Pathophysiology of Impaired Right and Left Ventricular Function in Chronic Embolic Pulmonary Hypertension*  

Changes After Pulmonary Thromboendarterectomy

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Study objectives: This study sought to evaluate the pathophysiology of left and right heart failure in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were hospitalized to undergo pulmonary thromboendarterectomy (PTE).

Design: Thirty-nine patients (16 women and 23 men; mean ± SD age, 55 ± 12 years) with severe CTEPH were examined before and 13 ± 8 days after PTE by way of transthoracic echocardiography and right heart catheterization.

Measurements and results: Examination results confirmed in all cases that before surgery the right ventricles were enlarged and systolic function was impaired. Moderate to severe tricuspid valve regurgitation was observed. Left ventricular eccentricity indexes reflected a leftward displacement of the interventricular septum. End-diastolic left ventricular size and systolic function had decreased, and the left ventricular filling pattern showed impaired diastolic function. After surgery, mean pulmonary artery pressure was significantly lower (48 ± 6 mm Hg vs 25 ± 7 mm Hg; p < 0.05). The calculated end-diastolic and end-systolic right ventricular areas had decreased: 30 ± 7 cm² vs 21 ± 5 cm² (p < 0.05) and 24 ± 6 cm² vs 14 ± 4 cm² (p < 0.05), respectively. Right ventricular fractional area change had increased (20 ± 7% vs 33 ± 8%; p < 0.05). Most of the patients exhibited a marked decrease in the severity of tricuspid regurgitation. Septal motion, left ventricular systolic function, and diastolic filling pattern returned to normal values (early to late diastolic left ventricular inflow ratio, 0.70 ± 0.33 vs 1.35 ± 0.51; p < 0.05). The mean cardiac index also improved (2.7 ± 0.6 L/min/m² vs 3.7 ± 0.8 L/min/m²).

Conclusions: In CTEPH, functions are impaired in the right as well as the left ventricles of the heart. Improved lung perfusion and the reduction of right ventricular pressure overload are direct results of PTE, which in turn bring a profound reduction of right ventricular size and a recovery of systolic function. Normalization of interventricular septal motion as well as improved venous return to the left atrium lead to a normalization of left ventricular diastolic and systolic function, and the cardiac index improves.

Key words: chronic thromboembolic pulmonary hypertension; echocardiography; pulmonary thromboendarterectomy

Abbreviations: CI = cardiac index; CTEPH = chronic thromboembolic pulmonary hypertension; E/A = early to late diastolic left ventricular inflow ratio; EDA = end-diastolic cavity area; ESA = end-systolic cavity area; FAC = fractional area change; LV = left ventricular; NS = not statistically significant; NYHA = New York Heart Association; PTE = pulmonary thromboendarterectomy; RV = right ventricular; TR = tricuspid regurgitation.

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Chronic thromboembolic pulmonary hypertension (CTEPH) constitutes a rare disease that is estimated to follow after <1% of all cases of acute pulmonary embolism. Several mechanisms are postulated to be responsible for the development of
chronic pulmonary hypertension after the acute embolic event. A recurrence of embolism has been reported subsequent to 2.5 to 7% of adequately treated pulmonary embolic events.1,2 Failure to resolve the embolus causes hypertensive lesions in the open vascular bed and further increases pulmonary vascular resistance. An in situ thrombus growth has also been reported.3

CTEPH causes right ventricular (RV) pressure overload, which leads to functional and morphologic alterations of both right and left ventricles. These changes result in a decreased cardiac index (CI). As has been shown for lung transplantation, repair of congenital heart disease, and pulmonary thromboendarterectomy (PTE), the hemodynamic and cardiac changes remain partially reversible, even after years of illness.5–17

Long-term outcome after PTE has been reported to be very satisfactory.5–7,8 A recent investigation of 22 patients, 48 to 72 months after they underwent PTE, showed a marked improvement of clinical condition as well as New York Heart Association (NYHA) functional class and a significantly reduced pulmonary vascular resistance in comparison with presurgical data.19 A 6-year survival rate of 75% has been reported by Archibald et al.19 and the perioperative mortality risk of PTE is <10%.1,6,20 In comparison, the 5-year survival rate without surgery is around 35% for severe CTEPH.21

We examined RV and left ventricular (LV) function and geometry in patients with CTEPH before and after PTE. The preexistent changes that had led to a diminished cardiac output and their alteration after reduction of the RV afterload were investigated, as well as the underlying pathophysiologic mechanisms. New insights into LV filling properties derived by Doppler echocardiography and new insights into the mechanisms of systolic LV function were taken into consideration.

Materials and Methods

Study Patients

Between April 1996 and October 1998, 39 patients (16 women and 23 men; mean ± SD age, 55 ± 12 years; age range, 25 to 71 years) undergoing PTE were included in a prospective study. The mean duration of symptomatic pulmonary hypertension was 39 ± 39 months (range, 4 to 170 months). According to the NYHA scale, severity was identified to be functional class IV in 11 cases, class III in 22 cases, and class II in 6 cases.

Patients were investigated 12 ± 8 days before and 13 ± 8 days after surgery. Four patients had coronary artery disease, two of which underwent additional coronary bypass surgery. None of the patients experienced previous or perioperative myocardial infarction. In one patient, a mitral valve replacement was necessary due to mitral valve prolapse with severe mitral regurgitation.

PTE

The endarterectomy of pulmonary arteries was performed with a standardized technique, using extracorporeal circulation, deep hypothermia, and periods of circulatory arrest.21–23

Transthoracic Echochardiography

Two-dimensional and Doppler echocardiography were performed, using standard techniques on commercially available equipment (Sonos 2500 [2.0/2.5 MHz] or Sonos 5500 [S4 Ultraband transducer 2–4 MHz]; Hewlett-Packard; Andover, MA). Images were obtained with patients lying in the left lateral position. Measurements were performed in end-expiration during examination. The results of three heart cycles were averaged for each variable. In case of atrial fibrillation, five heart cycles were averaged.

The RV end-diastolic cavity area (EDA) and RV end-systolic cavity area (ESA) were determined planimetrically in the apical four-chamber view. Fractional area change (FAC) was calculated as follows:24

\[
\text{RV-FAC} = \left( \frac{\text{RV-EDA} - \text{RV-ESA}}{\text{RV-EDA}} \right) \times 100
\]

The severity of tricuspid regurgitation (TR) was assessed by way of color Doppler echocardiography. In accordance with Miyatake et al.25 the area of the regurgitant jet was planimetrically determined in the apical four-chamber view: 4 + TR, jet area > 10 cm²; 3 + TR, jet area > 4 and ≤ 10 cm²; 2 + TR, jet area > 2 and ≤ 4 cm²; and 1 + TR, jet area > 0 and ≤ 2 cm².

In pulmonary hypertension, a dorsal and left-lateral displacement of the left ventricle occurs, rendering the echocardiographic determination of LV size and systolic function inaccurate from the apical position. Thus, LV-EDA and LV-ESA cross-sectional areas were determined in the parasternal short-axis view (at the level of the mitral valve-chordae tendinae transition) to measure systolic function. LV-FAC was used instead of the ejection fraction. End-diastole was defined as peak of the R wave of the QRS complex; for end-systole, the point of maximum LV posterior wall thickening was taken.26 LV-FAC was calculated as follows:

\[
\left( \frac{\text{LV-EDA} - \text{LV-ESA}}{\text{LV-EDA}} \right) \times 100
\]

End-diastolic eccentricity index of the left ventricle was measured according to Ryan et al.27 In order to prove early diastolic leftward septal motion, we took an early-diastolic index (measured at two stop-frames after maximal posterior wall thickening was observed), instead of the end-systolic eccentricity index (at the point of maximum LV posterior wall thickening).

LV diastolic function was evaluated by Doppler echocardiographic assessment of the transmural flow pattern, in accordance with Oh et al.28 and Appelton et al.29 Variables determined were peak flow velocity in early diastole and at atrial contraction (E- and A-wave velocities), early to late diastolic left ventricular inflow ratio (E/A), E-wave deceleration velocity, and isovolumic relaxation time. In each patient case, a Valsalva maneuver was performed before and after surgery to distinguish a “true-normal” from a pseudonormal diastolic filling pattern.

A Doppler echocardiography-derived index of overall LV function was calculated on the measurements of two intervals, expressing the LV performance index:

\[
\left( \frac{A - B}{B} \right)
\]

where A = the interval between cessation and onset of mitral inflow, and B = the ejection time of LV outflow.

Using Doppler echocardiography, the CI was determined according to Marshall and Weymann,31 with the following formula:

\[
\text{CI} = \frac{\text{stroke volume}}{\text{heart rate} \times \text{body surface area}}
\]
where TVI = time velocity integral of aortic outflow determined by Doppler echocardiography, LVOT = cross-sectional area of LV outflow tract, HR = heart rate, and BSA = body surface area.

Cardiac Catheterization

In all patient-cases included in this study, a hemodynamic examination was performed with a Swan-Ganz catheter to attain preoperative and postoperative determinations of the mean pulmonary artery pressure, mean pulmonary capillary pressure, pulmonary vascular resistance, and CI (thermodilution method). In 28 cases, coronary arteriography was also performed.

Statistical Methods

Statistical Analysis System version 6.12 (SAS Institute; Cary, NC) was employed to process the study results. Continuous variables were expressed as mean ± SD. Preoperative and postoperative continuous variables were compared by the Wilcoxon signed-rank test. The two-sided Cochran-Armitage trend test (exact p values) was used to determine the dependence of the E/A ratio on preoperative and postoperative NYHA functional class ratings. An E/A > 1 was considered a positive test result. All p values ≥ 0.05 were considered to be not statistically significant (NS) in both tests.

Results

Clinical Features

At discharge from hospital, all of the patients in this study could be assigned to a better functional class on the NYHA scale. No patients were found classified in class IV, 5 patients were class III, 15 patients were class II, and 19 patients could be classified in class I.

Echocardiographic Variables

There were certain few patients for which not all parameters in question could be determined with satisfactory accuracy (shown in detail in Tables 1–3). Before surgery, the area of the right ventricle was enlarged in all patients (both end-diastolic and end-systolic). Systolic function was impaired. On examination after surgery, both RV area measurements were smaller in all patients, and systolic function had improved (Table 1).

The patients were classified for preoperative tricuspid valve regurgitation as follows: 23 patients, 4 + TR; 12 patients, 3 + TR; 2 patients, 2 + TR; and 2 patients, 1 + TR. After surgery, severity decreased in most patients and TR classifications were as follows: 4 patients, 4 + TR; 12 patients, 3 + TR; 13 patients, 2 + TR; and 10 patients, 1 + TR (Table 1).

Before surgery, end-diastolic and early diastolic LV eccentricity indexes were both elevated. After surgery, both parameters returned to near-normal values (Table 2). After surgery, the mean cross-sectional area of the left ventricle increased significantly in the end-diastolic phase, whereby the end-systolic area remained unchanged. Thus, LV-FAC represented a significant increase (Table 2).

Preoperative LV diastolic function was, in general, abnormal: the maximal early diastolic filling velocity was lower and the maximal filling velocity at atrial contraction was slightly higher than the normal, age-adjusted range. After surgery, both parameters returned to normal values. The mean E/A was low before surgery, but lay within normal range afterwards. The lowered velocity of deceleration in early diastolic filling increased significantly. Neither before nor after surgery could a pseudonormalization or restrictive filling pattern be observed in any of the patients. Prolonged isovolumic relaxation time returned to normal (Table 2).

The E/A could be determined in 36 patient-cases. The patients with an E/A < 1 were classified with statistical significance in higher NYHA stages before and also after surgery. For patients in NYHA class IV before surgery, an E/A < 1 was found in 10 cases and an E/A > 1 was found in none. For patients in NYHA class III before surgery, an E/A < 1 was found in 19 cases and an E/A > 1 was found in 2 cases. For patients in NYHA class II before surgery, an E/A < 1 was found in three cases and an E/A > 1 was found in two cases.

After surgery, none of the patients could be

<table>
<thead>
<tr>
<th>Table 1—Preoperative and Postoperative Right Heart Variables*</th>
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<tr>
<td><strong>Echocardiographic Variables</strong></td>
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<tr>
<td><strong>Variables</strong></td>
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<tr>
<td>BV-FAC, %</td>
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<tr>
<td>BV-EDA, cm²</td>
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<tr>
<td>BV-ESA, cm²</td>
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<tr>
<td>TR area, cm²</td>
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* Date are presented as mean ± SD. TR area = area of Doppler echocardiography-derived TR jet.

† In one case, postoperative determination of RV size was not possible.
classified as NYHA class IV. For patients in NYHA class III after surgery, an E/A < 1 was observed in four cases and an E/A > 1 was found in one of the cases. For patients in NYHA class II after surgery, an E/A < 1 could be observed in five cases and an E/A > 1 was found in eight cases. For patients in NYHA class I after surgery, an E/A < 1 could be observed in 2 cases and an E/A > 1 was found in 16 cases.

The LV performance index declined substantially after surgery, indicating an improvement of diastolic as well as systolic LV function. The mean CI was below normal before surgery and increased significantly after PTE (Table 2).

Hemodynamic Variables

Pulmonary vascular resistance and mean pulmonary artery pressure were elevated in preoperative measurements. After PTE, a marked decrease could be shown for both parameters. Mean capillary wedge pressure lay within normal range in preoperative and postoperative measurements. Heart rate did not change after PTE (Table 3). Invasively determined CI was below normal before surgery, and it increased significantly after surgery.

Discussion

According to the results found in our study population and the changes that were observed after PTE, the pathophysiologic mechanism of cardiac failure in severe pulmonary hypertension can be described as follows below. See Figure 1 for a diagram summarizing the chain of causalities.

Size and Systolic Function of the Right Ventricle

Chronic pulmonary hypertension results in marked dilatation and a reduced systolic function in the right ventricle. As has been shown,14,15,32 PTE causes a significant decline in RV afterload, which results in a rapid decrease of RV size and improvement of the systolic function. Data acquired in our study confirm these findings.

TR

The dilatation and alteration of RV geometry lead to annular dilatation of the tricuspid valve, which causes functional TR.33 The results of this are increased RV preload, decreased efficiency of RV stroke work, and decreased RV output, which further increase tricuspid valve incompetence. Although several studies on PTE have been published, no investigators have systematically compared the preoperative and postoperative severity of TR. Only Jamieson and coworkers6 point out that in the setting of pulmonary hypertension, even severe cases of TR do not require valve surgery, as PTE induces substantial improvement of valvular function. In this study, moderate to severe functional TR could be detected in most of the patients. The severity of TR was found to be significantly reduced after surgery, however, which proves that PTE interrupts the pathophysiologic cycle described above.
LV Geometry

Due to ventricular interdependence within the restricted intrapericardial space, marked RV dilatation causes a significant alteration in LV geometry, which is characterized by a leftward displacement of the interventricular septum. This can be demonstrated during the whole heart cycle,27 but is most marked at early diastole, decreasing substantially by end-diastole.34 The elevated preoperative LV eccentricity indexes shown in our investigation confirm the previous findings. In our investigation, the same indexes returned to near normal values after PTE.

LV Diastolic Function

A number of investigators have emphasized that impaired LV diastolic filling is the most important cause of left heart failure in patients with pulmonary hypertension.26,34,35 A normalization of the previously altered diastolic filling pattern was shown in examination results after PTE.32 The prompt reversibility of impaired LV compliance confirms the assumption of a functional rather than a structural change of the LV myocardium.36

The preoperative finding of prolonged isovolumic relaxation time as well as the lowered E wave and E-wave deceleration velocities also indicate that changes of diastolic filling are most severe in the early diastole, which corresponds to the disproportional septal displacement during this phase of the heart cycle, as has been described elsewhere.34 The isovolumic relaxation time reflects the interval from aortic valve closure to the onset of mitral flow, and is determined primarily by the rate of LV relaxation.

Table 3—Preoperative and Postoperative Invasively Determined Variables*

<table>
<thead>
<tr>
<th>Invasively Determined Variables</th>
<th>Trend</th>
<th>Preoperative Values</th>
<th>Postoperative Values</th>
<th>n</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP, mm Hg</td>
<td>↓</td>
<td>48 ± 10</td>
<td>25 ± 7</td>
<td>39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MPCP, mm Hg</td>
<td>↔</td>
<td>9.3 ± 3.4</td>
<td>9.0 ± 2.3</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, dyne · s · cm⁻⁵</td>
<td>↓</td>
<td>805 ± 317</td>
<td>282 ± 155</td>
<td>39</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>↑</td>
<td>2.3 ± 0.5</td>
<td>3.4 ± 0.6</td>
<td>39</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>↔</td>
<td>84 ± 15</td>
<td>87 ± 13</td>
<td>39</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD. MPAP = mean pulmonary arterial pressure; MPCP = mean pulmonary capillary pressure; PVR = pulmonary vascular resistance.
and left atrial pressure. Its prolongation in pulmonary hypertension can be explained by a reduced LV preload due to right heart failure and, more importantly, the leftward shift of the interventricular septum during diastole, which decreases LV pressure decline velocity. This also results in the decreased E wave and E-wave deceleration velocities of presurgery measurements.

Our perception that lower cardiac output in pulmonary hypertension may be due to impaired LV diastolic function is supported by findings in the case of patients undergoing atrial septostomy. In this case, cardiac output improves after the intervention because of a decrease in RV preload and increase of LV preload due to the shunt flow.37

In this study, the significantly higher NYHA classification of the patients with an E/A < 1 (impaired diastolic LV filling), both before and after PTE, also supports the concept that impaired LV filling is a major pathophysiologic factor in patients with CTEPH. With PTE, LV geometry is restored and RV function improves, so that LV diastolic function returns to normal.

LV Systolic Function

Prior to surgery, impaired diastolic filling led to a decreased LV end-diastolic cross-sectional area (ie, reduced end-diastolic volume). Our measurements show a postoperative normalization of end-diastolic LV area (equal volume). Because end-systolic chamber sizes remain unchanged, the determinations that indicated impaired systolic LV function, as measured by FAC before surgery, also returned to normal range after PTE.

Overall LV Function

The Doppler echocardiography-derived LV performance index published by Tei and coworkers30 was demonstrated to be highly correlated with both peak diastolic LV pressure drop and peak systolic LV pressure rise, as well as the time constant of relaxation (τ). In our study, the mean LV performance index was 0.62 ± 0.26 before PTE, and it decreased to 0.38 ± 0.15 after surgery. This result indicates an increase of peak diastolic LV pressure drop and an improvement of systolic LV function after surgery. It confirms the findings discussed above. In addition, the lower index indicates a rise of peak systolic LV pressure rise, which could also confirm our above described finding of improvement in LV diastolic filling.

CI

The presurgery chain of causalities diminishing CI can be summarized as follows. Obliteration of the pulmonary vascular bed leads to a RV pressure overload as well as a reduced LV preload. RV enlargement causes a leftward shift of the interventricular septum. This alters LV geometry and results in a diastolic and systolic functional impairment. Thus, the CI returns to almost normal values after thromboendarterectomy of the pulmonary arteries (Fig 1).

Limitations

In this study, invasive and echocardiographic examinations were not performed simultaneously. However, heart rate and mean arterial BP did not differ significantly in these examinations. It is difficult to assess the size and systolic function of the right ventricle with great accuracy because of its shape and the difficulties in tracing endocardial borders. RV size may also appear different if the transducer is placed over the RV or the LV apex, or if it is slightly rotated. A reasonable image quality had to be achieved for the examination results to be included in this study.

Determining the severity of TR by way of color Doppler echocardiography technique has several limitations. Thus, care was taken to use the optimal gain setting for each study examination. In pulmonary hypertension, a dorsal and left-lateral displacement of the left ventricle occurs. Thus, in some cases, the optimal transducer position could not be achieved for alignment with mitral inflow, which is directed to the lateral wall of the left ventricle. The same occurred in some of the examinations in which aortic outflow was determined. In these cases, a correction was made for the angle between the Doppler echocardiographic beam and flow direction.

Clinical Implications

The pathophysiologic mechanisms delineated in this study show that clinical symptoms of patients with CTEPH are due to both RV and LV functional impairment. PTE interrupts the underlying cycle and results in an improvement of cardiac function and clinical symptoms as well. Thus, patients with severe CTEPH benefit from PTE.

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