Early Improvement in Left Ventricular Diastolic Function After Relief of Chronic Right Ventricular Pressure Overload*

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Chronic right ventricular pressure overload is associated with left ventricular diastolic dysfunction. Whether or not an abrupt reduction in pulmonary artery pressure in patients with chronic pulmonary hypertension results in early improvement of left ventricular diastolic function is unknown. To assess this, the Doppler indexes of left ventricular diastolic function and echocardiographic measures of left ventricular volume were analyzed in 22 patients (age, 41 ± 14 years, mean ± SD) before and within 1 week after pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Mean duration of cardiopulmonary symptoms was 37 months (range, 4 months to 9 years). After operation, mean pulmonary artery pressure and pulmonary vascular resistance decreased (50 ± 13 to 29 ± 9 mm Hg and 904 ± 654 to 283 ± 243 dynes · sec/cm², respectively, both p < 0.001), pulmonary artery wedge pressure was unchanged (11 ± 5 to 12 ± 5 mm Hg), and cardiac index increased (2.0 ± 0.5 to 2.8 ± 0.7 l/min/m², p < 0.001). Left ventricular end-diastolic volume and stroke volume increased significantly (58.5 ± 18.0 to 76.6 ± 25.0 ml and 30.3 ± 12.3 to 41.8 ± 12.5 ml, respectively, both p < 0.001) after surgery. Doppler measures of left ventricular diastolic function including peak early velocity of mitral inflow, deceleration of early filling, and early to late peak flow velocity ratio increased with surgery (48 ± 20 to 79 ± 24 cm/sec, p < 0.001, 2.6 ± 1.4 to 4.2 ± 1.8 m/sec², p < 0.002, and 1.04 ± 0.42 to 1.67 ± 0.60, p < 0.001, respectively), whereas peak atrial velocity did not change significantly (48 ± 10 to 49 ± 9 cm/sec). Furthermore, the indexes of left ventricular relaxation correlated with the end-systolic position of the interventricular septum as assessed by two-dimensional echocardiography (all p < 0.001). Thus, Doppler-derived indexes of left ventricular diastolic function improve markedly early after pulmonary thromboendarterectomy in patients with pulmonary hypertension despite long-standing symptoms. The changes in these indexes of left ventricular diastolic function, which correlate with changes in the position of the interventricular septum and occur in the setting of increases in left ventricular volume, suggest that abnormal left ventricular diastolic function seen in right ventricular pressure overload is a consequence of the right-left ventricular interaction and is mediated in large part through the interventricular septum. (Circulation 1989;80:823–830)

Abnormal transmitral flow velocity profiles obtained with Doppler echocardiography have been described in patients with chronic right ventricular pressure overload.1,2 Some investigators have attributed the redistribution of left ventricular filling into late diastole to the leftward displacement of the interventricular septum seen in pulmonary hypertension3–7 or to changes in intrinsic left ventricular compliance.8 Recent studies in patients with ischemic heart disease have shown that abnormal early diastolic velocities are due in part to abnormal left ventricular relaxation9–11 and that abnormal left ventricular geometry and nonuniformity of ventricular force and loading inactivation are partially responsible for prolongation of left ventricular relaxation.12 Because patients undergoing pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension show marked acute reductions in pulmonary artery pressures,13 they provide a unique opportunity to assess the reversibility of abnormal left ventricular diastolic function after right ventricular afterload.
reduction. In this study, changes in transmitral flow velocity profiles measured by Doppler echocardiography and left ventricular volumes were assessed early after pulmonary thromboendarterectomy. We also analyzed whether or not the changes in Doppler-derived indexes of left ventricular dysfunction were related to early changes in the position of the interventricular septum described previously in patients after pulmonary thromboendarterectomy.¹⁴

Methods

Study Population

Twenty-two patients who underwent thromboendarterectomy were included in the present analysis. There were 11 men and 11 women (mean age ± SD, 41 ± 14 years) with an average duration of cardiopulmonary symptoms before surgery of 37 months (range, 4 months to 9 years). All patients were in New York Heart Association functional Class III or IV at the time of surgery. These patients constitute a subgroup among the 38 patients who underwent pulmonary thromboendarterectomy between August 1986 and January 1988 at the University of California San Diego Medical Center. The remaining patients were not included in this analysis because of perioperative death in four patients, atrial fibrillation in one, significant left heart disease in one (two-vessel coronary artery disease and mild aortic stenosis), failure to perform either a preoperative or postoperative Doppler echocardiographic study in four, and poor quality Doppler echocardiographic studies in six patients.

As described previously, these patients underwent extensive evaluation before surgery to document proximal, surgically resectable pulmonary thrombi, including right- and left-sided heart catheterization, pulmonary angiography, and coronary arteriography.¹³,¹⁵,¹⁶ All patients underwent echocardiographic and hemodynamic evaluation before and after thromboendarterectomy.

Two-Dimensional and Pulsed Doppler Echocardiographic Studies

Preoperative two-dimensional and pulsed Doppler echocardiographic examinations were performed within 1 week before surgery in 16 patients, within 3 weeks in three patients, and within 3 months in three patients. All patients had stable symptoms without changes in clinical status between the time of the Doppler echocardiographic study and surgery. Within 1 week after surgery, all patients underwent repeat Doppler echocardiographic studies.

Two-dimensional echocardiography. Standard two-dimensional images were obtained from the parasternal short axis at the level of the papillary muscles and from the apex (apical two- and four-chamber views) using a Hewlett-Packard 77020A imaging system (Andover, Massachusetts). Images were recorded on a 0.5-in. videotape, and a cardiac cycle was displayed in a continuous loop format and analyzed on a commercially available off-line system (MicroSonics, Indianapolis, Indiana). The end-diastolic image was selected at the time of the peak of the R wave on the electrocardiogram, and the end-systolic image was defined as the frame in which the smallest left ventricular chamber size was seen.

Pulsed Doppler echocardiography. Pulsed Doppler echocardiography was performed using the same ultrasonograph system as above. A standard apical four-chamber view of the heart was obtained. The sample volume was positioned on the ventricular aspect of the mitral anulus where maximal peak flow velocities were obtained with minimal spectral broadening. No correction was made for the angle between the interrogating Doppler beam and apparent mitral inflow, but this angle was estimated to be less than 20° in all cases. Mitral inflow was recorded at 100 mm/sec paper speed, and the hard copy was subsequently analyzed with a digitizing pad interfaced to a microcomputer (MicroSonics). Pulsed Doppler interrogation for the presence and severity of mitral regurgitation was also performed.

Hemodynamic Studies

Preoperative right-sided heart catheterization was performed within 1 day of the Doppler echocardiographic studies in 12 of 22 (55%) patients, within 2 days in 19 of 22 (86%) patients, and within 4 days in the remaining three patients (14%). After operation, all patients received indwelling balloon flotation thermodilution catheters in the pulmonary artery, and hemodynamics were measured within 3 days of the Doppler echocardiographic study. Hemodynamics measured at rest included cardiac output, right atrial, pulmonary artery, and pulmonary artery wedge pressures. Pulmonary vascular resistance was calculated with a standard formula.¹⁷

Electrocardiographic data. Because of the known effect of heart rate and atrioventricular conduction on Doppler-derived indexes of mitral inflow,¹⁸ these values were determined from the electrocardiogram of each patient at the time of the preoperative and postoperative Doppler echocardiographic studies.

Analysis of Data

Two-dimensional echocardiography. A measure of interventricular septal flattening, the eccentricity index,¹⁹ was calculated at end diastole and end systole using the ratio of two perpendicular diameters of the left ventricle (Figure 1). Left ventricular end-systolic, end-diastolic, and stroke volumes were determined using a modified Simpson's rule formula.²⁰

Pulsed Doppler echocardiography. Peak early and late diastolic velocities were measured (Figure 2), and the ratio of early to late peak velocity was calculated. The deceleration slope of the early diastolic flow velocity was also determined as reported previously.²¹ These measures of diastolic filling
FIGURE 1. A parasternal short-axis two-dimensional echocardiographic view from a patient with chronic pulmonary hypertension. The eccentricity index is calculated using the ratio B/A.19

FIGURE 2. Tracings of mitral flow velocity profiles before (top) and after (bottom) pulmonary thromboendarterectomy. This patient’s mean pulmonary artery pressure decreased markedly from 55 to 28 mm Hg with an associated decrease in pulmonary vascular resistance from 1,350 to 150 dynes · sec/cm². The ratio of early to late peak velocity reversed after surgery because of the marked increase in early velocity. E, peak early diastolic velocity; A, peak late diastolic velocity; solid line, slope of early flow velocity deceleration.
TABLE 1. Hemodynamic and Electrocardiographic Indexes Before and After Pulmonary Thromboendarterectomy

<table>
<thead>
<tr>
<th>Index</th>
<th>Preoperative</th>
<th>p</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.0±0.5</td>
<td>‡</td>
<td>2.8±0.7</td>
</tr>
<tr>
<td>Mean pulmonary artery (mm Hg)</td>
<td>50±13</td>
<td>‡</td>
<td>29±9</td>
</tr>
<tr>
<td>Pulmonary artery wedge (mm Hg)</td>
<td>11±5</td>
<td>NS</td>
<td>12±5</td>
</tr>
<tr>
<td>Mean right atrium (mm Hg)*</td>
<td>11±7</td>
<td>NS</td>
<td>11±4</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>904±654</td>
<td>‡</td>
<td>283±243</td>
</tr>
<tr>
<td>PR interval (msec)</td>
<td>188±22</td>
<td>†</td>
<td>178±24</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76±15</td>
<td>†</td>
<td>82±15</td>
</tr>
</tbody>
</table>

Values are mean±SD.  
*pValues available in 17 patients.  
‡p<0.05, †p<0.01.

have been previously validated by comparison with radionuclide and hemodynamic studies of diastolic function.21,22 Three consecutive cardiac cycles were measured to calculate all Doppler echocardiographic values.

Statistical Analysis

All values are expressed as mean±SD. Comparisons among groups were performed by paired t test statistics. Linear regression analysis was carried out by the method of least squares.

Results

Catheterization Findings

Hemodynamic results are shown in Table 1. Significant postoperative increases in cardiac index (p<0.001), decreases in mean pulmonary artery pressure (p<0.001), and pulmonary vascular resistance (p<0.001) were noted after surgery. Pulmonary artery wedge pressure and mean right atrial pressure were unchanged. Small but significant changes in heart rate and electrocardiographic PR interval were also noted after surgery (p<0.05).

Two-Dimensional Echocardiographic Findings

Two-dimensional echocardiographic results are shown in Figure 3. After surgery, significant decreases occurred in the eccentricity index at end diastole (from 1.17±0.22 to 0.97±0.17) and end systole (from 1.34±0.23 to 1.04±0.10) compared with preoperative values (both p<0.001). After surgery, significant increases occurred in left ventricular end-diastolic volume (from 58.5±18.0 to 76.6±25.0 ml, p<0.001), stroke volume (from 30.3±12.4 to 41.8±12.5 ml, p<0.001), and end-systolic volume (from 28.5±12.3 to 34.8±15.3 ml, p<0.01).

Doppler Echocardiographic Findings

Pulsed Doppler echocardiographic results are shown in Figures 2 and 3. Compared with preoperative values, significant increases were noted in the postoperative values for peak early velocity (from 48±20 to 79±24 cm/sec, p<0.001), ratio of early to late peak flow velocities (from 1.04±0.42 to 1.67±0.60, p<0.001), and slope of the early diastolic flow velocity (from 2.6±1.4 to 4.2±1.8 m/sec², p<0.002). No significant change was noted in late peak flow velocity (48±10 vs. 49±9 cm/sec). Postoperative values for most individuals fell within the normal ranges reported by others.9,21–23 No significant degree of mitral regurgitation was seen with Doppler interrogation before or after surgery in any of the patients.

Relations Between Two-Dimensional and Doppler Echocardiographic Findings

The interventricular septal position at end systole, expressed as the eccentricity index, correlated significantly with the peak early velocity of mitral inflow (r=0.53, Figure 4A). Similarly, the same index showed a significant inverse correlation with the deceleration slope of early flow velocity (r=0.53, Figure 4B) and with the ratio of early to late peak filling velocities (r=0.48, Figure 4C) (all p<0.001). Significant correlations were also noted between the eccentricity index at end diastole and the above Doppler indexes (r=0.47, r=0.43, and r=0.46, respectively; all p<0.005).

Relations Between Changes in Two-Dimensional and Doppler Echocardiographic Findings in Individual Patients

Comparisons were made between changes in two-dimensional and Doppler echocardiographic values for individual patients after pulmonary thromboendarterectomy. The change in eccentricity index at end systole correlated with the change in peak early velocity (y=0.16+0.006x; r=0.53, p<0.01), with the change in deceleration of early filling (y=0.21+0.06x; r=0.51, p<0.02), and with the change in the ratio of early to late peak filling velocities (y=0.18+0.18x; r=0.55, p<0.01). The change in eccentricity index at end diastole correlated only weakly with the changes in the same Doppler indexes of left ventricular diastolic filling (p<0.02, p<0.10, and p<0.09, respectively).

Discussion

The present study shows that Doppler-derived indexes of left ventricular diastolic function improve early after reduction of pulmonary artery pressure by pulmonary thromboendarterectomy and that these early changes occur despite the presence of longstanding pulmonary hypertension. Furthermore, this improvement occurs in conjunction with a normalization of interventricular septal position and with an overall increase in left ventricular dimensions. These findings therefore suggest that right ventricular pressure overload and the resultant leftward displacement of the interventricular septum may be
responsible for the early diastolic abnormalities seen in these patients.

Abnormal interventricular septal position in the presence of right ventricular pressure or volume overload has been described by several investigators.\textsuperscript{1,3–8,14,19,24–26} This abnormal position has been attributed to the abnormal right-left ventricular transseptal pressure gradient during diastole or to elevated right ventricular systolic pressure\textsuperscript{3,6,7,24,25} and may be responsible for decreased left ventricular compliance as assessed by pressure-volume loops.\textsuperscript{27} Furthermore, we have previously shown that the position of the interventricular septum improves early after thromboendarterectomy for chronic thromboembolic pulmonary hypertension.\textsuperscript{14}

In the present study, improvement in Doppler-derived indexes of left ventricular diastolic function correlated with the normalization in the position of the interventricular septum suggesting that the leftward displacement of the interventricular septum is indeed responsible for impaired left ventricular diastolic function during right ventricular pressure overload.

Louie and colleagues\textsuperscript{1} have previously suggested that the end-systolic position of the interventricular septum influences the inflow characteristics of the left ventricle. They showed a relation between Doppler indexes of left ventricular diastolic function and the position of the interventricular septum in a group of patients with pulmonary hypertension. Results from the present study support and extend such a conclusion by showing significant correlations between changes in Doppler-derived indexes of left ventricular diastolic function and interven-
after surgical correction of pulmonary hypertension. Spatial distribution of force and loading inactivation, important determinants of relaxation in the intact heart, are likely to be nonuniform in patients with severe pulmonary hypertension before surgery resulting in prolonged relaxation. As shown by Visner and coworkers, chronic right ventricular pressure overload in an experimental animal can induce changes in three-dimensional cardiac geometry that alter left ventricular diastolic function and can be reversed quickly by unloading the right ventricle. Their data suggest that the dysynchronous shortening of the septal–free wall axis accounts for most of the changes in diastolic function and can alter early left ventricular diastolic function.

Furthermore, Doppler-derived indexes of left ventricular diastolic function are reportedly dependent on heart rate, preload, and atrioventricular delay. Increasing heart rate causes a redistribution of left ventricular diastolic filling from early to late diastole. Small but significant postoperative increases in heart rate were noted in the present study, but would have been expected to produce an effect opposite to the one observed. Intravenous nitroglycerin has been shown to decrease peak early left ventricular filling velocity and the ratio of early to late peak filling velocities as preload decreases. In the present study, however, there was no postoperative change in pulmonary artery wedge pressure compared with preoperative pressures. Furthermore, Doppler-derived indexes of left ventricular diastolic function improved in the presence of increased left ventricular volumes, providing additional support for improved diastolic filling of the left ventricle. In a previous study, left ventricular filling has also been shown to be influenced by variations in the PR interval. In that study, however, large variations in atrioventricular delay were induced to show changes in Doppler-derived left ventricular diastolic indexes. The small changes noted in our patients probably did not contribute substantially to the changes in left ventricular diastolic filling. In addition, marked changes in transmitral flow velocity profiles were found after surgery in several patients who had no prolongation of the PR interval. All patients in our study underwent pericardiotomy. Although pericardiotomy is known to influence the interaction between the left and right ventricles under normal conditions and may consequently alter the mitral velocity profile, there is evidence to suggest that this effect is diminished in the chronically dilated heart. We have observed no significant influence of pericardiomyotomy on interventricular septal position in individuals without pulmonary hypertension who have undergone cardiopulmonary bypass.

Limitations
Hemodynamic and Doppler echocardiographic data were not obtained simultaneously. In general, Doppler echocardiography was performed at a time...
when these patients were hemodynamically stable and within 72 hours of hemodynamic data acquisition. However, improvement of pulmonary hypertension has been shown to be long standing after pulmonary thromboendarterectomy.13

Doppler-derived indexes of left ventricular function may be influenced by heart rate and loading conditions.16,29 These indexes have, however, been shown to correlate well with other accepted measures of diastolic function, such as indexes derived from radionuclide angiography,21,32 and may provide useful information on left ventricular diastolic function despite the limitations due to their dependency on preload.9,10,23,33 In our study, although the left atrial to left ventricular pressure difference was not measured, the effect of preload on the measured changes of Doppler indexes was probably minimal because pulmonary artery wedge pressures were not significantly different before and after surgery. Also, some change in mitral valve orifice area may have produced some of the changes in Doppler indexes of diastolic function. However, the improvement of left ventricular diastolic function suggested by the Doppler-derived indexes of left ventricular diastolic function is corroborated by the finding of a significant postoperative increase in left ventricular dimensions.

We cannot rule out that some intrinsic abnormalities of left ventricular compliance may persist after reduction of right ventricular pressure overload. Such intrinsic abnormalities of left ventricular compliance have been described in a dog model after 8 months of pulmonary artery banding.8 Serial analysis of left ventricular pressure-volume relations in patients after pulmonary thromboendarterectomy may document the presence and reversibility of subtle impairment of left ventricular diastolic abnormalities in such patients. The near-normal transmitral flow velocity profiles found in our study after surgery argue strongly, however, against significant intrinsic left ventricular diastolic dysfunction in patients with chronic severe pulmonary hypertension.

Acknowledgments

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