiographic studies performed at regular intervals following transplantation.

Interobserver and intraobserver variability. The reproducibility of measurements of calculated LV mass and volume was estimated in a randomly selected sample of studies (n=30) by comparing measurements obtained by two independent observers, and then by comparing repeat measurements obtained by a single (blinded) observer respectively. Simple linear regression analysis was employed to calculate the correlation between the two sets of measurements. For each patient, the absolute difference between observers was divided by the mean value of the two measurements and expressed as the percentage of interobserver variability. A similar procedure was used for estimation of percentage intraobserver variability.

Statistical analysis. Analyses were performed using the SPSS (Release 6.1) for Windows program. Univariate comparisons of mean LV mass and volume indices, and mean change in LV mass index and LV volume index at selected time-since-transplant intervals (0, 1, 2, 3, 4, 8, 12, and 24 weeks posttransplant) were compared using Student's *t* test for independent samples, where mean change in these indices is the difference between the index at the specified time point and the index at initial examination (week 0). The individual dichotomous prognostic factors studied were: recipient age at transplant, donor-to-recipient weight ratio, ischemic time, and median systolic blood pressure z score. Paired data were compared using Student's *t* test for paired samples.

Multiple linear regression models were utilized to evaluate the

independent effects of these candidate variables on LV mass index and LV volume index while controlling for within-subject variation and time since transplantation. Age at transplant, donor-recipient weight ratio and ischemic time were modeled as continuous variables. Time since transplant and within-subject variation were modeled as a series of dummy variables. Potential interactions among the prognostic variables, and also between prognostic variables and time-since-transplant were evaluated. Results are reported as mean value \pm 95% confidence limits (1.96 times standard error of the mean) unless otherwise noted. A *P* value \leq 0.05 was considered statistically significant.

RESULTS

A total of 125 patients met inclusion criteria for the study; a total of 2204 echocardiograms on these patients were analyzed. Clinical and demographic data for these patients are summarized in Table 1. Indications for cardiac transplantation were hypoplastic left heart syndrome (HLHS) (n=36), variants of HLHS (n=20), complex congenital heart disease (n=33), dilated cardiomyopathy (n=22), Shone's complex (n=7), hypertrophic cardiomyopathy (n=2), restrictive cardiomyopathy (n=2), cardiac tumor causing refractory dysrhythmias (n=2), and Ebstein's anomaly (n=1). Twenty three additional patients did not survive until six months posttransplant, and these patients were excluded from the study.

Change in LV mass and volume with time following transplantation for all patients is shown in Figure 1. LV mass index increased from 132 ± 10.3 g/m³ in the first week posttransplant to 150 ± 7.9 g/m³ at 3 weeks posttransplant ($P < 0.01$), and then decreased to 112 ± 12.9 g/m³ at six months posttransplant ($P < 0.01$). LV volume index did not change significantly with time posttransplant.

Patients were dichotomized based on donor-recipient ratio ≤ 1.5 versus > 1.5 . The evolution of LV mass index in these two groups is shown in Figure 2. As anticipated, patients with donor-recipient weight ratio > 1.5 had significantly higher initial LV mass index than did patients with donor-recipient weight ratio ≤ 1.5 (156.3 ± 11.8 g/m³ versus 91.8 ± 9.9 g/m³, $P < 0.001$). LV mass index increased in both groups until 2–3 weeks posttransplant and then decreased. LV mass index remained significantly different between groups until 10 weeks posttransplant, after which time LV mass index was not significantly different between groups. After eight weeks posttransplant, LV mass index relative to baseline was significantly lower in patients with donor-recipient weight ratio > 1.5 when compared with patients with

TABLE 1. Demographic and clinical characteristics of all enrolled patients (n=125)

Parameter	Mean \pm SD
Age at transplantation (months)	18.1 \pm 35.6 Median=3 range: 0–205
Gender ratio (M:F)	1.1:1
Donor organ ischemic time (min)	277.4 \pm 115.9
Donor weight (kg)	12.4 \pm 10.3 median=10 range=2.2–84
Recipient weight (kg)	8.16 \pm 11.2 median=4.3 range: 2.18–94.5
Donor: recipient weight ratio	1.86 \pm .74

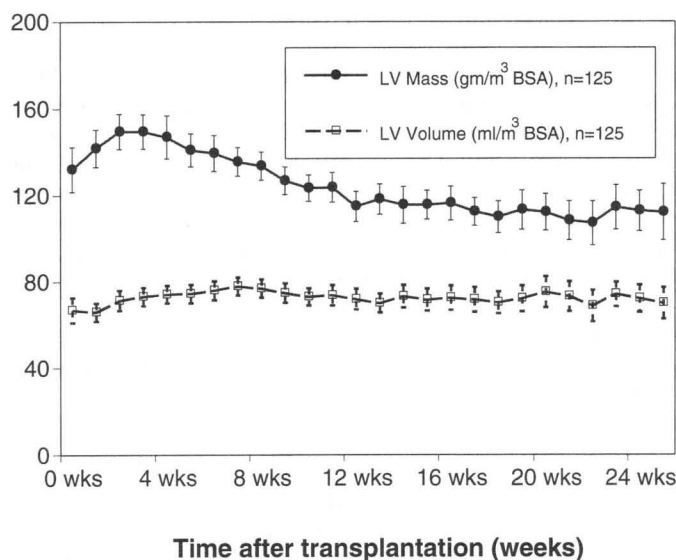


FIGURE 1. Change in indexed left ventricular mass and volume with time after transplantation for all 125 patients. Error bars indicate 95% confidence limits.

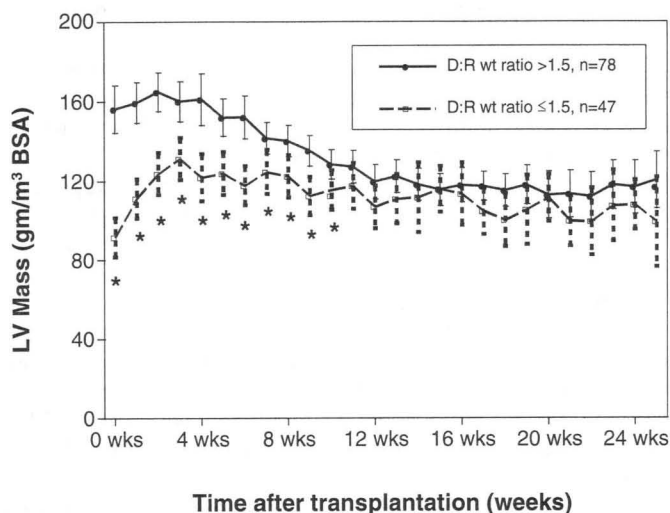


FIGURE 2. Change in indexed left ventricular mass with time after transplantation in patients with donor-recipient weight ratio ≤ 1.5 versus >1.5 . Error bars indicate 95% confidence limits. (*) $P<0.05$ for difference between groups.

donor-recipient weight ratio ≤ 1.5 (at 8 weeks, mean change in LV mass index = -2.2 g/m^3 compared to 33.4 g/m^3 respectively, $P<0.001$). This difference in magnitude of change in LV mass index between these groups (relative to baseline) persisted at the end of 24 weeks posttransplant (-92.1 g/m^3 compared with -33.6 g/m^3 respectively, $P<0.001$). LV volume index did not change significantly with time in either group, and was not significantly different between groups. However, after 12 weeks posttransplant, LV volume index relative to baseline was significantly lower in patients with donor-recipient weight ratio >1.5 when compared with patients with donor-recipient weight ratio ≤ 1.5 (mean change in LV volume index = -2.7 ml/m^3 compared with 18.9 ml/m^3 , respectively, $P=0.01$). This difference in magnitude of change in LV volume index between groups persisted at the end of

six months posttransplant (-38.4 ml/m^3 compared with -18.4 ml/m^3 , respectively, $P=0.02$).

Patients were then dichotomized based on age at transplant ≤ 12 months versus >12 months; change in LV mass index with time in these two groups is shown in Figure 3. Patients transplanted at age ≤ 12 months had significantly higher initial LV mass index than patients transplanted after age 12 months ($140 \pm 12.4 \text{ g/m}^3$ versus $111.3 \pm 15.5 \text{ g/m}^3$, $P<0.001$). LV mass index for both groups increased until 2–3 weeks posttransplant and then decreased. LV mass index remained significantly different between groups until 13 weeks posttransplant, after which time LV mass index was not significantly different between groups. The pattern of change in LV mass index with time, compared to baseline, was not significantly different between groups. LV volume index did not change significantly with time in either group, and was not significantly different between groups. The pattern of change in LV volume index with time, compared to baseline, was not significantly different between groups.

Patients were then divided into two groups based on ischemic time ≤ 277 minutes (the median value of the population) versus >277 min. Neither LV mass nor LV volume indices changed significantly with time within groups, and these parameters were not significantly different between groups. The patterns of change in LV mass and volume indices with time (compared to baseline) were not significantly different between groups. We also examined initial LV mass in the 30 patients with the shortest ischemic times, compared with the 30 patients with the longest ischemic times. There were no statistically significant differences in initial LV mass between these two groups.

Blood pressure. Due to large variations in systolic blood pressure that were noted within individuals, the median value of all measured z scores for each patient was utilized for analysis in the univariate model. Patients were dichotomized based on median systolic blood pressure ≤ 1 SD versus >1 SD. Neither LV mass nor LV volume index changed significantly with time within groups; these parameters were not significantly different between groups. Due to the large

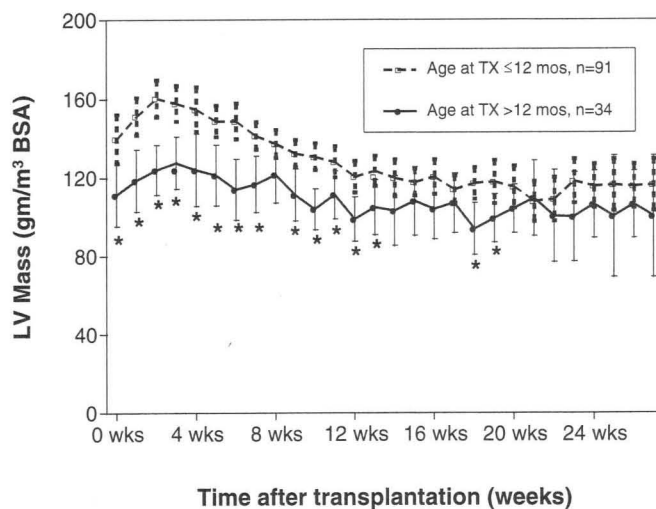


FIGURE 3. Change in indexed left ventricular mass with time after transplantation in patients aged ≤ 12 months versus >12 months at transplantation. Error bars indicate 95% confidence limits. (*) $P<0.05$ for difference between groups.

variations in blood pressure noted within individuals, and the absence of any significant association between blood pressure and LV mass or volume from univariate analysis, we did not study blood pressure in the multivariate model.

Multivariate analysis. The following variables were evaluated in the multiple linear regression model: donor-recipient weight ratio, age at transplant, time since transplant, and ischemic time. The results of multiple linear regression analysis, identifying independent predictors of change in LV mass and volume indices, are summarized in Table 2. The β -coefficient is the amount of change in the dependent variable for a given change in an independent variable while holding all other variables in the model constant; thus, the β -coefficient represents the independent effect of the variable under consideration.

LV mass index. Donor-recipient weight ratio was the most significant predictor of change in LV mass index posttransplant ($P<0.0001$). Age at transplant was also an independent predictor of change in LV mass index ($P=0.02$). There was no interaction between donor-recipient weight ratio, age at transplant, and ischemic time. Time since transplant (not shown in the table) had an additional, independent predictive effect on change in LV mass. The effect of time was significant at 2 weeks ($\beta=48.1$, 95% C.I.=11.4, 84.9; $P=0.01$), 3 weeks ($\beta=39.4$, 95% C.I.=2.6, 76.2; $P=0.04$), 8 weeks ($\beta=46.6$, 95% C.I.=9.8, 83.3; $P=0.01$), and 12 weeks ($\beta=53.5$, 95% C.I.=16.8, 90.3; $P=0.01$) posttransplant, indicating that as time since transplant increased, there was a decrease in LV mass that occurred dependent on time alone, independent of other potential determinants. There was a significant interaction between donor-recipient weight ratio and time since transplantation ($P<0.0001$); none of the other interactions that were tested were statistically significant. This multivariate model explains 46% of the variance in LV mass index ($r^2=0.46$).

LV volume index. Donor-recipient weight ratio was the most significant predictor of change in LV volume index posttransplant ($P<0.0001$). Time since transplant (not shown in the table) had an independent predictive effect on change in LV mass. The effect of time was significant at 2 weeks ($\beta=27.5$, 95% C.I.=7.6, 47.4; $P<0.01$), 3 weeks ($\beta=23.9$, 95% C.I.=4.0, 43.8; $P=0.02$), 4 weeks ($\beta=23.5$, 95% C.I.=3.6, 43.4; $P=0.02$), 8 weeks ($\beta=31.5$, 95% C.I.=11.6,

51.4; $P=0.002$) and 12 weeks ($\beta=42.4$, 95% C.I.=22.5, 62.3; $P<0.0001$) posttransplant, indicating that as time since transplant increased, there was a decrease in LV volume independent of other potential determinants and dependent on time alone. There was a significant interaction between donor-recipient weight ratio and time since transplantation ($P=0.02$); none of the other interactions that were tested were statistically significant. There was no interaction between donor-recipient weight ratio, age at transplant and ischemic time. This multivariate model explains 43% of the variance in LV volume index ($r^2=0.43$).

Interobserver and intraobserver variability. The results of testing for reproducibility of measurements are summarized in Table 3.

DISCUSSION

This study identifies determinants of adaptation of the transplanted left ventricle to the recipient circulation in the first six months following cardiac transplantation in infants and children. Donor-recipient weight ratio, age at transplantation and time since transplantation are independent predictors of change in LV mass and volume following transplantation. Donor-recipient weight ratio has an additional time-dependent effect on change in LV mass and volume indices posttransplant.

Following transplantation, LV mass index increased for the first four to six weeks and then decreased to baseline levels by three months. Previous studies have shown similar increases in LV mass in the first several weeks following transplantation followed by a decrease to normal range (24–28). However, the determinants of the remodeling process have not been systematically examined prior to the current study.

Criteria for body weight matching of adult donors and recipients have been liberalized to accept a weight mismatch of greater than 20% (6)—however, these criteria are routinely exceeded in infants and children. The mean donor-recipient weight ratio in the present study was $1.86\pm0.74:1$, and only 15% of all patients enrolled received a heart from a donor in the “ideal” ($\pm 20\%$) weight range. For the univariate analysis, patients were dichotomized based on an arbitrarily chosen donor-recipient weight ratio greater versus ≤ 1.5 . The evolution of change in LV mass index following transplantation with donor-recipient weight ratio >1.5 was significantly different from that noted with donor-recipient weight ratio ≤ 1.5 (Fig. 2). This analysis was also performed using the median weight ratio of 1.78:1 with similar results. Donor-recipient weight ratio was then assessed as a continuous variable for the multivariate analysis. This study shows that increased donor-recipient weight ratio is associated with a higher early posttransplant peak in LV mass index, followed

TABLE 2. Multiple linear regression analysis identifying significant predictors of change in left ventricular mass and volume indices following cardiac transplantation

	β coefficient ^a	95% confidence interval (β)	P value
LV mass index:			
Donor-recipient weight ratio	-45.6	(-64.8, -26.5)	<0.0001
Age at transplant	-0.27	(-0.50, -0.04)	0.02
Ischemic time	-0.004	(-0.11, 0.10)	0.94
LV volume index:			
Donor-recipient weight ratio	-17.31	(-27.7, -6.93)	0.001
Age at transplant	-0.11	(-0.24, -0.02)	0.09
Ischemic time	-0.02	(-0.08, 0.04)	0.5

^a The β coefficient is the amount of change in the dependent variable for a given change in an independent variable while holding all other variables in the model constant.

TABLE 3. Interobserver and intraobserver variability for measurement of left ventricular mass and volume

	Left ventricular mass	Left ventricular volume
Interobserver variability	$5.8\pm4.4\%$; $r^2=0.97$	$3.7\pm2.6\%$; $r=0.99$
Intraobserver variability	$3.1\pm2.1\%$; $r=0.99$	$1.9\pm1.5\%$; $r=0.99$

^a r : coefficient of correlation using simple linear regression analysis.

by a greater subsequent decline in LV mass index toward normal values.

It has been shown that, when there is a sustained alteration in the work load imposed on the ventricle, the altered systolic force or tension generated by the myocardial fibers elicits myocardial hypertrophy or atrophy until the load per fiber is again returned to the normal range (29). Load per fiber has been measured clinically as peak systolic wall stress, which is the major determinant of concentric atrophy and hypertrophy (30, 31). Thus, the transplanted heart would be expected to adapt to the functional demands of the recipient circulation over time. A large donor organ would be expected to exhibit regression of LV mass with time as an adaptive phenomenon, as was shown in our study. While peak systolic wall stress was not measured in the present study, a study of changes in peak systolic wall stress posttransplant would be an important addition to the existing body of information. Following oversize-donor transplantation, LV mass and volume index decrease to "normal" range (for recipient size) by four to six months.

Time since transplantation has not been assessed previously as a potential variable affecting LV mass or volume following transplantation. After controlling for other variables, time since transplantation was an independent predictor of change in LV mass and volume indices. The independent effect of time on change in LV mass and volume indices increases with increasing time posttransplant after adjusting for all other variables tested. In fact, we found that even after oversize-donor transplantation, there is an increase in LV mass index for four to six weeks. After this early increase, LV mass and volume indices decreased with time posttransplant in all patient groups; this late decrease in LV mass and volume was independently predicted by time since transplant. This phenomenon may represent the effect of intrinsic or time-dependent factors that regulate cardiac growth as described by Zak (32). These factors are unrelated to functional demands on the heart and may involve genetic programming as well as humoral growth factors. It is conceivable that unidentified humoral trophic factors may persist in the recipient circulation for a period after transplantation regardless of the size of the transplanted organ. This could lead to continued growth of LV myocardium in the early posttransplant period, manifesting as the early increase in LV mass and volume index that we observed regardless of donor-recipient weight ratio, even with an oversized donor heart. With the passage of time posttransplant, the effect of these intrinsic factors may be overridden by the effect of load-dependent adaptation of the heart.

Knowledge of the normal increase in LV mass in the first several weeks posttransplant is important in being able to critically evaluate echocardiographic algorithms which identify increased LV mass as a criterion for diagnosis of allograft rejection (11, 12). In the first several weeks posttransplant, an increase in LV mass may represent normal ventricular remodeling rather than rejection. Reliance on increased LV mass alone as a predictor of rejection may lead to overdiagnosis of rejection in the early posttransplant period, particularly in infant recipients of oversize-donor transplantation.

Falk (cited by Rakusan [33]), showed that the human heart exhibits its greatest rate of weight increase in the first year after birth, doubling its birth weight by age six months and tripling it by age one year. This may represent age-depen-

dent, intrinsic regulation of cardiac growth. This study identified age at transplant as an independent predictor of change in LV mass index posttransplant by multivariate analysis. Our findings suggest that the younger the patient at the time of transplant, the greater the magnitude of early increase and subsequent decrease in LV mass index with the remodeling process. There have been no previous studies examining age at transplant as a determinant of LV remodeling posttransplant. It is possible that this analysis identified age at transplant due to colinearity between age at transplant and donor-recipient weight ratio; however, no significant interaction was detected between these two variables. This confirms that the effect attributed to age at transplant is independent of the effect of donor-recipient weight ratio.

While the current study examines several factors as candidate variables that may affect ventricular remodeling, other important (unmeasured) factors may exist. It is possible that unmeasured time-dependent factors may account for the effect that was attributed to time in our analysis. The methodology for echocardiographic measurement of LV mass and volume is based on single-plane measurements and geometric assumptions. However, these methods conform to standard guidelines for measurement (20, 21). The interobserver and intra-observer variability in this study was quite low, and confirms the reliability of the methodology for the purpose of comparisons of serial studies. Our decision to exclude studies obtained during treatment of rejection may not have allowed for adequate washout of the effects of rejection, and may have resulted in a carry-over effect. However, there are no published data that allow estimation of the time course involved in the return of LV mass and volume to normal range after treatment of rejection. It is also possible that patients were experiencing clinically unrecognized allograft rejection during echocardiographic studies included in our study; however, the design of the current study does not allow for comparison of each echocardiogram with simultaneous endomyocardial biopsy grading of rejection.

In conclusion, the adaptation of the donor heart to the recipient circulation following transplantation is a dynamic process. There is a temporally predictable, reversible increase in LV mass following transplant, the extent of which is predicted by the donor-recipient weight ratio and recipient age at transplantation. Following oversize-donor transplantation, LV remodeling occurs in the first four to six months resulting in LV mass and volume indices that are appropriate for recipient size. Further studies are needed to examine the role of systolic wall stress in the remodeling process following transplantation.

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