Assessment of Left Ventricular Diastolic Function After Single Lung Transplantation in Patients With Severe Pulmonary Hypertension*

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Objectives: This study was designed to observe left ventricular filling by Doppler echocardiography before and after single lung transplantation in patients with severe pulmonary hypertension.

Background: Right ventricular pressure overload causes the deformation of the left ventricle by septal flattening toward its cavity, which may result in impaired left ventricular early filling. Recent studies have demonstrated the ability of single lung transplantation to restore right ventricular function in patients with severe pulmonary hypertension. However, changes in left ventricular filling after single lung transplantation have not been well studied.

Methods: We performed Doppler echocardiography in nine patients with severe pulmonary hypertension before, early (<3 months), and late (>1 year) after single lung transplantation. The study group consisted of eight female patients and one male patient with mean age of 32 years (range, 15 to 48 years). Six patients were diagnosed as having primary pulmonary hypertension and three as having secondary pulmonary hypertension. Nine age-matched normal subjects served as a control group. Doppler measurements included the following: transmitral flow early (E) and atrial (A) velocities, integrals (Ei and Ai), and left ventricular isovolumic relaxation time. The ratio of E/A and atrial filling fraction (Ai/Ei+Ai, AFF) were also determined. Left ventricular geometry was assessed from mid-short axis view with a circular shape factor (CSF).

Results: Early after lung transplantation, the left ventricular geometry became more circular with CSF (mean±SD) increasing from 0.63±0.09 to 0.88±0.05 (p<0.05). However, impaired early filling persisted in the patient group (E/A 0.7±0.1 vs preoperative 0.6±0.1, AFF 0.61±0.1 vs 0.64±0.1; both p=not significant). One year later, the left ventricular filling had returned to normal range with E/A 1.4±0.6 and AFF 0.35±0.1.

Conclusions: This study observed that the impaired left ventricular early filling persisted shortly after single lung transplantation in patients with severe pulmonary hypertension, despite findings that left ventricular geometry was restored earlier after reversal of pulmonary hypertension. The abnormal filling pattern appeared to be resolved 1 year later. The findings suggest the impaired early filling may be caused by intrinsic left ventricular abnormalities other than ventricular interaction in these patients.

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Key words: Doppler echocardiography; left ventricular filling; lung transplantation; pulmonary hypertension

Abbreviations: AFF=atrial filling fraction; CSA=cross-sectional area; CSF=circular shape factor; NS=not significant

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Right ventricular pressure overload causes the deformation of the left ventricle by septal flattening toward its cavity, which may result in impaired left ventricular early filling.1 Recent studies have demonstrated the ability of single lung transplantation to restore right ventricular function in patients with severe pulmonary hypertension.25 However, changes in left ventricular filling after single lung transplantation have not been well stud-
ied. Therefore, this study was designed to evaluate left ventricular filling dynamics before and after lung transplantation using Doppler echocardiography.

**Materials and Methods**

**Study Patients**

Between 1991 and 1996, 47 single lung transplantation procedures were performed in 45 consecutive patients at the University of Kentucky Hospital. Clinical diagnoses were severe pulmonary hypertension in 14 patients and end-stage of COPD in the remaining 31. Of the 14 pulmonary hypertension patients, 9 who had complete Doppler echocardiographic examinations preoperatively and postoperatively were selected for this study. Nine age-matched normal subjects served as a control group.

**Doppler Echocardiography**

Two-dimensional and Doppler echocardiography was performed in all study patients before, early (<3 months), and late (>1 year) after lung transplantation. Data were recorded on professional videotape and analyzed using a computer-assisted off-line work-station (Version 2.1; TomTec; Boulder, Colo).

Transmitral pulsed Doppler was obtained from an apical four-chamber view with a sample volume at the level of the mitral annulus. Three consecutive Doppler recordings were manually traced using a hand-held cursor, and the following variables were measured: peak early (E) and atrial (A) velocities and integrals (Ei, Ai). Ratio of E/A and atrial filling fraction (Ai/Ai+Ei, AFF) were then calculated. Heart rate was averaged from the previous measurements.

Left ventricular isovolumic relaxation time was measured as a time interval from aortic closure click to the beginning of the mitral inflow in the apical five-chamber view with a continuous wave cursor positioned to straddle the left ventricular inflow and outflow tract. A sweep speed of 100 cm/s was used for this recording.

A standardized index of eccentricity, circular shape factor (CSF), was employed to determine the degree of deviation of the left ventricular cross section from a perfect circle.  The planimetered cross-sectional area (CSA) from the mid-short axis view during end-systole was used to calculate mean left ventricular diameter: 

\[ d = \frac{2 \times (\text{CSA}/\pi)^{1/2}}{1} \]

The perimeter (P) for a perfect circle with this diameter was determined from 

\[ P = \pi d \]

This calculated perimeter was compared with the actual planimetered perimeter (observed perimeter) from the same echocardiographic image. Thus, the CSF was defined as follows: 

\[ \text{CSF} = \frac{\text{observed} P}{\text{calculated} P} \]

CSF=1.0 implies a circular shape, and CSF<1.0 implies increasing degree of eccentricity (Fig 1).

Continuous-wave Doppler was used to measure the peak velocity of tricuspid regurgitant flow for estimation of pressure gradient (mm Hg) between right ventricle and right atrium during systole: 

\[ \text{pressure gradient} = 4V^2 \]

where V is the peak velocity.

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**Figure 1.** Degree of the left ventricular (LV) geometric deformation determined by CSF. **Top:** two-dimensional echocardiographic images of LV cross-section obtained from mid-short axis view during end-systole. **Bottom:** measurements and calculations for CSF (see text for details). The LV image illustrated on the left appears nearly circular with a CSF of 0.99, while the one on the right is distorted by septal flattening and has a CSF of 0.74.

<table>
<thead>
<tr>
<th>Cross-Section Area (CSA)</th>
<th>16.48 cm²</th>
<th>18.14 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated Perimeter</td>
<td>14.38 cm</td>
<td>15.09 cm</td>
</tr>
<tr>
<td>Observed Perimeter</td>
<td>14.40 cm</td>
<td>17.48 cm</td>
</tr>
<tr>
<td>Circular Shape Factor (CSF)</td>
<td>0.99</td>
<td>0.74</td>
</tr>
</tbody>
</table>
velocity (m/s), and 10 was added as an estimate of the right atrial pressure to derive the right ventricular systolic pressure.10 Tricuspid regurgitation was evaluated from color Doppler flow images and graded as none, mild, moderate, or severe, depending on the maximal jet area seen from multiple views. This method is similar to that of grading mitral regurgitation.11 In addition, tricuspid annulus diameter as an index of right ventricular size was measured from an apical four-chamber view during enddiastole.

**Statistical Analysis**

Differences for each Doppler echocardiographic variable among preoperative, early, and late postoperative subgroups were analyzed by analysis of variance, and further comparisons between any two subgroups were carried out using Scheffé F test (StatView 512++; Macintosh; Agoura Hill, Calif). The unpaired t test was applied for comparing all measurements in preoperative and late postoperative subgroups, respectively, with those in control subjects. All descriptive data were expressed as mean values ± SD, and p<0.05 was considered significant.

**RESULTS**

**Clinical and Doppler Echocardiographic Features**

In the patient group, there were eight female patients and one male patient with mean age of 32 years (range, 15 to 48 years). Six patients were diagnosed as having primary pulmonary hypertension and the other three were diagnosed as having secondary pulmonary hypertension due to ventricular septal defect, atrial septal defect, and pulmonary vasculitis from systemic lupus erythematosus, respectively. Five patients received a left lung transplant and four received a right lung transplant.

Doppler echocardiography demonstrated marked right atrial and ventricular dilation with severe tricuspid regurgitation in eight of nine patients before the operation. Right ventricular systolic pressure was significantly elevated with a mean value of 90 mm Hg (range, 73 to 110 mm Hg). From mid-short axis view, the distorted left ventricular shape was observed throughout systole and diastole in all study patients with a mean CSA of 0.63±0.09 (p<0.01, compared with that in control subjects). Left ventricular filling was characterized by a diminished early filling (E: 32±6 cm/s; Ei: 2.8±1.0 cm; both p<0.01) and an enhanced atrial contribution to total filling (atrial filling fraction: 0.64±0.1, p<0.01). Finally, left ventricular isovolumic relaxation time was substantially prolonged with a mean value of 127±14 ms (p<0.01) (Table 1).

**Early Changes After Lung Transplantation**

All patients manifested dramatic decreases in right ventricular systolic pressure (from mean of 90 to 34, p<0.05), right ventricular size (from mean annulus diameter of 5.4 to 3.7, p<0.05), and severity of tricuspid regurgitation (trivial or mild in all patients) early (<3 months) after lung transplantation (Table 1). The dramatic improvement in left ventricular geometry was also documented in all patients by a significant increase in CSA (mean CSA of 0.63 to 0.8, p<0.05). Interestingly, the impaired early left ventricular filling (AFF 0.61±0.1 vs 0.64±0.1, p=not significant [NS]) and isovolumic relaxation time (115±16 vs 127±14, p=NS) did not significantly change compared with preoperative measure-

### Table 1—Changes in Doppler Echocardiographic Variables Before and After Single Lung Transplantation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Pre-TX</th>
<th>Early (3 mo)</th>
<th>Late (12 mo)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>80±13</td>
<td>87±15</td>
<td>89±12</td>
<td>81±12</td>
<td>NS</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>90±12</td>
<td>34±11</td>
<td>32±11</td>
<td>32±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVD, cm</td>
<td>3.1±0.3§</td>
<td>5.4±0.5§</td>
<td>3.7±0.5</td>
<td>3.8±0.5§</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>78±8</td>
<td>32±6</td>
<td>42±8</td>
<td>70±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>58±8</td>
<td>52±12</td>
<td>51±10</td>
<td>58±8</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>1.4±0.5</td>
<td>0.6±0.1</td>
<td>0.7±0.2</td>
<td>1.4±0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ei, cm</td>
<td>10.4±0.6</td>
<td>2.8±1.0</td>
<td>4.0±1.0</td>
<td>9.6±3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ai, cm</td>
<td>5.6±1.3</td>
<td>4.4±1.4</td>
<td>5.5±1.9</td>
<td>5.4±3.0</td>
<td>NS</td>
</tr>
<tr>
<td>AFF</td>
<td>0.37±0.1</td>
<td>0.64±0.1</td>
<td>0.61±0.1</td>
<td>0.35±0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>76±7</td>
<td>127±14</td>
<td>115±16</td>
<td>91±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CSF</td>
<td>0.90±0.2</td>
<td>0.63±0.9</td>
<td>0.88±0.5</td>
<td>0.87±0.81</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Data presented are mean values ± SD. TX= single-lung transplantation; early (3 mo)= early (<3 mo) after transplantation; late (12 mo)= late (>1 yr) after transplantation; HR= heart rate; RVSP= right ventricular systolic pressure; RVD= tricuspid annulus diameter; E= peak early filling velocity; A= peak atrial filling velocity; Ei= early filling integral; Ai= atrial filling integral; IVRT= left ventricular isovolumic relaxation time. p<0.05 for early (3 mo) vs pre-TX. p<0.05 for late (12 mo) vs pre-TX. p<0.05 for late (12 mo) vs control. p<0.01 for pre-TX vs control.
ments, despite dramatic alterations in left ventricular geometry following lung transplantation.

Late Changes After Lung Transplantation

One year later, the improvement in both right ventricular function and left ventricular geometry was sustained in all surviving patients. One patient died from respiratory failure 4 months after transplantation. A significant reduction in left ventricular relaxation time (from 127±14 to 91±8, p<0.05) was observed 1 year later after lung transplantation, which was associated with increases in left ventricular early filling, E from 32±6 to 70±12 cm/s (p<0.05) and Ei from 2.8±1.0 to 9.6±3.0 cm (p<0.05). No significant changes in atrial filling as measured by A or Ai were observed. Compared with Doppler measurements from the control group, all left ventricular diastolic variables but isovolumic relaxation time reached the normal range as defined by the control group.

Discussion

It is important to restore right ventricular function after single lung transplantation in pulmonary hypertension patients. A number of studies have shown that the right ventricular function improves dramatically immediately after transplantation, and the improvement is maintained for at least 2 years. Interestingly, our study indicated that the impaired left ventricular early filling persisted early after transplantation, despite the fact that pulmonary hypertension was alleviated and left ventricular geometry was restored. Our data also showed that the transmitral flow and isovolumic relaxation time might require up to 1 year to return to normal.

Louie et al. studied left ventricular filling by Doppler echocardiography in nine patients with primary pulmonary hypertension. They found a decrease in early filling, an increase in atrial contribution to total filling and a prolongation in isovolumic relaxation time in these patients. They also observed that the ventricular septum was flattened toward the left ventricular cavity at end-systole and early diastole, while at end-diastole, the ventricular septal configuration returned to a more normal shape. Our results agree with their findings regarding abnormal left ventricular filling; however, in our patients, the deformation of left ventricular geometry was seen throughout systole and diastole. Severe tricuspid regurgitation in our patients (eight of nine) may account for the difference. Regarding the mechanism of the left ventricular filling abnormalities in this setting, Louie et al hypothesized that the pattern of left ventricular filling might be altered by left ventricular geometric changes and in particular that early diastolic filling might be compromised.

Clearly, our study showed that shortly after lung transplantation, the impaired left ventricular early filling did not change, although right ventricular systolic pressure fell significantly and left ventricular geometry was restored in these patients. These findings suggest that factors other than ventricular geometry may play a role in alteration of filling dynamics. A previous study from our laboratory by Booth et al. showed that in atrial septal defect patients, the left ventricular compliance and muscle stiffness were adversely affected in the setting of chronic preload reduction. We speculate that because of severe pulmonary hypertension, the left ventricle experiences underfilling for years, resulting in a delayed diastolic adaptation after preload is restored. Based on Doppler filling pattern (reduced E wave) and prolonged isovolumic relaxation time observed from our patients, the abnormal left ventricular relaxation may be a factor that causes diastolic dysfunction. Thus, there are intrinsic factors other than ventricular interaction or geometry that may contribute to left ventricular diastolic dysfunction in patients with right ventricular volume or pressure overload.

Data from this study indicate that after transplantation, there is a temporal delay in physiologic return of normal filling patterns as assessed by transmitral Doppler, compared with the anatomic return of normal left ventricular geometry. Persistent symptoms such as shortness of breath, fatigue, and decreased exercise capacity in postoperative lung transplant patients may partially relate to this dissociation between physiologic and anatomic recovery.

Study Limitations

In this study, Doppler echocardiography was utilized to determine left ventricular filling dynamics. There are a number of variables affecting transmitral Doppler parameters, such as age, heart rate, mitral regurgitation, and loading conditions.

Age is unlikely to have significant impact on our results. Our patient age was relatively young (average, 32 years). As seen in the control group, the normal subjects had a predominant early filling pattern with E=78±8 cm/s and AFF=0.37±0.10. However, the pretransplant patients had a predominant atrial filling pattern with E=32±6 cm/s and AFF=0.64±0.10.

There was no significant difference of heart rate between patient and control groups, although it was slightly higher in the patient group (Table 1). Thus, it is unlikely that heart rate alone affected our results.

Absence or trivial degree of mitral regurgitation...
was seen in all patients and did not change over time. Therefore, this variable was not considered a factor in producing an increase in E wave.

Left ventricular loading conditions are likely to have undergone dramatic changes after lung transplantation. The increases in the preload resulting from improved pulmonary blood flow and reduced pulmonary artery resistance are able to augment Doppler early filling velocity. However, peak E velocity did not increase significantly until late (>1 year) after transplantation.

Left ventricular diastolic geometry was not assessed in this study. Left ventricular early diastolic geometry may be related to early filling. However, a previous study indicated that in patients with right ventricular pressure overload, the degree of septum distortion at early diastole was not significantly changed with respect to that at end-systole.1

Finally, the study population was small and further large-scale studies are required.

CONCLUSIONS

This study observed left ventricular filling dynamics by Doppler echocardiography before and after single lung transplantation in patients with severe pulmonary hypertension. The impaired early filling persisted shortly after transplantation, despite restoration of left ventricular geometry after reversal of pulmonary hypertension. The abnormal filling was not resolved until 1 year later. The findings suggest the impaired early filling may be caused by intrinsic left ventricular abnormalities other than ventricular interaction or geometry in these patients.

REFERENCES

1 Louie EK, Rich S, Brundage BH. Doppler echocardiographic assessment of impaired left ventricular filling in patients with right ventricular pressure overload due to primary pulmonary hypertension. J Am Coll Cardiol 1986; 8:1298-1306
14 Kuo LC, Quinones MA, Rokey R, et al. Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. Am J Cardiol 1987; 59:1174-78

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