Different Time Course of Changes in Tricuspid Regurgitant Pressure Gradient and Pulmonary Artery Flow Acceleration After Pulmonary Thromboendarterectomy
—— Implications for Discordant Recovery of Pulmonary Artery Pressure and Compliance ——

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Background  Pulmonary artery pressure (PAP) is reduced dramatically after pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, it is unclear whether pulmonary artery compliance increases in conjunction with the reduction in PAP. Pulmonary artery compliance may affect right ventricular afterload and prognosis.

Methods and Results  In 33 patients with CTEPH (9 men, 22–76 years), changes in the tricuspid regurgitation pressure gradient (TRPG) and the acceleration time (ACT) of pulmonary artery flow (a surrogate parameter of pulmonary artery compliance) were examined before and after pulmonary thromboendarterectomy using echocardiography to clarify factors affecting the changes. At 6 months, both TRPG and ACT normalized (≤30 mmHg, ≥100 ms, respectively) in 25 patients (group A) but not in 8 (group B). In group B, there were 5 with normal TRPG and shortened ACT at 6 months that normalized at 17±3 months. Group A patients showed shorter disease period and shorter period without anticoagulation than group B patients (p=0.04, 0.02 respectively). All patients in group A had the proximal type, and 2 patients of group B had the distal type (p=0.05). Clinical improvement was more remarkable in group A.

Conclusions  The recovery of PAP and the ACT of pulmonary artery flow was not always concordant after pulmonary thromboendarterectomy, suggesting a presence of a time lag in the recovery between pressure and compliance in some patients. A long period of CTEPH, a long period without anticoagulation and the distal embolism type may be predictive factors of an unfavorable operative result with reduced pulmonary artery compliance, and hence poor recovery of clinical performance. (Circ J 2007; 71: 1771–1775)

Key Words:  Chronic thromboembolic pulmonary hypertension; Pulmonary artery compliance; Pulmonary thromboendarterectomy

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but life-threatening disease that eventually progresses to right heart failure. In addition, CTEPH is associated with abnormal left ventricular (LV) systolic and diastolic functions caused by ventricular interaction under right ventricular (RV) pressure overload1–4. It has been reported that pulmonary thromboendarterectomy is useful for dramatically reducing pulmonary artery pressure (PAP)5–7 and to improve LV systolic and diastolic functions3,4 and to obtain long-term survival8,9. On the other hand, few data exist regarding the change in pulmonary artery compliance after pulmonary thromboendarterectomy. Moreover, factors affecting changes in PAP and compliance after thromboendarterectomy are unclear. Because PAP and compliance may affect RV afterload and prognosis, it is of clinical value to define their changes after thromboendarterectomy.

Doppler echocardiography is a useful method for estimating PAP and compliance non-invasively, using the tricuspid regurgitant peak pressure gradient (TRPG) calculated by the simplified Bernoulli equation10 and the acceleration time (ACT) of pulmonary artery flow, respectively11. The aims of the present study were to examine the changes in PAP and ACT of pulmonary artery flow before and after pulmonary thromboendarterectomy using echocardiography, and to clarify the factors affecting these changes in patients with CTEPH.

Methods

Subjects
We retrospectively analyzed 51 consecutive patients with CTEPH who underwent pulmonary thromboendarterectomy. The exclusion criteria were: (1) moderate or severe
organic valvular heart disease; (2) congenital heart disease; (3) chronic obstructive pulmonary disease; (4) severe ischemic heart disease requiring any interventions; and (5) those without follow-up echocardiographic examination. After excluding 18 patients, 33 patients were enrolled in the present study (9 men, 24 women; age range at operation 22–76 years (mean, 52±12 years)). All patients had long-standing respiratory symptoms of CTEPH such as dyspnea, shortness of breath, and easy fatigability. CTEPH was diagnosed in all patients by the standard criteria, including right heart catheterization, computed tomography and pulmonary angiography before pulmonary thromboendarterectomy. The mean duration of symptoms (New York Heart Association (NYHA) III or IV) from onset to operation was 40±44 months.

According to the intraoperative classification of Thistlethwaite et al., pulmonary thromboembolic disease is divided into 4 groups: type 1, fresh (acute) thrombus in the main lobar pulmonary arteries; type 2, intimal webbing, and thickening and fibrosis with or without organized thrombus proximal to the segmental arteries; type 3, fibrosis, intimal webbing, and thickening with or without organized thrombus within the distal segment arteries only; and type 4, microscopic distal arteriolar vasculopathy without visible thromboembolic disease. In the present study, when there was discrepancy in the disease type between the right and left sides, the classification of the more proximal thromboembolism was used for analysis. Types 1 and 2 were defined as the proximal type, and types 3 and 4 as the distal type in our present study. None of our patients had type 1 or type 4.

Echocardiography

Standard echocardiography was performed using commercially available equipment with 2.0–4.0MHz transducers. All recordings were made on 0.50-inch VHS videotape for analysis.

The peak tricuspid regurgitation (TR) velocity was measured by continuous-wave Doppler echocardiography, and the pulmonary artery systolic pressure was estimated by the simplified Bernoulli equation. Pulmonary artery flow was recorded by pulsed-wave Doppler echocardiography and ACT was measured from the onset of ejection to the time of peak velocity. In the present study, ACT was regarded as an index of pulmonary artery compliance. TRPG and ACT were evaluated before and after pulmonary thromboendarterectomy. The ranges of normal TRPG and ACT were defined as less than 30mmHg and more than 100 ms, respectively.

Right Heart Catheterization

Thirty-one patients underwent right heart catheterization before and after operation: 1 patient did not undergo right heart catheterization at all and 1 patient underwent right heart catheterization only before pulmonary thromboendarterectomy. Right heart catheterization was performed in the standard manner, with a 7Fr Swan-Ganz catheter inserted from the right internal jugular vein. Hemodynamic measurements were obtained at the end of expiration. The cardiac output was obtained by the thermodilution method (mean of 3 injections).

Statistical Analysis

All data are expressed as mean±SD. Correlation coefficients with related p-values were reported. The univariate analysis for continuous variables was performed by t-test or nonparametric Mann-Whitney test, nominal variables by Fisher’s exact test. All statistical analyses were performed with StatView 5.0 software (SAS, Cary, NC, USA).

Results

Changes in TRPG and ACT

TRPG was 74.6±18.6mmHg and ACT was 68.9±14.9 ms before pulmonary thromboendarterectomy, compatible with severe pulmonary hypertension and a stiff pulmonary artery. After 3.5±5.4 months of pulmonary thromboendarterectomy, TRPG had decreased (23.9±10.9 mmHg, p<
0.0001) and ACT was prolonged (109.7±22.4 ms, p<0.0001) significantly (Figs 1, 2). Although ACT improved statistically as a whole, it was over a wide range as compared with TRPG, indicating that there was discordance between the grade of recovery in PAP and that in pulmonary artery compliance after thromboendarterectomy (Fig 3).

**Patient Subgroups**

The patients were divided into 2 groups according to TRPG and ACT at 6 months after pulmonary thromboendarterectomy. Patients with both normalized TRPG and ACT were group A and those without normalized TRPG and/or ACT were group B (25 and 8 patients, respectively). In group B, TRPG was normalized but ACT was not in 5 patients and both were not normalized in 3 patients at 6 months after operation.

**Factors Affecting Changes in PAP and ACT of Pulmonary Artery Flow After Pulmonary Thromboendarterectomy**

Table 2 is a comparison of disease severity. Preoperative TRPG in group A was significantly higher than in group B (p=0.03), whereas there was no difference in the preoperative ACT, indicating that the preoperative TRPG and ACT values did not influence the postoperative improvements. On the other hand, in group A, the morbid period (period of preoperative symptoms of CTEPH) was shorter (p=0.04), and the period without anticoagulation therapy was significantly shorter, than in group B (p=0.02). In addition, all patients in group A had the proximal type, but only 2 patients of group B had the distal type (p=0.05). There was no difference in the preoperative and postoperative cardiac indices between the 2 groups as evaluated by cardiac catheterization. NYHA functional class was not different before pulmonary thromboendarterectomy, but group B showed a more severe NYHA functional class (p=0.02). The clinical characteristics of the 2 groups are shown in Table 1. There was no difference in age or cardiovascular risk factors between the 2 groups. In addition, there was no difference in the underlying coagulation abnormalities such as lupus anticoagulant, anticardiolipin antibodies, deficiencies of protein C, protein S, and antithrombin III, and presence of factor V Leiden mutation.

**Table 1 Clinical Background of the Patients**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=25)</th>
<th>Group B (n=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±11</td>
<td>53±17</td>
<td></td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>6 (24)</td>
<td>3 (38)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>1 (4)</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>6 (24)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Coagulation abnormality (%)</td>
<td>5 (20)</td>
<td>2 (25)</td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences in these variables between group A and group B.

**Table 2 Comparison of the 2 Groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=25)</th>
<th>Group B (n=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative TRPG (mmHg)</td>
<td>78±19</td>
<td>62±13</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative ACT (ms)</td>
<td>68±15</td>
<td>73±16</td>
<td>NS</td>
</tr>
<tr>
<td>Morbidity period (months)</td>
<td>32±26</td>
<td>68±72</td>
<td>0.04</td>
</tr>
<tr>
<td>Period of anticoagulation (months)</td>
<td>19±20</td>
<td>30±52</td>
<td>NS</td>
</tr>
<tr>
<td>Period of disease without anticoagulation (months)</td>
<td>13±20</td>
<td>38±36</td>
<td>0.02</td>
</tr>
<tr>
<td>Type of embolism (proximal/distal)</td>
<td>250</td>
<td>6/2</td>
<td>0.05</td>
</tr>
<tr>
<td>Preoperative cardiac index (L·min⁻¹·m⁻²)</td>
<td>2.1±0.6</td>
<td>2.3±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative cardiac index (L·min⁻¹·m⁻²)</td>
<td>2.6±0.5</td>
<td>2.5±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative NYHA (I/II/III/IV)</td>
<td>0/5/14/6</td>
<td>0/2/4/2</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative NYHA (I/II/III/IV)</td>
<td>17/8/0/0</td>
<td>2/5/1/0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TRPG, tricuspid regurgitant peak pressure gradient; ACT, acceleration time of the pulmonary artery flow; NYHA, New York Heart Association.
significantly higher class than group A after pulmonary thromboendarterectomy (p=0.02).

Changes in the ACT of Pulmonary Artery Flow

Fig 4 shows the temporal changes in ACT (as a surrogate parameter of pulmonary artery compliance) in group B. 5 patients had a normalized TRPG only at 6 months after pulmonary thromboendarterectomy. All of these patients showed ACT normalization at 17±3 months after pulmonary thromboendarterectomy, indicating that ACT could eventually recover to the normal range. Three patients had no improvement of TRPG and/or ACT at 6 months after pulmonary thromboendarterectomy; 1 patient without a normalized TRPG and ACT had normalization at 12 months after pulmonary thromboendarterectomy. We had no follow-up data for the other 2 patients.

Discussion

Present Study

Pulmonary thromboendarterectomy is an effective treatment for patients with CTEPH, reducing TRPG and improving ACT.16 In the present study, we successfully confirmed those findings using serial echocardiographic observations. Moreover, we demonstrated that the recovery of PAP and the ACT of pulmonary artery flow was not always concordant after pulmonary thromboendarterectomy in patients with CTEPH and that the recovery of ACT was sometimes later than the reduction in PAP. To the best of our knowledge, this is the first study to show this. In addition, our data demonstrated that a long period of CTEPH, a long period without anticoagulation and the distal type of embolism were predictive of an unfavorable operative result with poor recovery of ACT of pulmonary artery flow.

Implications for Pulmonary Artery Compliance After Pulmonary Thromboendarterectomy

It has been reported that pulmonary hypertension is a predictive factor of poor prognosis in patients with CTEPH treated either medically or surgically.17-19 However, a clinically significant decrease in pulmonary artery compliance after normalization of PAP has not been reported. In the present study, pulmonary artery compliance estimated by ACT normalized within a maximum of 19 months after PAP normalization. However, patients with a shortened ACT after normalization of PAP showed a significantly higher NYHA functional class at 6 months after pulmonary thromboendarterectomy as compared with patients with normalized PAP and ACT. These findings indicate that improvement in pulmonary artery compliance may be related to the good post-surgical course.

Predictive Factors of Favorable Operative Outcome With the Good Recovery of PAP and ACT of Pulmonary Artery Flow After Pulmonary Thromboendarterectomy

There are some studies of the predictive factors of a favorable operative outcome in patients who undergo pulmonary thromboendarterectomy.20-22 However, it is difficult to confirm this because the endpoints vary among the studies, such as recovery of TR jet area, or PAP and pulmonary resistance assessed by cardiac catheterization.

Tscholl reported that female sex and severity of disease, such as the preoperative pulmonary vascular resistance, NYHA functional class, right atrial pressure, and mean PAP, were useful preoperative predictors when low postoperative pulmonary artery resistance (<500 dynes·s⁻¹·cm⁻⁵) evaluated by cardiac catheterization was regarded as an indicator of successful operative outcome.20 Menzel et al reported that the severity of TR after pulmonary thromboendarterectomy correlated with RV end-diastolic and end-systolic cavity areas, but not with age or morbidity period.7 On the other hand, Reesink et al reported that preoperative endothelin-1 levels may be useful for better identification of patients at risk for persistent pulmonary hypertension after pulmonary thromboendarterectomy.23

In the present study, in which favorable operative outcome was defined as normalization of PAP and ACT of pulmonary artery flow, there was no difference between the 2 groups in sex or preoperative severity of disease such as NYHA functional class, cardiac output, and ACT. A short morbidity period correlated with successful operative outcome in the present study. In a previous study, intimal thickening of the pulmonary arteriolar walls caused by prolonged elevation of PAP often lead to an unfavorable operative outcome.21

A long morbidity in CTEPH may lead to irreversible structural remodeling of the pulmonary artery, which makes it difficult to achieve a successful operative outcome with reduced pulmonary artery compliance. Consequently, a long morbidity may lead to persistent pulmonary hypertension or reduced pulmonary artery compliance after pulmonary thromboendarterectomy. Even with a long morbidity, irreversible structural remodeling may be mitigated by early introduction of anticoagulation therapy after disease onset, indicating that anticoagulation may inhibit the recurrence of embolic events, the sustained high PAP and the subsequent structural remodeling of the pulmonary arteriolar walls. In fact, in the endarterectomy specimen, group B patients showed intimal thickening with neointimal formation and organized thrombus in the pulmonary artery more frequently than group A patients (group A: 32%, group B: 50%). Furthermore, it has been reported that the distal type of CTEPH can also lead to an unfavorable operative outcome with reduced PAP because it is difficult to achieve successful reperfusion in the distal area by pulmonary thromboendarterectomy. Therefore, in the distal type of CTEPH, pulmonary thromboendarterectomy often can not improve the persistent pulmonary hypertension and pulmonary vascular resistance.5,22 In the present study, pulmonary thromboembolic disease was classified into 2 types based on the intraoperative findings; namely, the proximal and distal types. Patients with the distal type showed short ACT of pulmonary artery flow, which was difficult to improve after pulmonary thromboendarterectomy. Therefore, patients with the distal type might have a poorer outcome than those with the proximal type, independent of the severity of pulmonary thromboembolism.

Study Limitations

One limitation is the small number of patients. In addition, our study was retrospective and therefore optimal and serial echocardiography was not always available. It was sometimes difficult to determine the onset of CTEPH accurately from the medical history only of patients without objective measurements. In this study, we defined the onset of disease as the time of sudden onset of dyspnea, palpitations, or manifest cardiovascular collapse. Because the morbidity was significantly different between group A and group B, any error arising from a lack of objective measurements may be negligible. On the other hand, it has been reported
that half of the cases with CTEPH do not have acute episode, and approximately 30% have repeated acute episodes. Furthermore, a multifatorial process occurring over months to years reportedly correlates with the severity of CTEPH, but the exact etiology is unknown.

Although we substituted ACT for pulmonary artery compliance in the present study, it may be influenced by other factors such as cardiac output and RV function besides the mean PAP. ACT is not exactly equivalent to pulmonary artery compliance because the timing of peak forward flow is the timing when backward wavefronts from the periphery reach forward wavefronts, ACT should theoretically reflect peripheral artery compliance. Moreover, a previous clinical study showed that ACT was more influenced by pathological changes in the pulmonary vascular bed than by PAP. In the present study we supposed that the shortened ACT after normalization of TRPG was determined mainly by low pulmonary artery compliance because ACT was scattered over a wide range as compared with TRPG. Jones et al reported that shortened ACT was found to be an early event in the development of pulmonary hypertension in serial noninvasive assessment of progressive pulmonary hypertension in a rat model. They found that the ACT was shortened when pulmonary artery systolic pressure was still normal (<25–30 mmHg). This may indicate that a shortened ACT may represent changes in the characteristics of the pulmonary vasculature that are not reflected in the pulmonary artery systolic pressure.

Conclusion

The recovery of PAP and ACT of pulmonary artery flow was not always concordant after pulmonary thromboendarterectomy, suggesting a time lag in the recovery between pressure and compliance in some patients. A long morbidity of CTEPH, a long period without anticoagulation and the distal embolism type may be predictive factors of an unfavorable operative result with reduced pulmonary artery compliance, and hence poor recovery of clinical performance.

References