

Left Ventricular Diastolic Function

Doppler Echocardiographic Changes Soon After Cardiac Transplantation

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In acute cardiac rejection, left ventricular diastolic function is altered, and a restrictive ventricular filling pattern occurs. Doppler echocardiographic indexes of mitral inflow have been proposed as sensitive markers of the rejection process. As rejection progresses, the restrictive ventricular filling pattern is reflected by a shortening of isovolumic relaxation time and mitral valve pressure half-time and by an increase in early transmitral filling velocity. Diastolic function is also compromised in the nonrejecting cardiac transplant recipient during the early postoperative period. This study examined the progression in Doppler-derived mitral filling indexes in 25 recent cardiac transplant recipients who demonstrated no histological evidence of transplant rejection. Isovolumic relaxation time, mitral valve pressure half-time, and early transmitral filling velocity were measured at postoperative weeks 1, 2, 4, and 6 on the day that surveillance right ventricular endomyocardial biopsies were performed. The initial indexes were comparable to previously described restrictive parameters and over the 6-week study period evolved into a nonrestrictive filling pattern. This evolution reflects a progressive improvement in postoperative diastolic function and a decrease in left heart filling pressures. None of the evaluated clinical characteristics, including preoperative pulmonary pressures, total ischemic time of the transplanted heart, cardiopulmonary bypass time, and age of the donor heart, correlated with this process. Given the increasing use of Doppler echocardiography as a means of screening for transplant rejection, it is important to have a thorough understanding of normal postoperative changes in left ventricular diastolic function. (*Circulation* 1990;82:872–878)

Cardiac transplantation is an established therapy for patients with severe myocardial dysfunction. Although the use of cyclosporine has markedly improved survival of transplant recipients, early detection of allograft rejection remains a major clinical problem. Doppler echocardiographic indexes of diastolic function have been proposed as a means of noninvasive screening for allograft rejection.^{1,2} Deterioration of diastolic function associated with acute rejection presents hemodynamically as restrictive physiology.³ This is characterized by shortening of the left ventricular isovolumic relaxation time (IVRT) and reproducible changes in Doppler measurements of early diastolic filling.⁴ This physiology has been shown to be reversible with adequate rejection therapy.²

Hemodynamic studies performed in the early post-transplant period have demonstrated elevated right and left heart filling pressures and restrictive filling dynamics.^{5,6} This pattern occurs irrespective of rejection status and resolves during the first 4–8 postoperative weeks. Given the increasing use of Doppler echocardiography as a method of screening for restrictive diastolic filling indicative of acute rejection, it is important to understand normal changes in the early postoperative period.

The present study assesses Doppler echocardiographic indexes of left ventricular diastolic function in the early postoperative period in a group of nonrejecting cardiac transplant recipients and examines whether clinical factors influenced the observed changes in diastolic filling.

Methods

Patients

The study population comprised 25 patients (21 men and four women) who had undergone orthotopic cardiac transplantation at Stanford University Medical Center. The mean age of the patients was 48

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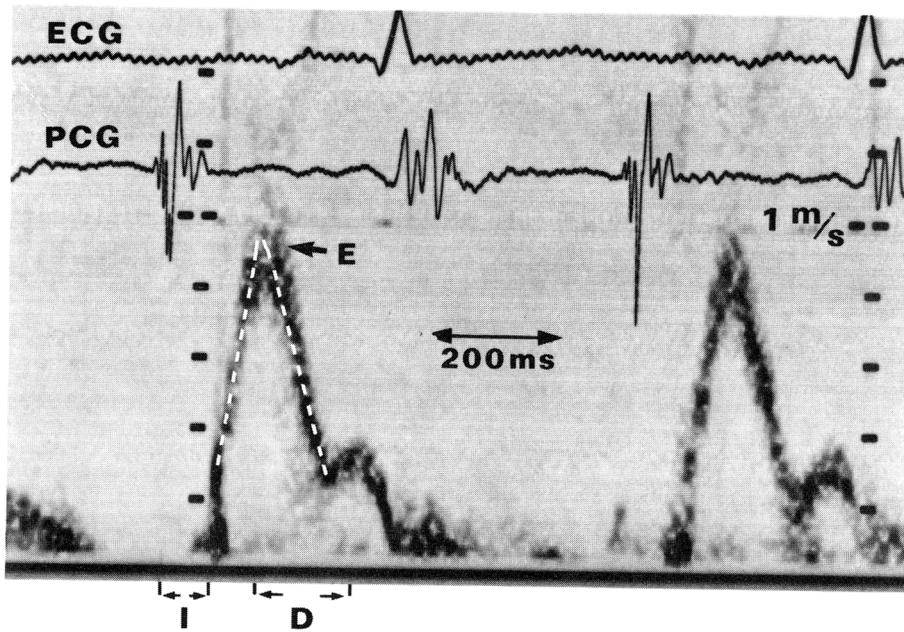


FIGURE 1. Recording of trans-mitral pulsed Doppler echocardiogram, electrocardiogram (ECG), and phonocardiogram (PCG). E, peak early flow velocity; I, isovolumic relaxation time; D, deceleration time, which divided by 220 equals the pressure half-time.¹⁰

years (range, 37–59 years). All patients gave informed consent to the serial evaluation approved by the Committee for the Protection of Human Subjects in Research at Stanford University Medical Center. Of the 25 patients, none had evidence of rejection on their first three serial screening biopsies, and 10 had a complete echocardiographic study and normal biopsy 6 weeks after transplantation. Of the 15 patients who were not included in the 6-week data, 11 had histological evidence of rejection and four patients did not return for a follow-up echocardiographic study.

Immunosuppression

All patients received OKT3 monoclonal antibody (5 mg/day) during the first 10 days after transplantation. The maintenance immunosuppression regimen included cyclosporine (2–4 mg/kg/day), prednisone (0.2–1.0 mg/kg/day), and azathioprine (0.2–2.0 mg/kg/day). Ten patients required antihypertensive therapy, either captopril or hydralazine, during the study. All were started on the antihypertensive regimen before their first Doppler echocardiographic evaluation. Two patients were receiving low-dose dopamine at the time of their first Doppler evaluation.

Clinical Parameters

Clinical characteristics examined included donor and recipient ages and graft ischemic times (time from cross-clamping of the donor aorta to release of the recipient aorta). Serial monitoring of weight, heart rate, and systemic arterial blood pressure was performed at the time of Doppler evaluation. Preoperative right heart pressures were measured with a balloon flow-directed catheter during a pretransplant screening evaluation.

Doppler Studies

The first Doppler echocardiographic study was performed between 4 and 7 days after transplantation and within 24 hours of the first endomyocardial biopsy. Subsequent studies were performed at 2, 4, and 6 weeks after transplantation, also within 24 hours of an endomyocardial biopsy. The Doppler echocardiographic evaluation included M-mode, two-dimensional, and pulsed-wave Doppler ultrasound examinations and was performed with a Hewlett-Packard Model 77020A imaging system with a 2.5-MHz transducer. M-mode measurements were performed from the parasternal long-axis view. Doppler tracings of the transmittal flow-velocity curve were obtained with the apical four-chamber view with the sample volume placed between the tips of the mitral leaflets, where maximal diastolic flow velocity is recorded. Simultaneous strip-chart recordings of Doppler tracings, electrocardiogram, and phonocardiogram were obtained at a paper speed of 100 mm/sec. The phonocardiogram was recorded with a 100-Hz filter at 12 dB/octave with a Hewlett-Packard microphone applied to the precordium where the aortic component of the second heart sound (A_2) was loudest.

Endomyocardial Biopsies

At least four specimens of right ventricular tissue were obtained at endomyocardial biopsy and graded for rejection according to the Billingham criteria.⁷ Only patients with no pathological evidence of cardiac rejection (i.e., no cellular infiltrate or necrosis) were included in this study.

Baseline Data

Baseline Doppler data of long-term transplant recipients with restrictive and nonrestrictive physiolo-

ogy are from a study reported from our laboratory by Valantine et al.⁸ Restrictive physiology was defined hemodynamically as an early diastolic rapid filling wave of at least 4 mm Hg on the left ventricular pressure tracing.

Data Analysis

Right ventricular end-diastolic diameter and left ventricular end-systolic and end-diastolic diameters were measured from M-mode recordings by the leading-edge-to-leading-edge method.⁹

Parameters of left ventricular diastolic function assessed are shown in Figure 1—IVRT measured from aortic valve closure on the phonocardiogram to the start of transmitral flow, peak early diastolic mitral flow velocity (E), and rate of peak early mitral flow deceleration expressed as pressure half-time (PHT).¹⁰ The influence of recipient atrial contraction on left ventricular filling has been documented by an invasive hemodynamic study.¹¹ Early diastolic events in the donor heart are significantly influenced by recipient atrial depolarization coincidentally occurring in late systole.¹² Thus, for analysis of IVRT, E, and PHT, only the cycles in which recipient atrial contraction occurred in diastole or early systole were used.

Statistics

For each study, Doppler values were obtained from an average of eight successive beats, excluding cycles in which recipient atrial contraction affected the data. The results of the 1-, 2-, 4-, and 6-week studies are given as mean values \pm 1 SD. Results from the 2-, 4-, and 6-week studies were compared with the 1-week results with analysis of variance by Fisher's PLDS method, and progressive changes over time were evaluated with a simple least-squares linear regression analysis. Linear regression analysis was also used to identify clinical and hemodynamic variables that correlated significantly with changes in individual Doppler parameters.

Results

Clinical Data

Hemodynamic data and M-mode measurements are shown in Table 1. Differences in the values obtained at 2, 4, and 6 weeks compared with 1-week values are examined for statistical significance. The initial heart rates were high and decreased at the end of the study. There was no significant variation in systolic blood pressure. The relative weight changes at 2, 4, and 6 weeks with the first week as the baseline demonstrated a small but not statistically significant weight loss. At 1 week after transplantation, right and left ventricular cross-sectional M-mode measurements and left ventricular percent fractional shortening were within reported normal limits.¹³ Serial right ventricular measurements seem to decrease during the first 4 weeks after transplantation, but the trend did not continue at 6 weeks. Left ventricular

TABLE 1. Serial Hemodynamic and Two-dimensional Echocardiographic Data

	Week			
	1	2	4	6
Hemodynamics				
HR (beats/min)				
Mean	89.4	81.9	83.1	75.4
SD	13.4	5.64	8.04	10.4
<i>p</i>	...	NS	NS	0.004
SBP (mm Hg)				
Mean	135	132	133	144
SD	20.2	14.4	14.9	19.1
<i>p</i>	...	NS	NS	NS
DBP (mm Hg)				
Mean	75	78	87	75
SD	12.8	8.5	11.2	10.4
<i>p</i>	...	NS	0.001	NS
RWC (kg)				
Mean	...	-2.54	-2.83	-1.22
SD	...	3.12	3.7	3.35
<i>p</i>	...	NS	NS	NS
Two-dimensional echocardiography				
RV (cm)				
Mean	2.69	2.49	2.41	2.58
SD	0.61	0.65	0.57	0.41
<i>p</i>	...	NS	NS	NS
LV D (cm)				
Mean	4.62	4.7	4.58	4.63
SD	0.44	0.61	0.48	0.6
<i>p</i>	...	NS	NS	NS
LV S (cm)				
Mean	2.96	2.95	2.87	2.99
SD	0.38	0.53	0.52	0.45
<i>p</i>	...	NS	NS	NS
%FS				
Mean	35.8	36.6	37.5	34.7
SD	5.86	6.99	7.32	4.97
<i>p</i>	...	NS	NS	NS

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RWC, relative weight change compared to 1 week weight; RV, right ventricle; LV D, left ventricular diastolic dimension; LV S, left ventricular systolic dimension; %FS, percent fractional shortening.

chamber measurements and percent fractional shortening also did not change significantly.

1-Week Doppler Data

Doppler indexes of mitral inflow are shown in Table 2. The values measured 1 week after transplantation are similar to parameters previously reported from this laboratory in transplant patients suffering from chronic restrictive physiology.⁸ IVRT and PHT are significantly shorter and early diastolic filling velocity is slightly higher than in nonrestrictive transplant patients. In each patient, Doppler indexes were compared with preoperative pulmonary systolic pres-

TABLE 2. Doppler Echocardiographic Data of Study Group and Previously Reported Transplant Patients

	R	Week				
	(10 patients)	1 (25 patients)	2 (25 patients)	4 (25 patients)	6 (10 patients)	NR (55 patients)
IVRT (msec)						
Mean	65	65	71	79	95	84
SD	16	18	17	24	17	13
<i>p</i>	NS	<0.05	<0.05	...
E (m/sec)						
Mean	0.82	0.77	0.76	0.68	0.63	0.73
SD	0.22	0.20	0.20	0.16	0.12	0.16
<i>p</i>	NS	NS	<0.05	...
PHT (msec)						
Mean	34	39	42	51	48	50
SD	17	8	10	14	11	12
<i>p</i>	NS	<0.05	NS	...

R, restrictive; NR, nonrestrictive; IVRT, isovolumic relaxation time; E, peak early filling velocity; PHT, pressure half-time.

Data from Valantine et al.⁸

tures, preoperative pulmonary vascular resistances, durations of cardiopulmonary bypass, total ischemic times, and ages of donor hearts. None of these preoperative or operative variables correlated significantly with the 1-week Doppler parameters. The selected correlation coefficients are shown in Table 3.

Serial Doppler Data

Serial measurements of the Doppler indexes evolved from an initially restrictive pattern toward a nonrestrictive pattern. IVRT and PHT progressively increased, and by 4 weeks they were significantly different than values obtained at 1 week (Figure 2). Peak early filling velocity decreased during the period of evaluation, and this change reached statistical significance by 6 weeks. The 6-week Doppler indexes were similar to values measured in transplant patients with a hemodynamically confirmed nonrestrictive filling pattern.⁸ There were no significant differences in Doppler indexes among patients with different antihypertensive and immunosuppressive regimens.

Discussion

Restrictive filling of the left ventricle is characterized by delayed myocardial relaxation and reduced compliance; this results in abnormally large increases in early diastolic left ventricular pressures with small

increments in volume and abrupt termination of filling in the first one third to one half of diastole.^{14,15} Doppler characteristics of restrictive and nonrestrictive filling in a population of cardiac transplant patients have been previously reported from this laboratory.⁸ Patients underwent Doppler and hemodynamic evaluations during their annual evaluation an average of 6 years after transplantation. Despite normal systolic function, most patients had abnormal filling characterized by prolonged IVRT and PHT, indicating abnormal left ventricular relaxation. A few patients (15%) had a restrictive filling pattern evidenced by a shortened IVRT and PHT and increased early diastolic filling velocity compared with "normal" transplant patients. These findings correlated with the presence of a sharp early diastolic dip followed by an abrupt rise in pressure on the left ventricular pressure tracing. They also correlated with increased filling pressures and may have been related to incidence of rejection.⁸ In the present study, patients demonstrated a similar restrictive physiology in the absence of rejection during the early postoperative period. However, during the subsequent 6 weeks, these indexes gradually progressed to a nonrestrictive filling pattern. These findings may be explained by initially impaired left ventricular diastolic function and an associated postoperative volume load. As diastolic function improved and the patients reached a volume equilibrium, preload decreased, left ventricular IVRT and PHT prolonged, and early filling velocity decreased.

The Doppler-derived IVRT and transmitral inflow pattern reflect a complex interaction of physiological parameters. IVRT is determined by aortic pressure at valve closure, rate of left ventricular pressure fall, and height of left atrial pressure. Systolic blood pressures were normal and varied insignificantly during the study. Left atrial pressure, indirectly evaluated by measuring pulmonary capillary wedge pres-

TABLE 3. Correlation Coefficients From Linear Regression Analysis Among Selected Data

	SBP	IT	CBT	PAS
IVRT	0.066	0.343	0.284	0.319
E	0.275	0.088	0.439	0.127
PHT	0.011	0.006	0.399	0.158

SBP, systolic blood pressure; IT, total ischemic time; CBT, cardiopulmonary bypass time; PAS, pulmonary artery systolic pressure; IVRT, isovolumic relaxation time; E, peak early filling velocity; PHT, pressure half-time.

None of the correlation coefficients reached statistical significance.

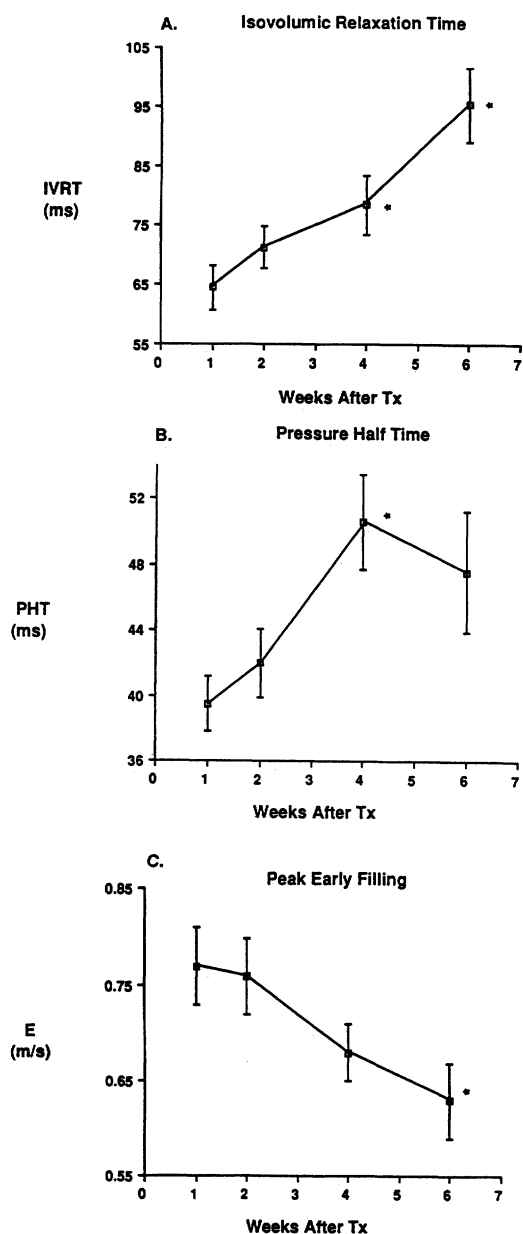


FIGURE 2. Graphs of Doppler echocardiographic indexes of mitral inflow measured serially for as long as 6 weeks after cardiac transplantation. Panel A: IVRT, isovolumic relaxation time. Panel B: PHT, pressure half-time. Panel C: E, peak early filling velocity. Values are given as mean \pm SEM. *Statistical significance ($p < 0.05$) compared with values obtained 1 week after transplantation.

sure, has been shown to be elevated in the immediate postoperative period and to normalize subsequently during 4–8 weeks.^{5,6} All other variables being constant, a progressive decrease in absolute left atrial pressure would prolong the IVRT, as seen in the present study populations. A lower left atrial pressure is consistent with a decrease in intravascular volume but may also indicate an improvement in allograft atrial and ventricular compliance. The role of each of these various components cannot be assessed without specific hemodynamic data.

A decreased rate of relaxation produces prolongation in IVRT as long as left ventricular filling pressures are not elevated.¹⁶ While impaired relaxation properties of the ventricle would be an additional explanation for the progressive prolongation of IVRT documented in this study, it is more likely that relaxation improved during the first 6 postoperative weeks. Ischemia may transiently affect active relaxation properties of the myocardium, but there was no direct correlation between duration of the ischemia and Doppler parameters. This may be because the first Doppler examinations were not performed until 4–7 days after surgery, but it is more probable that the effect of the elevated left atrial pressure on shortening IVRT overrides the opposite effect of a decreased rate of relaxation.

The early peak diastolic flow velocity reflects the atrioventricular driving pressure.^{16,17} This is established by left atrial pressure and function as well as by rate of left ventricular relaxation and extent of left ventricular filling. Isolated decreases in left atrial pressure lower the peak early filling velocity.¹⁸ Because peak early filling velocity gradually decreased during the study, it appears that resolution of early postoperative elevated left atrial pressures overrides any effect of an improving relaxation rate on the peak early filling velocity.

Extent of left ventricular diastolic filling is regulated in part by the passive compliance of the left ventricle and extrinsic or extracardiac compressive factors.¹⁹ Abbreviated filling is reflected by shortening of PHT. Operative ischemia could possibly compromise passive compliance immediately after transplantation, which then improves during the first 6 postoperative weeks; this may account for the initially abbreviated and then prolonged early mitral deceleration time.

The pericardium is not closed at the end of the operation, but early postoperative pericardial effusions do occur on a regular basis. A study from this laboratory demonstrated that the presence of a minimal-to-moderate amount of pericardial fluid, similar to the amount found in patients in the present study, did not correlate with any of the evaluated mitral Doppler parameters.²⁰ This suggests that extrinsic compression is not a major influence on diastolic indexes in the early postoperative period.

The initial restrictive Doppler indexes recorded soon after transplantation, which subsequently improve, are the result of a set of complex and separate but interrelated factors. Thus, it is difficult to correlate individual Doppler indexes with any one parameter of diastolic function. The initially shortened IVRT and increased early filling velocity reflect the predominant influence of elevated atrioventricular driving pressure, and the shortened PHT shows a decreased extent of filling. In the setting of preserved left ventricular systolic function, the elevated filling pressures and abbreviated extent of filling are in part a consequence of compromised myocardial diastolic properties and restrictive left ventricular physiology;

this physiology is reflected in the Doppler diastolic filling pattern.

These data are supported by a recently reported hemodynamic study.⁶ Elevated right heart filling pressures and an elevated pulmonary capillary wedge pressure were found 24–48 hours after transplantation. These normalized during the course of 8 weeks and showed that a restrictive pattern of filling could be augmented with an intravenous volume challenge. This occurred in the setting of preserved, unchanging systolic function, similar to the present study. The hemodynamic observations did not correlate with the history of episodes of pathologically confirmed rejection.⁶

Doppler echocardiography is being investigated as a means of screening for cardiac allograft rejection.^{1,2} At our institution, transplant patients are followed with serial Doppler echocardiographic evaluations. Using the patient as his or her own control, when a trend is noted in the Doppler parameters that is suggestive of increasing restrictive physiology, patients may undergo an endomyocardial biopsy sooner than routinely scheduled. The incidence of rejection is highest in the early postoperative period, when results from the present study show that the nonrejecting heart is evolving away from a restrictive toward a nonrestrictive filling pattern. It is important to understand these early postoperative changes because they may decrease the sensitivity of the Doppler echocardiographic patterns for rejection monitoring during this period.

Limitations

Although these Doppler data suggest resolution of an initially restrictive left ventricular filling pattern and elevated left heart filling pressures, there is no direct hemodynamic confirmation of this process. This study is limited in that it relies on hemodynamic observations and correlates with Doppler findings from previous reports. The physiology of hemodynamic changes soon after transplantation has not been fully investigated; thus, the various factors discussed in the present study are speculative. Future research would benefit from measurements of the left atrium–left ventricle pressure gradient, rate of relaxation, and left ventricular compliance characteristics. This information is difficult to acquire; even when it is available, assessment of left ventricular diastolic function remains extremely complex and controversial.^{21,22}

Because of the high patient drop-out rate between 4 and 6 weeks, the 6-week data have limited statistical value, although a trend is suggested. In the 10 patients in whom complete 6-week data were obtained, Doppler echocardiographic trends similar to those of the total patient population occurred. In this subset of patients, the change in IVRT reached statistical significance at 4 weeks, and the changes in the PHT and early filling velocity reached statistical significance at the 6-week study.

Conclusions

The present study demonstrates a Doppler-derived mitral inflow pattern soon after cardiac transplantation that is suggestive of restrictive physiology and elevated left heart filling pressures; this pattern improves during the first 4–6 postoperative weeks. While no clinical characteristics correlate with this process, previous hemodynamic studies confirm the proposed physiology. Given the increasing use of Doppler echocardiography in screening for transplant rejection, it is important to be familiar with these physiological changes and to be cautious in interpreting them as signs of acute rejection during the early postoperative period.

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