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Abnormal Left Ventricular Diastolic Filling in Chronic Thromboembolic Pulmonary Hypertension

True Diastolic Dysfunction or Left Ventricular Underfilling?

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Objectives The purpose of this study was to investigate the cause of abnormal left ventricular (LV) Doppler diastolic filling characteristics in chronic thromboembolic pulmonary hypertension (CTEPH).

Background In CTEPH, LV diastolic function often appears abnormal. It is unclear whether this "impaired relaxation" (E<A) filling pattern is caused by septal hypertrophy, right ventricular (RV) enlargement and LV chamber distortion, or low LV preload and underfilling.

Methods We studied 61 patients with an E<A transmitral pattern and CTEPH who underwent pulmonary thromboendarterectomy (PTE). We compared the results of pre- and postoperative transthoracic echocardiography and right heart catheterization measurements.

Results After PTE, mitral E velocity increased (from 54 ± 16 cm/s to 81 ± 20 cm/s, $p < 0.001$), whereas A velocity decreased (77 ± 22 cm/s to 71 ± 20 cm/s, $p < 0.001$). E/A ratio normalized (0.72 ± 0.16 cm/s to 1.22 ± 0.40 cm/s, $p < 0.001$). Pulmonary venous systolic and diastolic velocities both increased (57 ± 13 cm/s to 68 ± 16 cm/s and 39 ± 15 cm/s to 70 ± 21 cm/s, respectively, $p < 0.001$ for both). Diastolic velocity of the septal mitral annulus (E_m) did not change after PTE (8.0 ± 3.1 cm/s to 8.1 ± 2.0 cm/s, p = ns), whereas the velocity of the lateral mitral annulus increased (9.3 ± 3.2 cm/s to 11.8 ± 3.1 cm/s, $p < 0.001$). Mean pulmonary capillary wedge pressure increased from 9.3 ± 3.2 mm Hg to 10.6 ± 3.8 mm Hg ($p = 0.035$). Despite these marked changes in LV inflow, M-mode measurements of LV septal and posterior wall thickness were normal before PTE and did not change after surgery (septal: 10 ± 2 mm vs. 10 ± 1 mm; posterior: 10 ± 2 mm vs. 10 ± 1 mm; p = NS for both comparisons).

Conclusions The results of this study strongly suggest that the impaired relaxation pattern observed in patients with CTEPH is not solely the result of geometric effects of RV enlargement and LV chamber distortion but is caused in large part by low LV preload and relative underfilling. (J Am Coll Cardiol 2007;49:1334–9) © 2007 by the American College of Cardiology Foundation

Chronic thromboembolic pulmonary hypertension (CTEPH) has been recognized as an important cause of severe pulmonary hypertension. Untreated patients with this condition develop progressive right ventricular (RV) failure and have a poor prognosis, with a mortality of 90% in 5 years (1). Echocardiography in these patients often demonstrates severe RV enlargement and overload. In the absence of coexistent systemic hypertension or coronary artery disease, left ventricular (LV) systolic function is usually normal (2).

In contrast, LV diastolic filling patterns frequently are abnormal in this patient population. Most commonly, reversal of the normal E>A transmitral filling pattern is seen (3). The significance of this "impaired relaxation" LV diastolic filling pattern is not well understood. Some researchers have hypothesized that it represents an alteration of diastolic LV function because of compressive effects and progressive septal hypertrophy resulting from chronic RV pressure overload (4–6). Others have suggested that it may be the result of low right-sided cardiac output and LV underfilling (3).

The definitive treatment of CTEPH is surgical pulmonary thromboendartectomy (PTE). Successful PTE leads to

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a reduction in pulmonary artery pressures (PAP) and pulmonary vascular resistance (PVR), with improvement of RV systolic function (7). The pre- and postoperative echocardiographic examinations in this population facilitate the evaluation of the abnormal diastolic filling patterns in CTEPH. We undertook this study to investigate whether the abnormal transmitral filling patterns observed in patients with CTEPH are a result of LV compression and true diastolic dysfunction or a result of low preload and LV underfilling.

Methods

Patient population. We examined the pre- and postoperative transthoracic echocardiograms and invasive hemodynamic data of 61 consecutive patients with surgically accessible CTEPH and an impaired relaxation (E<A) transmitral Doppler pattern who underwent PTE at our institution. The study group was composed of 26 men and 35 women with a mean age of 57 ± 13 years (range 30 to 79). All patients had New York Heart Association functional class III to IV symptoms and had physical findings of RV overload, including elevated jugular venous pressure, a RV heave, and a pronounced P_2 component of the second heart sound.

Echocardiography. All patients had a complete transthoracic echocardiogram performed 10 ± 13 days before PTE, including pulsed-wave Doppler transmitral filling patterns, pulmonary venous Doppler evaluation, and tissue Doppler imaging of the mitral and tricuspid annulus using an HDI 5000 (ATL/Philips, Bothell, Washington) or Sonos 5500 (Philips, Bothell, Washington) cardiac ultrasound system. Transmitral flow patterns were assessed in the apical 4-chamber view. Care was taken to place the pulsed-wave Doppler sample volume at the mitral leaflet tips. Patients with atrial fibrillation were excluded from analysis. Postoperative echocardiography was repeated 10 ± 6 days after PTE.

Right heart catheterization. All patients underwent right heart catheterization within 48 h of their echocardiogram and had invasive measurement of right atrial pressure, PAP, cardiac output, pulmonary capillary wedge pressure (PCWP), and PVR. Thermodilution cardiac output was used to calculate PVR using the formula: PVR = 80 · (mean PAP − mean PCWP)/cardiac output. Invasive measurements were repeated immediately after PTE in the operating room or in the surgical intensive care unit.

Statistics. GraphPad Prism version 4.0 (GraphPad Software, San Diego, California) was used for statistical calculations. We performed a 2-tailed paired Student *t* test to compare pre- and postoperative measurements of mitral inflow parameters, tissue Doppler parameters, PAP, and PVR. All data are described as mean ± standard deviation. Logarithmic regression analysis was performed to help determine the relationship between transmitral E velocity and PVR with 95% confidence intervals. A p value of <0.05 was considered statistically significant. This study was reviewed and approved by the Institutional Review Board of the Human Research Protection Program at the University of California, San Diego.

Abbreviations and Acronyms

CTEPH = chronic thromboembolic pulmonary hypertension
D = diastolic component of pulmonary venous flow velocity
E_m = early diastolic mitral annular velocity
LV = left ventricle/ventricular
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
PCWP = pulmonary capillary wedge pressure
PTE = pulmonary thromboendarterectomy
RV = right ventricle/ventricular
S = systolic component of pulmonary venous flow velocity

Results

All 61 patients had normal LV systolic function as well as moderate-to-severe pulmonary hypertension with evidence of RV pressure overload on echocardiography. All patients were in sinus rhythm during both the echocardiogram and cardiac catheterization. The demographic, echocardiographic, and hemodynamic data are shown in Table 1. Preoperatively, all patients had Doppler evidence of impaired relaxation, with a mean E-wave velocity of 54 ± 16 cm/s, mean A-wave velocity of 77 ± 22 cm/s, and a mean E/A ratio of 0.72 ± 0.16. After PTE, there was a significant increase in E velocity (81 ± 20 cm/s, $p < 0.0001$ compared with preoperative values), whereas A velocity decreased slightly to 71 ± 20 cm/s ($p = 0.001$). This translated to a normalization of the E/A ratio at 1.22 ± 0.40 ($p < 0.0001$).

Pulmonary venous interrogation revealed systolic-predominant flow signals preoperatively, with a mean systolic (S) velocity of 57 ± 13 cm/s and a mean diastolic (D) velocity of 39 ± 15 cm/s. Both S and D velocities increased significantly after PTE, with the mean S velocity increasing to 68 ± 16 cm/s ($p < 0.0001$ compared with preoperative values) and the mean D velocity increasing to 70 ± 21 cm/s ($p < 0.0001$). Figure 1 shows an example of a typical patient's pre- and postoperative mitral inflow and pulmonary venous Doppler pattern.

Despite the abnormal preoperative E/A ratios, tissue Doppler interrogation of the septal portion of the mitral annulus revealed normal mean early diastolic (E_m) tissue velocity of 8.0 ± 3.0 cm/s whereas the lateral portion of the mitral annulus had a similar mean E_m velocity of 9.4 ± 3.2 cm/s. Tissue velocities remained normal after surgery and were unchanged in the septal region (mean E_m velocity of 8.1 ± 2.0 cm/s, $p = 0.66$ compared with preoperative values). Lateral E_m velocity increased to 11.8 ± 3.1 cm/s ($p < 0.0001$). The resulting E/E_m ratios also changed significantly after surgery (septal: 7.8 ± 3.8 vs. 10.9 ± 4.6, $p < 0.001$; lateral: 6.2 ± 2.2 vs. 7.4 ± 3.2, $p = 0.004$). Although marked RV hypertrophy was present in this population, M-mode measurements of LV septal and pos-

Table 1 Demographic, Echocardiographic, and Hemodynamic Characteristics

n	61
Gender (M/F)	26/35
Mean age, yrs (range)	57 (30–79)

	Preop	Postop	Mean Change (Postop to Preop)	p Value
Echocardiographic variables (mean ± SD)				
LVEDD (mm)	42 ± 7	46 ± 6	4 ± 7	<0.001
LVESD (mm)	25 ± 6	27 ± 5	2 ± 5	0.003
IVS (mm)	10 ± 2	10 ± 1	0 ± 2	ns
LVPW (mm)	10 ± 2	10 ± 1	0 ± 2	ns
Mean LVEF (%)	66 ± 9	68 ± 8	2 ± 20	ns
Mean E velocity (cm/s)	54 ± 16	81 ± 20	27 ± 23	<0.001
Mean A velocity (cm/s)	77 ± 22	71 ± 20	−6 ± 15	<0.001
E/A ratio	0.72 ± 0.16	1.22 ± 0.40	0.50 ± 0.38	<0.001
Mean S velocity (cm/s)	57 ± 13	68 ± 16	11 ± 28	<0.001
Mean D velocity (cm/s)	39 ± 15	70 ± 21	31 ± 28	<0.001
Mean septal E_m velocity (cm/s)	8.0 ± 3.1	8.1 ± 2.0	0.1 ± 3.5	ns
Mean lateral E_m velocity (cm/s)	9.3 ± 3.2	11.8 ± 3.1	2.7 ± 4.5	<0.001
E/E_m ratio (septal)	7.8 ± 3.8	10.9 ± 4.6	3.1 ± 4.8	<0.001
E/E_m ratio (lateral)	6.2 ± 2.2	7.4 ± 3.2	1.2 ± 3.4	0.004
Hemodynamic data				
RA pressure (mm Hg)	10.3 ± 4.9	9.7 ± 3.3	−0.6 ± 6.0	ns
Mean PAP (mm Hg)	47 ± 10	30 ± 8	−17 ± 4	<0.001
Cardiac output (l/min)	3.7 ± 1.1	5.3 ± 1.5	1.6 ± 1.5	<0.001
PVR (dyne s/cm^5)	893 ± 389	335 ± 146	−558 ± 351	<0.001
PCWP (mm Hg)	9.2 ± 3.2	10.6 ± 3.8	1.4 ± 3.1	0.035

D = diastolic component of pulmonary venous flow velocity; E_m = early diastolic mitral annular velocity; IVS = interventricular septum; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVPW = left ventricular posterior wall; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right artrial.

terior wall thickness were normal before PTE and did not change after surgery (septal: 10 ± 2 mm vs. 10 ± 1 mm; posterior: 10 ± 2 mm vs. 10 ± 1 mm, p = NS for both comparisons). Figure 2 summarizes the Doppler echocardiographic findings.

The changes in echocardiographic measurements were accompanied by substantial reductions in mean PA pressure (from 47 ± 9 mm Hg to 30 ± 8 mm Hg, $p < 0.0001$) and mean PVR (from 893 ± 390 dyne s/cm^5 to 335 ± 146 dyne s/cm^5, $p < 0.0001$). Cardiac output significantly improved from 3.7 ± 1.1 l/min to 5.3 ± 1.5 l/min ($p < 0.0001$). Mean PCWP increased after PTE from 9.3 ± 3.2 mm Hg to 10.6 ± 3.9 mm Hg (p = 0.035). The transmitral E velocity correlated inversely with PVR ($r = 0.54$, $p < 0.0001$), with a nonlinear logarithmic regression analysis showing the best fit. These results are shown in Fig. 3. Inter- and intraobserver variability in Doppler velocity measurements were tested in a random sample of 6 patients and were both <5%.

Discussion

In this study of patients with CTEPH, diastolic abnormalities of mitral inflow resolved rapidly after successful PTE. This resolution was manifested primarily by a substantial increase in E velocity: as PVR decreased after successful surgery, there was a predictable increase in E velocity. Furthermore, both S and D velocities increased significantly after PTE, suggesting a higher preload state for the LV after a decrease in PVR. The increase in E/E_m ratio is also consistent with an increase in LV filling pressure and, indeed, we found a significant increase in mean PCWP after PTE (consistent with a previous report from our laboratory) (3). Importantly, although an E<A transmitral Doppler pattern was present, early diastolic mitral annular (E_m) velocities were normal before PTE. Although septal E_m velocity did not change after surgery, lateral E_m velocity increased significantly. Finally, M-mode measurements of LV septal and posterior wall thickness were normal before PTE and did not change after surgery. These findings support the notion that the LV inflow diastolic abnormalities seen in patients with CTEPH are more a reflection of LV underfilling than a marker of true diastolic dysfunction from septal hypertrophy and LV compression.

We suspect that the rise in lateral annular E_m velocity observed after PTE is a result of increased LV preload. Although it is well established that transmitral inflow Doppler measurements are load-dependent (8,9), there initially was some controversy regarding the load-dependence of tissue Doppler measurements. Sohn et al. (10) demonstrated that E velocity and deceleration time

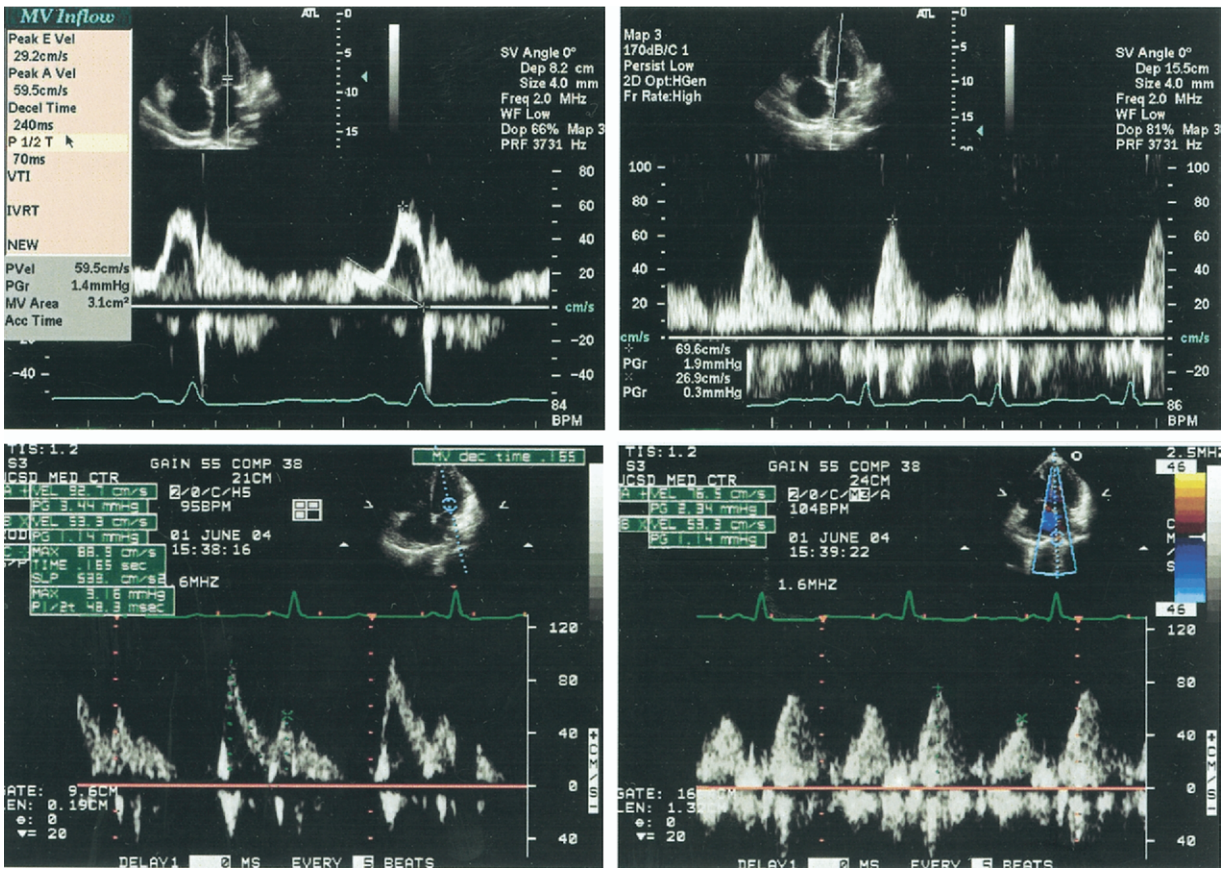

Figure 1 **Example of Transmitral and Pulmonary Venous Doppler Interrogation Before and After Pulmonary Thromboendarterectomy**

Transmitral pulsed-wave Doppler interrogation **(left)** and pulmonary venous Doppler interrogation **(right)** in a patient with chronic thromboembolic pulmonary hypertension before **(above)** and after **(below)** pulmonary thromboendarterectomy.

were preload dependent but that E_m velocity in the same patients was unchanged under various loading conditions. However, Firstenberg et al. (11) found that E_m velocities were indeed load-dependent, decreasing concordantly with LV preload. Similarly, Oguzhan et al. (12) found that acute hemodialysis caused a significant decline in Doppler tissue velocities in both the septal and lateral mitral annular positions. Although one might expect septal E_m velocity to increase as well after PTE, we recently have found that cardiac surgery with cardiopulmonary bypass leads to a decrease in septal E_m velocity (but no effect on lateral E_m) (13).

Interdependence between the right and left ventricles was described by the French physiologist P.I. Bernheim in 1910 (14). He hypothesized that the geometric changes from progressive LV enlargement and hypertrophy could directly compress the RV and thereby reduce RV filling. This so-called "Bernheim effect" could lead to elevated central venous pressure and peripheral edema in cases of LV overload. The "reverse" Bernheim phenomenon (i.e., enlargement of the RV leading to compression and underfilling of the LV) also has been described in both animals and humans with pulmonary hypertension and RV failure (5,15). For example, Marcus et al. (16) studied 12 patients with primary pulmonary hypertension using magnetic resonance imaging (MRI) and found a reduction in LV peak filling rate and LV stroke volume compared with control patients. Similarly, several echocardiographic studies (3,17) have shown a high incidence of decreased early LV filling in pulmonary hypertension and RV enlargement.

The point of some contention is not if this phenomenon occurs, but why. On the one hand, direct ventricular interaction could limit LV diastolic filling. The LV does appear distorted and compressed in the setting of severe RV pressure overload; the interventricular septum appears hypertrophied and functions more as part of the RV than the left. It is certainly plausible that these changes could lead to LV diastolic dysfunction and abnormal early diastolic relaxation. For example, Gan et al. (18) recently reported a study using MRI, right heart catheterization, and transesophageal echocardiography in patients with pulmonary arterial hypertension (PAH, not CTEPH). With cardiac MRI, they found impaired early diastolic filling in patients with PAH compared with control patients. They also found that leftward curvature of the interventricular septum correlated

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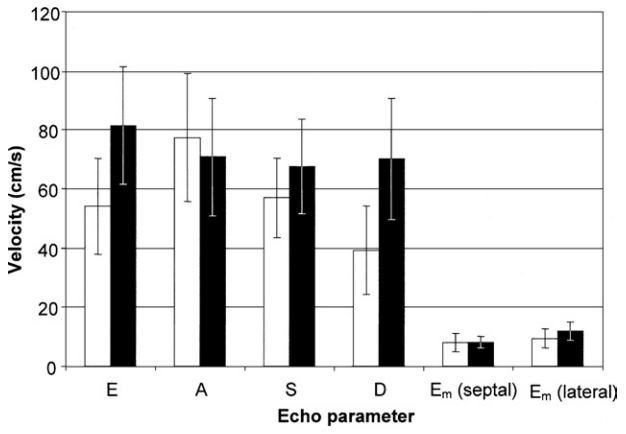

Figure 2 **Preoperative and Postoperative Parameters in Patients Undergoing PTE**

The p values are significant for all comparisons between preoperative and postoperative parameters except E_m (septal). All variables are presented as mean ± standard deviation. **Solid bars** = postoperative; **open bars** = preoperative. A = A velocity; CTEPH = chronic thromboembolic pulmonary hypertension; D = diastolic pulmonary venous flow velocity; E = E velocity; E_m = early mitral annular tissue Doppler velocity; PTE = pulmonary thromboendarterectomy; S = systolic pulmonary venous flow velocity.

with LV filling rate and so concluded that direct ventricular interaction impairs ventricular filling in pulmonary hypertension. Of note, they also reported an E<A transmitral pattern, a lower stroke volume index, and a lower cardiac index in PAH versus control patients. Tissue Doppler imaging was not performed. Their reported mean systolic and diastolic pulmonary venous flow velocities (59 ± 16 cm/s and 42 ± 10 cm/s, respectively) in patients with PAH (18) are remarkably similar to the preoperative velocities in our study. In addition, PCWP in the PAH group was normal at 7 ± 5 mm Hg. However, transesophageal echocardiography and right heart catheterization were not performed in the control group and, thus, the differences in Doppler filling patterns and LV filling pressure could not be compared.

On the other hand, the high pulmonary vascular resistance and low cardiac output observed in severe PAH and CTEPH could lead to underfilling of the left heart. Indeed, LV underfilling in normal individuals can cause reversal of the transmitral E/A ratio and simulate impaired LV relaxation (19). Although previous work in our laboratory has shown a markedly abnormal LV eccentricity index in CTEPH (20), our current data show that the interventricular septum is not particularly hypertrophied, and its thickness matches that of the LV posterior wall. Also, even though the LV in CTEPH appears compressed within the pericardium by the RV, pericardiectomy leads to no change in LV shape or diastolic pressure/volume relationships (21). Although the present study does not exclude a direct effect on LV diastolic function from chamber distortion in CTEPH, it does demonstrate the importance of diastolic LV underfilling. We would also submit that the results of Gan et al. (18), described previously, are not inconsistent with the hypothesis that LV underfilling contributes to altered diastolic inflow.

The dramatic increases in transmitral E and pulmonary venous flow velocities after PTE are consistent with a marked improvement in LV preload. The rapid normalization of the E/A ratio after PTE and the presence of normal preoperative interventricular septal thickness by echo would also argue against any significant lingering effects from septal hypertrophy. Finally, the coexistence of an E<A transmitral filling pattern and an essentially normal mitral annular E_m velocity before PTE is perhaps the most persuasive evidence of LV underfilling with relatively preserved diastolic function.

Study limitations. First, preoperative transthoracic echocardiography and right heart catheterization were not performed simultaneously in this study, and up to 48 h elapsed between the 2 procedures. Because the nature of pulmonary hypertension was chronic in this patient population, we do not believe that simultaneous measurement would have yielded substantially different results. After PTE, the time between initial hemodynamic measurements and echocardiography was longer (mean of 10 days), and it is possible that hemodynamic and Doppler parameters fluctuated during this period. In general, however, patients in this study remained stable after PTE. Echocardiography was delayed until patients left the surgical intensive care unit and could be positioned properly for examination in the noninvasive cardiac laboratory.

Second, we used only transthoracic echocardiography for cardiac imaging and did not perform cardiac MRI or obtain endomyocardial biopsy at the time of surgery. Although a recent study by Lamberts et al. (22) found an increased collagen content in both the RV and LV in rats with

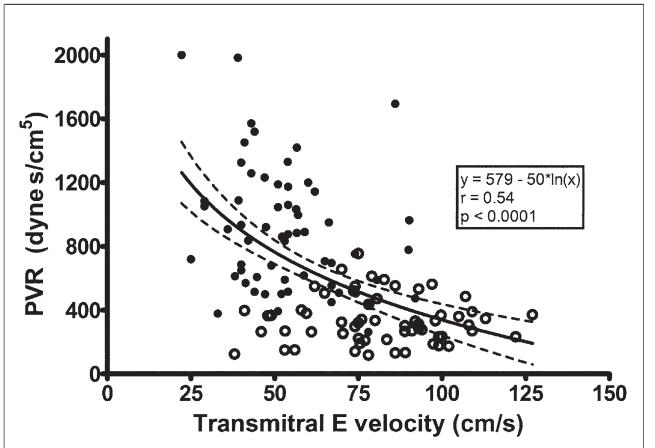

Figure 3 **Comparison of E and PVR in Patients With CTEPH Undergoing PTE**

Solid circles = preoperative patients; **open circles** = postoperative patients. Logarithmic regression analysis with 95% confidence intervals is also shown. PVR = pulmonary vascular resistance; other abbreviations as in Figure 2.

monocrotaline-induced pulmonary hypertension, we have no way to evaluate myocardial collagen content in our patient population. Finally, because the study began before routine Doppler evaluation of myocardial strain was available, we are unable to comment on RV strain before and after PTE. This is an area of active research.

Conclusions

In patients with CTEPH, successful reduction of RV afterload after pulmonary thromboendarterectomy predictably improves LV preload and transmitral diastolic flow patterns. Pulmonary venous Doppler velocities also increase substantially and shift from a systolic-dominant pattern to a diastolic-dominant pattern. Despite the abnormal (E<A) preoperative transmitral Doppler flow pattern, mitral annular (E_m) velocity is normal. After successful thromboendarterectomy, transmitral Doppler E velocity increases significantly and the E/A ratio becomes normal. Mitral E_m velocity increases somewhat but remains in the normal range. Thickness of the interventricular septum and LV posterior wall are normal preoperatively and do not change after surgery. The finding of an abnormal transmitral filling pattern (E<A) together with a normal mitral E_m velocity before thromboendarterectomy supports the concept that the "abnormal relaxation" pattern of transmitral LV filling in CTEPH is due in large part to low LV preload and underfilling rather than RV hypertrophy, enlargement, and LV compression.

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