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Echocardiographic Characterization of the Improvement in Right Ventricular Function in Patients With Severe Pulmonary Hypertension After Single-Lung Transplantation

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Objectives. **This study was designed to characterize immediate, early and long-term changes in right ventricular structure and function, as defined by two-dimensional and Doppler echocardiography, after single-lung transplantation in patients with severe pulmonary hypertension.**

Background. **Single-lung transplantation has recently been shown to dramatically improve hemodynamics in patients with primary pulmonary hypertension who had unsuccessful medical therapy.**

Methods. **Fourteen patients with severe pulmonary hypertension who underwent single-lung transplantation were studied with transthoracic and transesophageal two-dimensional and Doppler echocardiography. Right ventricular dimensions were measured in the apical four-chamber view. Right ventricular ejection and acceleration times and peak velocity of tricuspid regurgitation were measured by Doppler study. Results of right heart catheterization were available early (<3 months) after transplantation in 10 of 13 patients and late after transplantation (6 months to 2 years) in 11 patients.**

Results. **In the early posttransplantation studies, right ventricular dimensions decreased and fractional area change and ejection fraction increased in all patients, but right ventricular wall thickness did not change significantly. Tricuspid regurgitation lessened markedly in all patients. Long-term decreases in right ventricular dimension and improvement in systolic function were sustained. Right ventricular wall thickness significantly decreased compared with the early postoperative value (0.76 ± 0.1 cm compared with 0.63 ± 0.14 cm, $p < 0.02$).**

Conclusions. **Two-dimensional echocardiography demonstrates sustained improvement in right ventricular function after single-lung transplantation for severe pulmonary hypertension despite severe preoperative dysfunction.**

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Severe pulmonary hypertension invariably results in significant right atrial and ventricular enlargement, with severe right ventricular dysfunction. Progressive hemodynamic deterioration in patients with primary pulmonary hypertension is associated with a poor long-term prognosis, with a median survival from the time of diagnosis of 2.8 years (1). Recently, single-lung transplantation has been shown to dramatically improve hemodynamics in patients with severe pulmonary hypertension who had unsuccessful medical therapy (2–10). In the initial report from our institution, the pulmonary artery systolic pressure and resistance were documented to decrease to nearly normal levels immediately after transplantation, with immediate improvement in right ventricular function (7,8). However, the extent to which chronic right ventricular compensatory changes regress over the long term after transplantation has not been defined. Accordingly, this study was designed to characterize immediate, early and long-term changes in right ventricular structure and function by use of echocardiography. Changes in right ventricular chamber dimensions, wall thickness and diastolic and systolic function with transthoracic and transesophageal two-dimensional Doppler echocardiography were characterized in patients before and after single-lung transplantation.

Methods

Study patients. Fourteen consecutive patients (10 women and four men with a presumed diagnosis of primary pulmonary hypertension who underwent single-lung transplantation [12 right lung, 2 left lung]) were studied. The surgical procedure and the clinical response of seven of the patients have been reported elsewhere (7).

Echocardiography. Two-dimensional and Doppler transthoracic echocardiography were performed before the transplantation procedure (mean 93 ± 58 days) in all patients. Posttransplant studies were performed early (<90 days) after the operation in 14 patients. Twelve patients underwent late

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follow-up studies (172 to 809 days). In addition, before receiving a transplant, 13 patients underwent biplane transesophageal echocardiography with color flow imaging and intravenous agitated saline solution contrast injections to accurately evaluate the presence of intracardiac shunts and to exclude other intracardiac or pulmonary artery abnormalities. Six patients underwent intraoperative transesophageal echocardiographic examination before and immediately after lung transplantation.

The calculation of right ventricular chamber sizes was based on data obtained in the transthoracic two-dimensional echocardiographic apical four-chamber view (11,12). End-diastolic and end-systolic areas were measured off-line by two observers unfamiliar with the clinical status of patients. Three consecutive cardiac cycles were measured without controlling for respiration, and values were averaged for all area measurements. Right ventricular fractional area change (RV FAC) was calculated as follows:

$$\text{RV FAC} = [(\text{EDA} - \text{ESA})/\text{EDA}] \times 100,$$

where EDA is the end-diastolic area and ESA the end-systolic area. Right ventricular volumes (RV Vol) at end-diastole and end-systole were derived by the area-length method:

$$\text{RV Vol} = [(0.85)(\text{area})^2]/\text{RV LAX},$$

where RV LAX is the right ventricular long-axis length measured in cm. The right ventricular ejection fraction (RVEF) was determined as follows:

$$\text{RVEF} = [(\text{RV EDV} - \text{RV ESV})/\text{RV EDV}] \times 100,$$

where RV EDV is the right ventricular end-diastolic volume and RV ESV is the right ventricular end-systolic volume. Right ventricular wall thickness was measured at end-diastole in a view (subcostal four-chamber or parasternal long or short axis) that allowed best definition of the right ventricular free wall.

Pulsed and continuous wave Doppler spectral recordings were obtained in all patients. The right ventricular ejection time (in ms) was measured as the time from onset to cessation of transpulmonary systolic flow by use of pulsed wave Doppler recordings at the pulmonary valve annulus from the parasternal short-axis view. The acceleration time (in ms) was derived as the time interval from the onset of flow to peak velocity. The spectral envelope of transpulmonary valve systolic flow was also analyzed for derivation of the flow velocity integral and is expressed in cm. Peak diastolic flow velocities across the tricuspid and mitral valves were obtained by Doppler echocardiography from the apical four-chamber view. The ratio of the early diastolic wave to atrial component was calculated with the sample volume placed at the valve leaflet tips. Continuous wave Doppler was used to determine the peak velocity of regurgitant flow across the tricuspid valve during systole for estimation of right ventricular systolic pressures. The instantaneous pressure (P) drop (in mm Hg) across the tricuspid valve was calculated as $P = 4V^2$, where V is the peak velocity, and 10 was added as an estimate of the right atrial pressure to derive the pulmonary artery systolic pressure. In addition, on the basis of color flow Doppler images, the tricuspid regurgitant jet was semiqualitatively characterized as mild, moderate or severe.

Transesophageal echocardiography was primarily used for preoperative assessment for the presence of atrial septal defects, and the transgastric short-axis view at the left ventricular papillary muscle level was used to derive end-diastolic and end-systolic right ventricular areas. In six patients, the response of the right ventricular size and function to single-lung transplantation was assessed immediately after the operation.

Ten randomly selected studies were analyzed 1 to 3 months after the initial review to determine observer variability who were unaware of patient identity or treatment by observers. Intraobserver and interobserver variability was <10% for all echocardiographic measurements.

Measurement of right heart pressures. Right atrial, right ventricular, pulmonary artery and pulmonary artery occlusive pressures were measured with a flow-directed balloon-tipped pulmonary artery catheter leveled to the midaxillary line. Cardiac output was estimated by thermodilution technique. Pulmonary vascular resistance is reported in Wood U. Right heart and pulmonary artery catheterization procedures were performed before and after transplantation at intervals of 1, 3 and 6 months and 1 and 2 years. Right heart catheterization was performed for early follow-up in 10 of 13 patients at 1 month and in the remaining 3 patients at 3 months. Late follow-up studies (6 months to 2 years) were also available for 11 patients.

Statistical analysis. All measurements represent the mean value ± SD of three consecutive cardiac cycles. Differences among early, preoperative and late postoperative transthoracic echocardiographic values were analyzed by analysis of variance for repeated measures. Differences between studies were analyzed by the Scheffé F test. Preoperative and immediately postoperative transesophageal echocardiographic measurements were analyzed by a paired *t* test. A statistically significant difference was assumed at $p < 0.05$.

Results

Preoperative echocardiographic evaluation. Transthoracic two-dimensional echocardiography demonstrated marked right atrial and ventricular dilation, with reduced right ventricular fractional area change and ejection fraction in all patients (Table 1). All but two patients had pulsed wave Doppler evidence of shortened pulmonary artery acceleration time (<100 ms). Continuous wave Doppler examination of the tricuspid regurgitation jet yielded an estimation of pulmonary artery systolic pressure that was consistent with the findings at cardiac catheterization, indicative of severe pulmonary hypertension. In 11 of 14 patients the Doppler-estimated and catheter-measured pressures were >70 mm Hg

Table 1. Right Ventricular Variables by Transthoracic Echocardiography

	Study			
	Preop	Early Postop	Late Postop	p Value
RV EDA (cm^2) (n = 13)	31.3 ± 7.3	17.3 ± 6.3	16.9 ± 4.6	< 0.0001
RV ESA (cm^2) (n = 13)	25.4 ± 7.0	9.9 ± 4.0	9.5 ± 3.8	< 0.0001
RV FAC (%) (n = 13)	19.7 ± 6.5	43.8 ± 8.9	44.7 ± 10.3	< 0.0001
RV EF (%) (n = 13)	28.3 ± 8.1	59.9 ± 11.0	59.9 ± 14.0	< 0.0001
RV ET (ms) (n = 12)	265.4 ± 44.2	273.7 ± 33.8	292.6 ± 46.9	0.19
PA acceleration time (ms) (n = 12)	68.1 ± 26.9	104.8 ± 25.3	104.8 ± 24.4	< 0.0005
PV TVI (cm) (n = 12)	9.5 ± 3.9	15.9 ± 2.8	16.9 ± 3.9	< 0.0001

Values presented are mean value ± SD. EDA = end-diastolic area; EF = ejection fraction; ESA = end-systolic area; ET = ejection time; FAC = fractional area change; PA = pulmonary artery; PV = pulmonary valve; RV = right ventricle; TVI = time-velocity integral; Postop = after transplantation; Preop = before transplantation.

(peak regurgitant jet velocity >4.0 m/s). All patients had significant right ventricular free wall hypertrophy (mean 0.76 ± 0.10 mm [range 0.54 to 0.91]).

Transthoracic two-dimensional color flow and continuous wave Doppler evaluation demonstrated significant tricuspid and pulmonary valve regurgitation in all patients. In 10 of 13 patients the severity of tricuspid regurgitation was moderate to severe. Pulmonary regurgitation was mild in the majority of patients (86%).

Transesophageal echocardiography demonstrated a patent foramen ovale in nine patients (69%) and atrial septal defects in two (15%) (one defect was an ostium secundum and the other a sinus venosus defect). Five of the 11 intracardiac shunts had not been identified by transthoracic echocardiography or during preoperative evaluation with right heart catheterization.

Early response to lung transplantation. All patients manifested dramatic decreases in pulmonary artery pressures, which were assessed by right heart catheterization 2 months after single-lung transplantation (Table 2), and cardiac output had increased to normal values. There was no change in the pulmonary artery occlusive pressure or heart rate. Pulmonary vascular resistance, while decreasing dramatically, remained mildly elevated (1.8 ± 0.7 Wood U). There was one death from sepsis on day 6 after transplantation.

The dramatic decrease in pulmonary artery pressure was associated with immediate decreases in right ventricular dimensions, as documented intraoperatively in the six patients who underwent preoperative and immediate postoperative transesophageal echocardiographic examination. Both the end-diastolic and end-systolic areas decreased significantly in all six patients, from a mean value of 24.4 ± 3.4 to 19.0 ± 3.8 cm^2 ($p < 0.002$) and 21.0 ± 3.0 to 13.2 ± 2.7 cm^2 ($p < 0.0001$), respectively, whereas the right ventricular fractional area change increased significantly from preoperative values (13.9 ± 2.0% to 30.6 ± 3.2%, $p < 0.0001$).

Improvement in right ventricular areas and function was also evident from all echocardiographic studies obtained within the 3 months after transplantation. Table 1 summarizes the findings of transthoracic echocardiography in studies performed at 59 ± 28 days after transplantation. There was a decrease in right ventricular end-diastolic and end-

Table 2. Preoperative Versus Postoperative Hemodynamic Data

	Study			
	Preop	Early Postop	Late Postop	p Value
RAP (mm Hg) (n = 12)	8.0 ± 3.7	1.9 ± 2.2	2.5 ± 2.4	< 0.0001
RVS (mm Hg) (n = 12)	98.9 ± 16.9	29.9 ± 16.9	28.7 ± 4.5	< 0.0001
RVD (mm Hg) (n = 12)	11.8 ± 7.2	2.8 ± 3.4	4.8 ± 2.7	< 0.0001
PAS (mm Hg) (n = 12)	100.4 ± 18.1	30.1 ± 11.6	28.0 ± 4.9	< 0.0001
PAD (mm Hg) (n = 12)	43.5 ± 6.6	13.5 ± 6.9	12.0 ± 4.2	< 0.0001
PAM (mm Hg) (n = 12)	65.6 ± 13.8	18.4 ± 7.7	17.8 ± 3.9	< 0.0001
PVR (Wood U) (n = 8)	14.7 ± 3.8	1.7 ± 0.7	2.0 ± 0.8	< 0.0001
PCWP (mm Hg) (n = 12)	9.1 ± 4.2	9.0 ± 8.3	7.6 ± 2.1	0.77
CI (liters/min per m^2) (n = 9)	2.5 ± 0.9	3.5 ± 0.7	3.2 ± 0.7	0.02
HR (beats/min) (n = 10)	84.7 ± 13.0	87.0 ± 9.2	84.5 ± 10.1	0.8

Values presented are mean value ± SD. CI = cardiac index; HR = heart rate; PAD = pulmonary artery diastolic pressure; PAM = pulmonary artery mean pressure; PAS = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RVD = right ventricular diastolic pressure; RVS = right ventricular systolic pressure; other abbreviations as in Table 1.

Table 3. Mitral and Tricuspid Valve Indexes by Transthoracic Echocardiography

	Study			
	Preop	Early Postop	Late Postop	p Value
TV peak E (cm/s) (n = 10)	47 ± 26	45.2 ± 15.6	49.4 ± 12.2	0.88
TV peak A (cm/s) (n = 11)	47.1 ± 15.4	50.2 ± 13.9	50.5 ± 14.1	0.83
TV E/A ratio (n = 10)	1.4 ± 1.1	0.9 ± 0.4	0.9 ± 0.26	0.65
MV peak E (cm/s) (n = 12)	40.8 ± 13.7	50.9 ± 17.7	56.5 ± 13.7	0.03
MV peak A (cm/s) (n = 11)	48.0 ± 10.5	60.4 ± 13.6	59.5 ± 13.8	0.003
MV E/A ratio (n = 9)	0.89 ± 0.40	0.86 ± 0.30	0.94 ± 0.19	0.76

Values presented are mean value ± SD. A = atrial contraction wave; E = early filling wave; MV = mitral valve; TV = tricuspid valve; other abbreviations as in Table 1.

systolic areas, resulting in significant improvement in right ventricular fractional area change and ejection fraction. Right ventricular free wall thickness did not change significantly in the early posttransplantation period compared with the value before transplantation (0.76 ± 0.1 vs. 0.74 ± 0.18 cm, p = NS).

Right ventricular ejection times between the early postoperative and preoperative studies were not significantly different (Table 1). The acceleration time of the pulmonary systolic flow velocity did increase significantly, however. Consistent with the improvement in right ventricular systolic function, the pulmonary time-velocity integral increased significantly in all patients early after transplantation. Analysis of right ventricular diastolic filling, as characterized by the peak early (E) and atrial (A) diastolic flow velocities and the E/A ratio across the tricuspid valve revealed little difference between values before transplantation and early and late follow-up (Table 3). However, an increase in peak mitral diastolic E and A velocities was noted early after transplantation. Color flow and continuous wave Doppler studies showed an immediate decrease in the severity of tricuspid regurgitation in all patients. Although 6 of the 13 patients continued to have evidence of tricuspid regurgitation on color flow images, it was trivial in all. Pulmonary valve regurgitation lessened as well. Only three patients continued to demonstrate minimal regurgitation at early follow-up. In addition, color flow Doppler images revealed a pronounced increase in the flow velocity intensity of pulmonary venous inflow by way of the transplanted lung into the left atrium in the postoperative study. This was best observed in the apical four-chamber view and was probably related to increased flow in the transplanted lung.

Long-term response to pulmonary transplantation. The improvements observed in right ventricular chamber areas and systolic function early after transplantation were sustained in all but one patient, who died 1 year after transplantation. In this patient, transthoracic echocardiography demonstrated dilation of the right ventricle, with a decrease in the fractional shortening and a diminution in the pulmonary valve systolic time-velocity integral. Hemodynamic studies demonstrated recurrence of severe pulmonary hypertension. In the remaining 12 patients, right ventricular fractional area shortening and ejection fraction remained normal. In the 12 patients whose right ventricular wall thickness could be accurately assessed preoperatively and in the late postoperative study, a significant decrease was observed (0.78 ± 1.2 vs. 0.63 ± 0.14 cm, $p < 0.02$), but the thickness remained increased (>5 mm) in all but 2 patients.

There were no differences in the pulsed wave Doppler indexes of right ventricular systolic function or in the diastolic flow patterns across the tricuspid and mitral valve in the late postoperative follow-up compared with early postoperative studies (Table 3). Similarly, the initial improvements in tricuspid and pulmonary valve regurgitation, cardiac output, pulmonary artery and right heart pressures observed immediately after operation have remained unchanged in the 12 surviving patients, although a mild increase in pulmonary vascular resistance persists for the group as a whole. However, when the one patient who redeveloped pulmonary hypertension is excluded, mean pulmonary vascular resistance for the group decreases to 2.08 Wood U (p = 0.8).

Discussion

Comparison with previous studies. Single-lung transplantation for primary pulmonary hypertension has been shown to result in dramatic improvement in pulmonary artery pressures and right ventricular systolic function. Yeoh et al. (5) studied four patients with two-dimensional echocardiography and radionuclide ventriculography 1 to 3 months after single-lung transplantation and found decreases in right ventricular dimensions and improvement in ejection fraction in all. In another study of 12 patients who underwent transplantation for pulmonary fibrosis, Carere et al. (6) found sustained improvement in right ventricular ejection fraction by radionuclide ventriculography. In the present study, the decrease in the pulmonary artery pressure and vascular resistance resulted in immediate improvement in right ventricular ejection fraction and diminution in chamber dilation. However, a longer period of time was required before there was apparent regression in the right ventricular free wall hypertrophy. This result is consistent with the findings of Rich and Brundage (13), who reported regression of right ventricular hypertrophy (by 12-lead electrocardio-

gram) after reduction of pulmonary artery pressure with calcium channel blocker therapy after 1 year of treatment.

Single-lung transplantation in severe pulmonary hypertension. The dramatic and sustained decreases in right ventricular chamber areas and restoration of normal systolic function that occurred after single-lung transplantation indicate that chronic right ventricular dysfunction in patients with severe pulmonary hypertension is reversible and that marked right ventricular dysfunction does not preclude single-lung transplantation or the expectation of subsequent and sustained long-term improvement. These findings support a role for single-lung transplantation as opposed to heart-lung transplantation in the treatment of patients with primary pulmonary hypertension (7,8). Preoperative transesophageal echocardiography was also found to be useful in evaluating patients referred for lung transplantation. In five patients, significant right to left atrial shunting (missed on transthoracic echocardiography contrast studies) was discovered by transesophageal echocardiography. Atrial septal defects were noted in two of the five patients, raising the possibility of secondary pulmonary hypertension. However, their response to single-lung transplantation was the same as that of patients without atrial septal defects. Identification of intracardiac shunts before operation helps to determine the surgical approach. Simultaneous right single-lung transplantation and shunt repair avoid potential postoperative complications, such as shunting, hypoxemia or paradoxic embolism, alone or in combination.

Diastolic dysfunction in severe pulmonary hypertension. Severe pulmonary hypertension and right ventricular dilation may also lead to right and left ventricular diastolic dysfunction (14–16). Pulsed Doppler analysis of flow velocities across the tricuspid valve did not reveal significant changes in either early diastolic or atrial velocities or the early diastolic/atrial velocity ratio after the transplantation procedure. Although these findings may be due to altered loading conditions and a decrease in the severity of tricuspid regurgitation, we are unable to fully explain them. However, it is possible that they reflect persistent right ventricular diastolic abnormalities after transplantation. Increased early diastolic and atrial flow velocities across the mitral valve were observed after transplantation, which may be due to increased right ventricular stroke volume or improved left ventricular filling due to "normalization" of the position of the ventricular septum, both resulting from relief of increased impedance to right ventricular outflow.

Conclusions. Echocardiographic analysis of right ventricular function after single-lung transplantation for severe pulmonary hypertension indicates that despite severe preoperative dysfunction, dramatic and sustained improvement in right ventricular function occurs subsequent to reversal of pulmonary hypertension. Two-dimensional and Doppler echocardiography are suitable noninvasive techniques for the long-term follow-up of pulmonary artery pressures and right ventricular function in patients who have undergone single-lung transplantation.

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