Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pulmonary Circulation

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

The prognosis of patients with chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary thromboendarterectomy (PTE) depends on multiple factors, including the degree to which thrombi have occluded the small peripheral pulmonary arteries.[1,2] However, pathological features of the small pulmonary arteries can only be assessed with a lung biopsy in patients who undergo PTE. In the present study, a lung biopsy was performed during PTE to evaluate the severity of pulmonary vascular disease and the postoperative prognosis. More accurate criteria for the lung biopsy diagnosis of CTEPH were established retrospectively based on postoperative hemodynamic parameters and clinical symptoms. Then, a lung biopsy was performed and the results were assessed using these criteria for prognosis.

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Methods

The ethics committee of Tohoku University Hospital approved the study protocol and all patients at Fujita Health University provided written informed consent.

A lung biopsy was performed on a total of 41 patients (13 men, 28 women) with CTEPH who underwent PTE from August 2009 to February 2012.[1] There were twice as many female patients as male patients (Table 1).[3] Thirty-four patients had central-type CTEPH and 7 had peripheral-type CTEPH.[4,5] The mean age was 56.7±11.4 years among patients with central-type CTEPH and 56.4±13.4 years among those

Received August 12, 2013; revised manuscript received September 19, 2013; accepted October 3, 2013; released online November 27, 2013 Time for primary review: 17 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-13-1016

with peripheral-type CTEPH. We performed a lung biopsy at the site with the most severe narrowing of the pulmonary artery, as determined by pulmonary angiography.

The lung biopsy tissues sampled from the lobe, which had the most obstructive lesions, were approximately 3×1×1.5 cm and the wound was closed by a continuous suture. They were fixed in 10% formalin and divided into 2 blocks in each case. Fifteen semiserial histological sections were obtained from each block at intervals of 50 μm, thus providing 30 sections from each case. All sections were stained with Elastica-Goldner stain.[1,6,7]

Because the degree of occlusion in the small pulmonary arteries contributes most to the evaluation of prognosis after PTE, the degree of occlusion in each small pulmonary artery was rated on a 4-point scale.[8] Small pulmonary arteries with 50% or less occlusion were rated as 1 (**Figure 1**; **Score 1**), those with 50–60% occlusion as 2 (**Figure 1**; **Score 2**), those with 60–70% occlusion as 3 (**Figure 1**; **Score 3**) and those with 70% or more occlusion as 4 (**Figure 1**; **Score 4**). The index of occlusion in small pulmonary arteries in CTEPH (IOCTEPH) was defined by using the following equation:

$$\mathrm{IOCTEPH} = \frac{1\times n_1 + 2\times n_2 + 3\times n_3 + 4\times n_4}{n_1 + n_2 + n_3 + n_4}$$

Diagnosis by lung biopsy was made for 12 patients in order to verify the criteria for prognostication after the study of 41 patients.

Table 1. Clinical Findings in Patients With Chronic Thromboembolic Pulmonary Hypertension

	Patient	Male	Female	Mean age (years)
Central type	34	13	21	56.7±11.4
Peripheral type	7	0	7	56.4±13.4
Total	41	13	28	56.6±11.6

Results

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**).

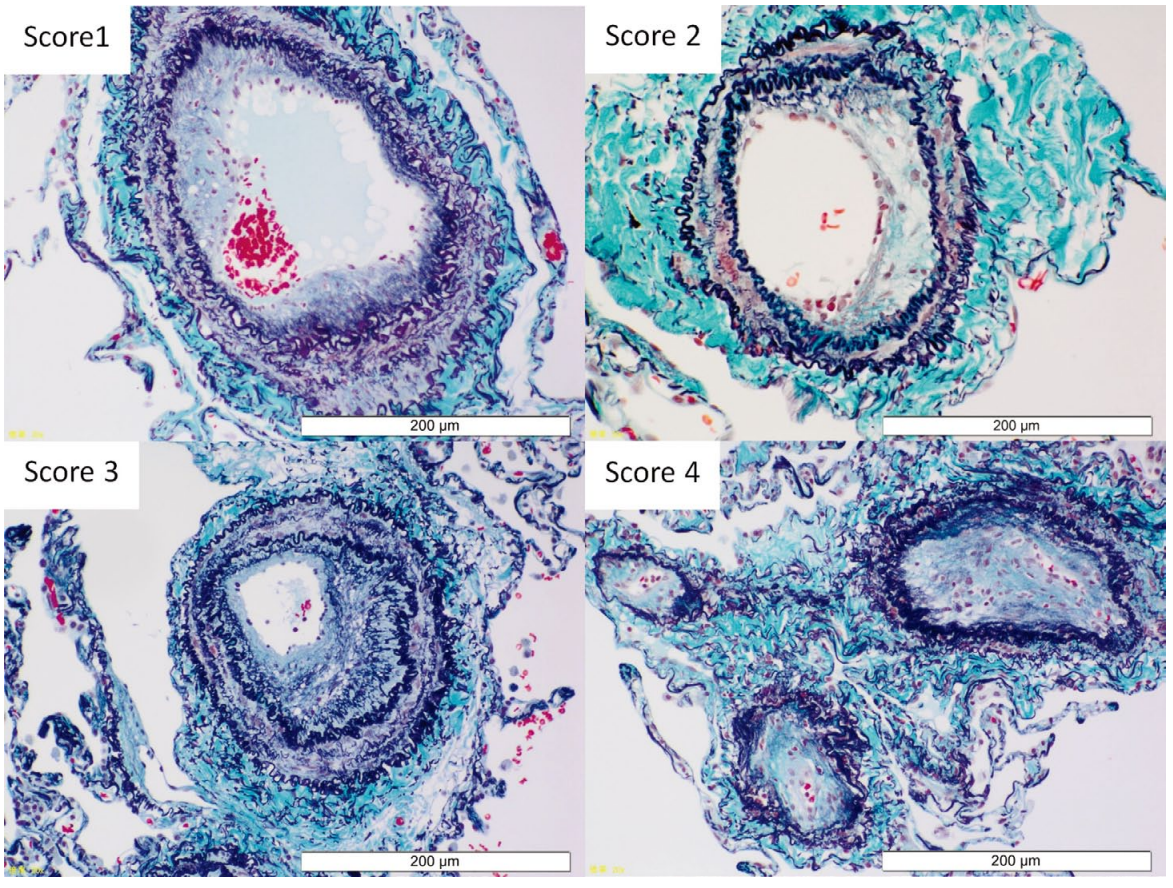

Figure 1. Degree of thrombotic occlusion corresponding to index scores between 1 and 4.

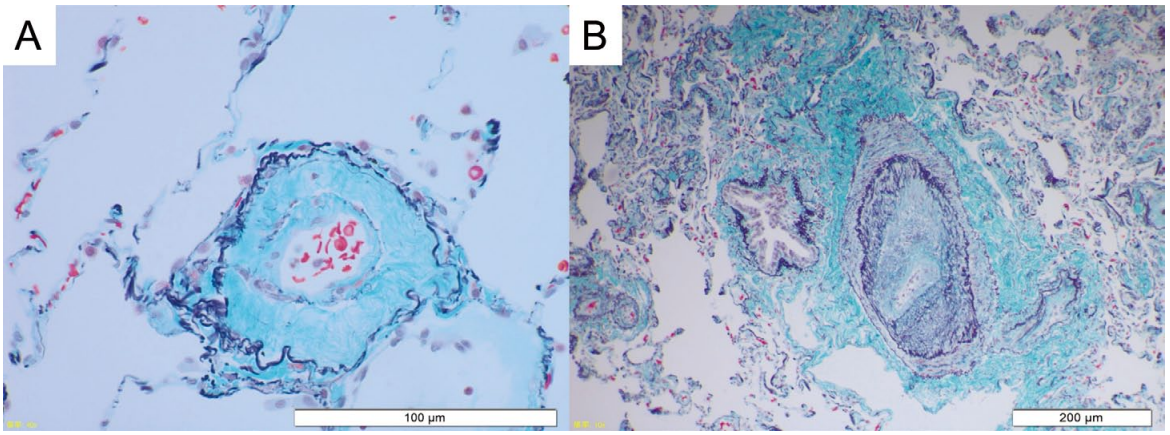

Figure 2. (**A**) Pulmonary vein with intimal fibrous thickening in chronic thromboembolic pulmonary hypertension. (**B**) Preacinar small pulmonary artery with occlusion by post-thrombotic intimal fibrosis in some stages. Many elastic fibers are observed in the older stages.

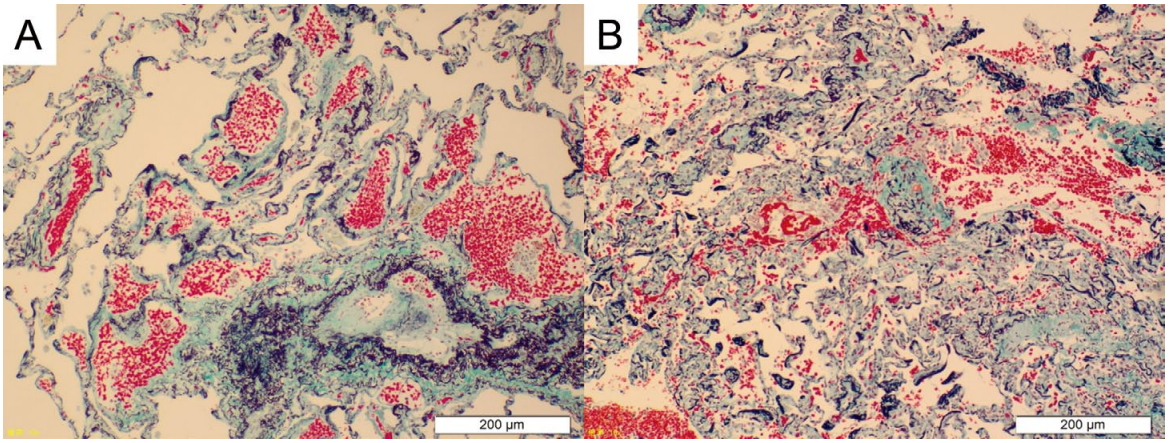

Figure 3. (**A**) Lung biopsy findings in the patient rated (E) who died after surgery. There are many collateral vessels around the occluded small pulmonary arteries. (**B**) Autopsy findings in the same patient of (**A**). Collateral vessels are ruptured by the sudden pressure load generated by pulmonary thromboendarterectomy, leading to a massive pulmonary hemorrhage.

3) Most patients had old thrombi with a 2- to 4-layer structure. Older layers contained fibers with greater elasticity (Figure 2B). Some small pulmonary arteries were completely obstructed and disorganized, and had lost their vascular function.
4) The degree of thickening of the small pulmonary arteries is important as it reflects intravascular pressure and blood flow. Medial thickening is considered as evidence of current or fairly recent blood flow.
5) When there are few thrombi in the preacinar or intraacinar small pulmonary arteries with severe medial atrophy, complete occlusion exists upstream. When complete occlusion is resolved by surgery, a pressure load is generated, causing pulmonary hemorrhage or edema.
6) Slight recanalization was observed in 2 patients with new thrombi, while recanalization was barely noticeable in other patients.
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-

Table 2. Preoperative and Postoperative Data in Patients With Chronic Thromboembolic Pulmonary Hypertension

	Preoperative			Postoperative		
	NYHA	mPAP	PVR	NYHA	mPAP	PVR
Central type	3.1±0.3	45.1±10.3	1,016.0±440.6	1.1±0.4	20.3±9.1	241.9±176.9
Peripheral type	3.0±0.0	41.4±6.9	1,170.0±567.8	1.6±0.5	26.6±7.3	370.3±102.2

NYHA, average of New York Heart Association classification; mPAP, average of mean pulmonary arterial pressure (mmHg); PVR, average of pulmonary vascular resistance (dynes·sec/cm^5).

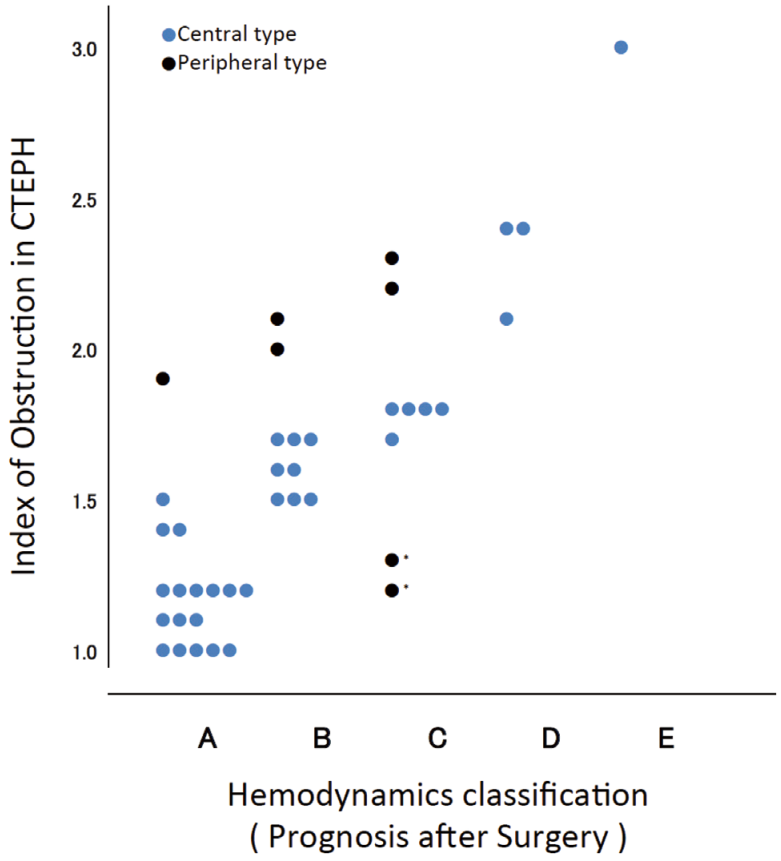

Figure 4. Comparison between the index of occlusion in small pulmonary arteries in chronic thromboembolic pulmonary hypertension (IOCTEPH) and rating from (A to E) based on postoperative hemodynamic parameters. (A–E) also show the prognosis after surgery. *Patients showed low IOCTEPH because of medial atrophy.

tively as A, B, C, D or E, based on postoperative hemodynamic parameters and clinical symptoms: (A) no problems are likely after PTE; (B) neither operative death nor hospital death occurs, but pulmonary hypertension remains; (C) neither operative death nor hospital death occurs, but there is a small possibility of remote death; (D) no operative death occurs, but there is a high possibility of hospital death or remote death; (E) operative death or hospital death is very likely.

The absence of pulmonary hypertension, that is, PAMP below 20 mmHg or a PVR below 200 dynes·sec/cm^5, was defined as: severe postoperative pulmonary hypertension represented by PAMP of 40 mmHg or higher (A), or a PVR of 600 dynes·sec/cm^5 or higher was rated as (D). The perioperative course of these patients was critical and PTE was not recommended. (B) was defined as PAMP of 20–29 mmHg or a PVR of 200–399 dynes·sec/cm^5, and (C) was defined as PAMP of 30–39 mmHg or a PVR of 400–599 dynes·sec/cm^5. Hospital death was rated as (E).

Postoperatively, clinical symptoms were rated as NYHA 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 postoperstive 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-

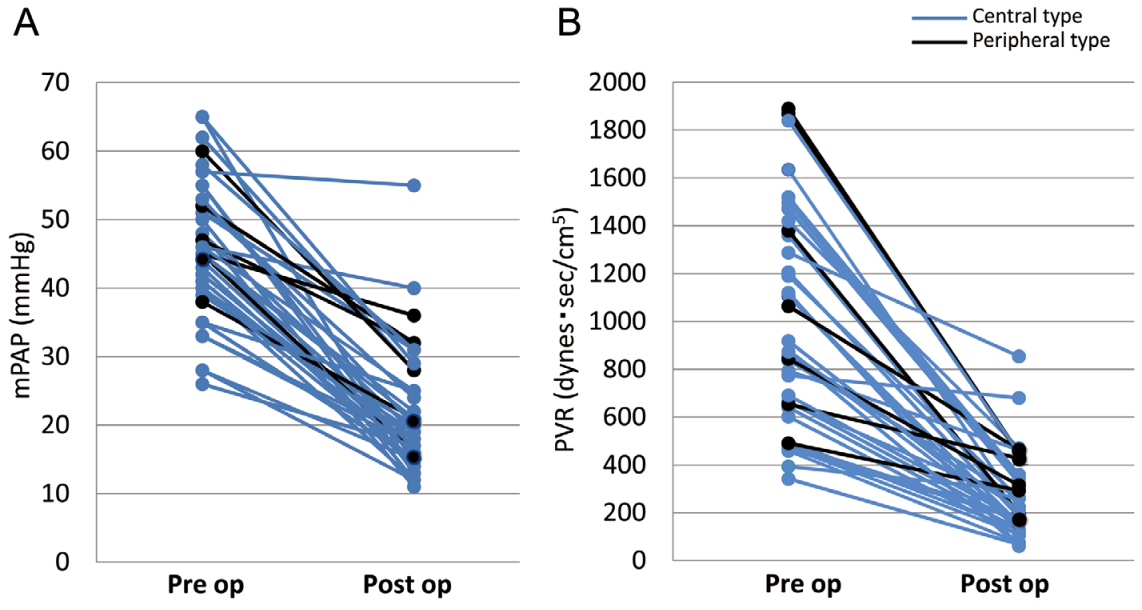

Figure 5. Pulmonary artery mean pressure (PAMP) (**A**) and pulmonary vascular resistance (PVR) (**B**) of each patient before (pre op) and after (post op) surgery.

struction of the collateral vessels and a pulmonary hemorrhage (**Figure 3B**). Among patients with peripheral CTEPH, 1 each was classified as (A), (B) and (D) and 4 as (C), indicating that most patients had severe disease.

Next, the IOCTEPH was calculated for each patient and retrospectively compared with the (A–E) classification based on hemodynamic values (**Figure 4**). There was a significant correlation between the IOCTEPH and the (A–E) (hemodynamic classification); that is, there was a correlation between IOCTEPH and mPA ($P<0.01$) as well as between IOCTEPH and PVR ($P<0.01$) for the central-type CTEPH. In this type, IOCTEPH of 1.0–1.4 corresponds to (A), 1.5–1.7 to (B), 1.8–2.0 to (C), 2.1–2.4 to (D) and 3.0 to (E) (1 patient with collateral circulation). In patients with peripheral-type CTEPH, all the observed categories (A–D) showed high IOCTEPH and 2 patients with medial atrophy had low IOCTEPH. Criteria regarding indications for surgery could not be developed for the peripheral type due to the low number of patients.

Preoperative and postoperative PAMP and PVR values are shown in **Figures 5A** and **B**, respectively. Patients with a postoperative PAMP of 30 mmHg or higher had a preoperative PAMP of 45 mmHg. Patients with a postoperative PVR of 400 dynes·sec/cm^5 or higher had a preoperative PVR of 800 dynes·sec/cm^5 or higher. It is thus indicated that a lung biopsy should be performed prior to surgery in patients with a preoperative PAMP of 45 mmHg or higher and those with a preoperative PVR of 800 dynes·sec/cm^5 or higher.

After retrospectively developing the criteria for lung biopsy evaluation including IOCTEPH, lung biopsy diagnosis was made for 12 patients during surgery in accordance with these criteria based on hemodynamic values. The IOCTEPH was consistent with postoperative hemodynamic values and clinical symptoms. However, there was 1 case of death associated with surgery due to postoperative pulmonary hemorrhage. In this patient, a preoperative PAMP was 48 mmHg and a PVR was 962 dynes·sec/cm^5, and severe medial atrophy in the 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,[9] PTE has become a common surgery.[10] Although lesions in the small pulmonary arteries in CTEPH have been described in detail,[11] 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.[2] 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,[12,13] 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.

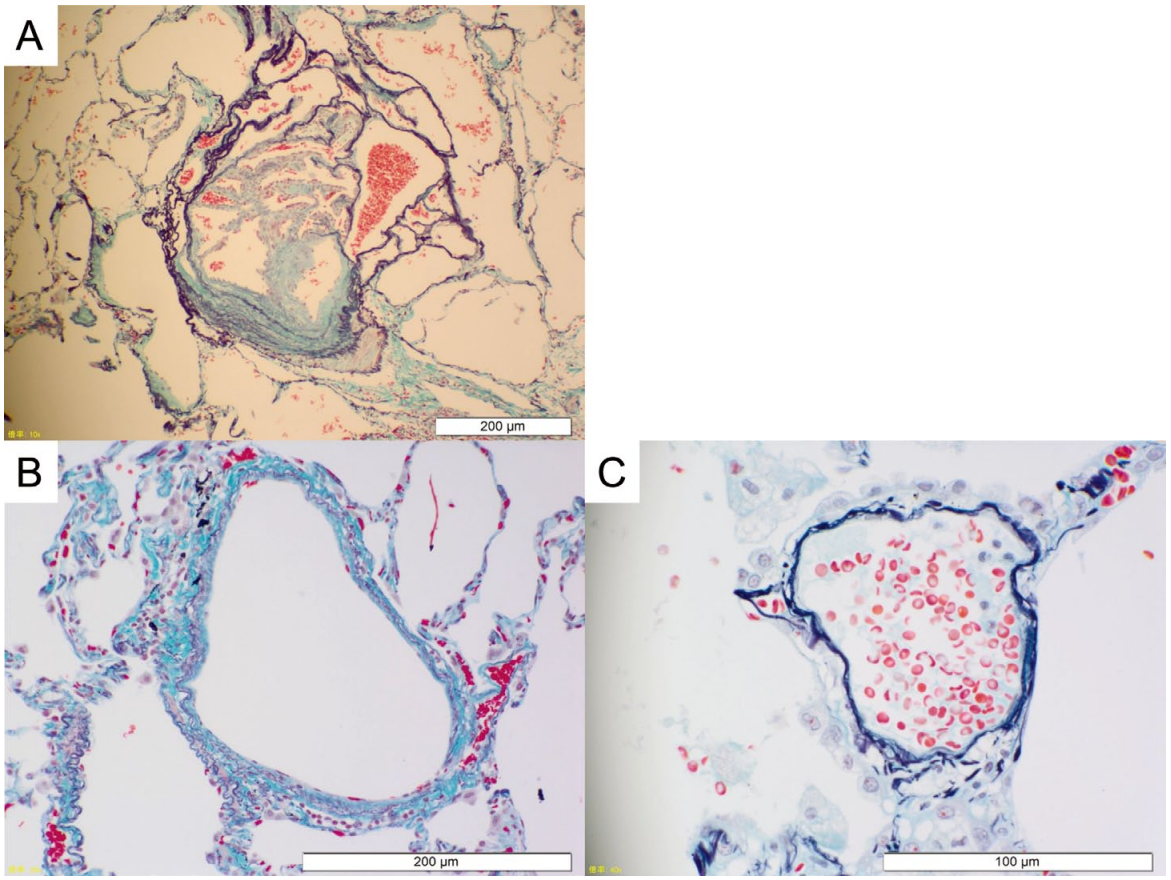

Figure 6. Severe medial atrophy of a preacinar small pulmonary artery (**A**,**B**) and an intraacinar small pulmonary artery and pulmonary hemorrhage (**C**) from fragile vascular walls caused by the sudden pressure load generated by pulmonary thromboendarterectomy.

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[14] and are thought to benefit from bosentan.[15,16] Recently, percutaneous transluminal pulmonary angioplasty has been performed for peripheral-type CTEPH.[17,18] 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

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/cm^5 or higher.

Disclosures

Conflict of interest: None declared.

References

1. Yamaki S. Pulmonary vascular disease associated with pulmonary hypertension in 445 patients: Diagnosis from lung biopsy and autopsy. *Gen Thorac Cardiovasc Surg* 2013; **61:** 24–31.
2. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest* 1993; **103:** 685–692.
3. Shigeta A, Tanabe N, Shimizu H, Hoshino S, Maruoka M, Sakao S, et al. Gender differences in chronic thromboembolic pulmonary hypertension in Japan. *Circ J* 2008; **72:** 2069–2074.
4. Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg* 2002; **124:** 1203–1211.
5. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, et al. Pulmonary endartectomy: Experience and lessons learned in 1500 cases. *Ann Thorac Surg* 2003; **76:** 1457–1462.
6. Yamaki S, Horiuchi T, Miura M, Haneda K, Ishizawa E, Suzuki Y. Secundum atrial septal defect with severe pulmonary hypertension. Open lung biopsy diagnosis of operative indication. *Chest* 1987; **91:** 33–38.
7. Yamaki S, Yasui H, Kado H, Yonenaga K, Nakamura Y, Kikuchi T, et al. Pulmonary vascular disease and operative indications in complete atrioventricular canal defect in early infancy. *J Thorac Cardiovasc Surg* 1993; **106:** 398–405.
8. Yamaki S, Tezuka F. Quantitative analysis of pulmonary vascular disease in complete transposition of the great arteries. *Circulation* 1976; **54:** 805–809.
9. Moser KM, Braunwald NS. Successful surgical intervention in severe chronic thromboembolic pulmonary hypertension. *Chest* 1973; **64:** 29–35.
10. Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, et al. Long-term outcome after pulmonary thromboendartectomy. *Am J Respir Crit Care Med* 1999; **160:** 523–528.
11. Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970; **42:** 1163–1184.
12. Wagenvoort CA, Mooi WJ. Biopsy pathology of the pulmonary vasculature. *In*: Gottlieb L, editor. Pulmonary veno-occlusive disease. London: Chapman and Hall Medical, 1989; 128–147.
13. Dunnill MS. The pathology of pulmonary embolism. *Br J Surg* 1968; **55:** 790–794.
14. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. *Curr Probl Surg* 2000; **37:** 165–225.
15. Bonderman D, Nowotny R, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Klepetko W, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2599–2603.
16. Hoeper MM, Kramm T, Wilkens H, Schulze C, Schafers HJ, Welte T, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2363–2267.
17. Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. *Circ J* 2012; **76:** 485–488.
18. Yamada N. Percutaneous transluminal angioplasty for distal-type chronic thromboembolic pulmonary hypertension. *Circ J* 2012; **76:** 307–308.