Histopathological Examination by Lung Biopsy for the Evaluation of Operability and Postoperative Prognosis in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Background: To evaluate the prognosis after pulmonary thromboendarterectomy (PTE) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), a lung biopsy was performed in 34 patients with central CTEPH and in 7 patients with peripheral CTEPH during PTE.

Methods and Results: Postoperative prognosis was classified from A to E based on the postoperative hemodynamic parameters and clinical condition, and was compared with the index of occlusion (IOCTEPH), which indicates the degree of occlusion in the small pulmonary arteries. Criteria of (A–E) were established only for central CTEPH. Category (A) corresponded to an IOCTEPH from 1.0 to 1.4, (B) from 1.5 to 1.7, (C) from 1.8 to 2.0, and (D) from 2.1 to 2.4. One patient with an index of 3.0 was rated as (E). This patient had collateral vessels around the obstructed small pulmonary arteries and died postoperatively. In all 12 patients who underwent PTE after the criteria were established, postoperative hemodynamic parameters and clinical conditions were consistent with the IOCTEPH. One patient with a high degree of medial atrophy in their small pulmonary arteries died after PTE.

Conclusions: These results indicate that a lung biopsy during PTE is useful for prognostication in patients with CTEPH. (Circ J 2014; 78: 476–482)

Key Words: Lung biopsy; Operative indication; Prognosis; Pulmonary vascular disease
Operative Indications of CTEPH

There was no perioperative complication as a result of a lung biopsy. Examination of the histopathological lung-biopsied samples from patients with CTEPH yielded the following findings:

1) The degree of occlusion in the preacinar small pulmonary arteries and intraacinar small pulmonary arteries strongly determined the postoperative prognosis. Unless the occlusion in the preacinar small pulmonary arteries was 70% or more, complete occlusion of the intraacinar small pulmonary arteries peripheral to the corresponding preacinar small pulmonary arteries was not observed frequently.

2) Fibrous thickening of the intima of the pulmonary veins was observed in most patients, while the degree of pulmonary venous occlusion was 70% or less (Figure 2A).

Results

<p>| Table 1. Clinical Findings in Patients With Chronic Thromboembolic Pulmonary Hypertension |
|--------------------------------|-----|-----|-----|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Male</th>
<th>Female</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central type</td>
<td>34</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Peripheral type</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>13</td>
<td>28</td>
</tr>
</tbody>
</table>

Figure 1. Degree of thrombotic occlusion corresponding to index scores between 1 and 4.
7) The patient who died after the surgery had a large number of collateral vessels surrounding the obstructed small pulmonary arteries (Figure 3A).

Thus, surgery should not be performed when collateral circulation has formed or when there is severe atrophy of the small peripheral pulmonary arteries. In the absence of these findings, the degree of occlusion of each individual small pulmonary artery is considered to affect the prognosis.

The severity of clinical symptoms (as assessed using the New York Heart Association classification [NYHA]) and hemodynamic parameters before and after surgery are shown in Table 2. In patients with central CTEPH, NYHA class, pulmonary artery mean pressure (PAMP), and pulmonary vascular resistance (PVR) greatly improved after surgery. However, in patients with peripheral CTEPH, postoperative improvement of NYHA, PAMP and PVR was not as pronounced.

Disease severity was re-evaluated, that is, rated retrospec-
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class I in all 29 patients with central or peripheral CTEPH classified as (A) or (B). Patients classified as (C) included 2 patients whose symptoms were rated as NYHA class I and 5 whose symptoms were rated as class II. Patients classified as (D) consisted of 1 with class I symptoms, 2 with class II symptoms, and 1 with class III symptoms. Therefore, we speculated that the categories (A–E), determined by PAMP or PVR, closely reflect the clinical severity of symptoms.

From the results of this postoperative hemodynamic data, in patients with central CTEPH, 17 were classified as (A), 8 as (B), 5 as (C), 3 as (D) and 1 as (E). The patient rated as (E) showed a PAMP of 55 mmHg and a PVR of 1,559 dynes · sec/cm$^5$ before PTE. She died of a pulmonary hemorrhage after PTE in the hospital. Prior to surgery, most of the small pulmonary arteries in this patient were obstructed by thrombi, and pulmonary circulation was maintained by collateral vessels formed in the surrounding area (Figure 3A). After surgery, pressure generated by the removal of the thrombus in the main pulmonary artery was transmitted to the collateral vessels, leading to de-
Preacinar and intraacinar small pulmonary arteries (Figure 6) was noted. In more than half of the preacinar small pulmonary arteries, thrombosis was mild, but medial atrophy was significant (Figure 6). These findings suggest that patients with atrophy in more than half of the preacinar small pulmonary arteries should not be treated with surgery.

Discussion

Since it was first performed for the treatment of CTEPH by Moser et al. in 1973, PTE has become a common surgery. Although lesions in the small pulmonary arteries in CTEPH have been described in detail, few studies have compared the histopathological findings of thrombi and the clinical presentation, or have examined the relationship between pathological findings of the small peripheral pulmonary arteries on lung biopsy and the prognosis after PTE. Moser et al. reported plexiform lesions, similar to those observed in congenital heart disease, in CTEPH. Such lesions were not noted in our study. Although we found lesions similar to fibrous intimal thickening seen in congenital heart disease, in CTEPH. Such lesions were not noted in our study. Although we found lesions similar to fibrous intimal thickening seen in congenital heart disease, examination of serial sections of these lesions did not confirm the concentric structure, but rather revealed cushion-like or elevated eccentric intimal fibrosis unique to thrombi. Although thrombi in pulmonary veins have been previously reported, the fibrous intimal thickening observed in the present study was clearly different from thrombi. It consisted of a layer of old fibrous thickening identical to the thickening observed in pulmonary veno-occlusive disease. Intimal fibrous thickening in small veins was seen in almost all the patients examined in this study, but it resulted in incomplete obstruction of the intravascular lumen. Therefore, it was considered not to affect hemodynamics and was excluded from the criteria regarding whether surgery was indicated.

In central CTEPH, IOCTEPH was well-correlated with postoperative hemodynamic parameters and clinical symptoms.
Operative Indications of CTEPH

For this reason, we concluded that open lung biopsy prior to PTE is useful in patients with a high preoperative PAMP or PVR and also severe clinical symptoms. The patient who died after surgery had many collateral vessels around the obstructed small pulmonary arteries. We concluded that such patients should not be treated with surgery because when the pressure is suddenly transmitted to the collateral vessels upon surgical removal of the upstream obstruction, pulmonary hemorrhage occurs. Such a pressure load is also generated in patients with severe atrophy in the small pulmonary arteries by removal of the obstruction, causing pulmonary hemorrhage or edema. Therefore, we considered surgery to be contraindicated in these patients as well. In particular, we speculated that surgery should not be performed when more than half of the preacinar small pulmonary arteries have medial atrophy. However, if severe atrophy of media in small pulmonary arteries is found by performing an open lung biopsy prior to surgery, percutaneous cardio-pulmonary support just after surgery might be effective to prevent a pressure load from suddenly occurring after PTE.

While IOCTEPH was shown to be well-correlated with postoperative hemodynamics and clinical symptoms in patients with central CTEPH in this study, patients with peripheral CTEPH had high IOCTEPH even when pulmonary arterial pressure was relatively low. In clinical practice, many patients with peripheral CTEPH are not treated with surgery because of the absence of central occlusion and are thought to benefit from bosentan. Recently, percutaneous transluminal pulmonary angioplasty has been performed for peripheral-type CTEPH. In our study, criteria on whether surgery is indicated could not be developed for peripheral-type CTEPH due to the low number of patients. Recanalization has been frequently reported, but is generally not observed in old thrombi with multiple layers. In our study, recanalization was noted only in 2 patients with new thrombi.

Conclusions

Diagnosis made by lung biopsy during PTE in 41 patients with CTEPH allowed for the retrospective development of criteria on whether PTE is indicated. In most patients with central CTEPH, hemodynamic values and clinical symptoms improved after surgery, suggesting a satisfactory surgical outcome. However, there was 1 case of operative death. The high degree of occlusion in the small peripheral pulmonary arteries, as indicated by a high IOCTEPH and the large number of collateral vessels surrounding obstructed small pulmonary arteries, were suspected to be causative factors. The lung biopsy diagnosis subsequently made in 12 patients demonstrated that the criteria we developed were reliable, but there was 1 case of operative death. In this patient, almost no thrombi were found in the small peripheral pulmonary arteries.
pulmonary arteries, but medial atrophy was observed. We speculated that after surgery, pressure generated by re-established blood flow caused a fatal pulmonary hemorrhage. We conclude that histopathological assessment of pulmonary vascular disease by intraoperative lung biopsy was useful to predict the prognosis after PTE for CTEPH, and that it will be possible to predict postoperative hemodynamics and clinical symptoms based on the pathological diagnosis during surgery by lung biopsy in patients with a PAMP of 40 mmHg or higher or a PVR of 800 dynes · sec/cm² or higher.

**Disclosures**

Conflict of interest: None declared.

**References**