Histopathological Multiple Recanalized Lesion Is Critical Element of Outcome After Pulmonary Thromboendarterectomy

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SUMMARY

Pulmonary thromboendarterectomy (PEA) is a curative therapy for chronic thromboembolic pulmonary hypertension (CTEPH), but the postoperative mortality remains unsatisfactory (4-10%). Residual pulmonary hypertension is the most common cause of perioperative death. Although PEA specimens seem to contain lesions responsible for hemodynamic improvement, relevant histopathological findings have still to be identified.

The aim of this study was to identify histopathological findings that predict postoperative residual pulmonary hypertension after PEA.

PEA specimens obtained from 51 consecutive patients with CTEPH were histopathologically assessed. The patient characteristics and disease location were reviewed by medical records. The associations with residual pulmonary hypertension were analyzed.

The mean values of preoperative and postoperative vascular resistance (PVR) were 1142 ± 454 and 496 ± 368 dynes-sec/cm⁵, respectively. Twenty of 51 patients (39%), including 2 patients who died, continued to have residual pulmonary hypertension (PVR ≥ 500 dynes-sec/cm⁵). Statistical tests indicated that male, proximal disease type and the presence of histopathological multiple recanalized thrombus were associated with good surgical outcome (PVR < 500 dynes-sec/cm⁵). The positive and negative predictive values for surgical outcome estimated by the presence of multiple recanalized lesions were higher than the values estimated by proximal disease type (85% and 88% versus 73% and 71%, respectively). Moreover, the number of multiple recanalized lesions was significantly correlated to the reduction in PVR ($P = 0.03$).

The presence of histopathological multiple recanalized lesions was significantly associated with a decrease in PVR after PEA. Histopathological study may be a potent diagnostic strategy for accurately predicting surgical outcome in the early perioperative period. (Int Heart J 2011; 52: 377-381)

Key words: Pulmonary hypertension, Pulmonary embolism, Heart failure, Embolism, Pathology, Surgery, Prognosis

The quality of life and prognosis of chronic thromboembolic pulmonary hypertension with pulmonary artery pressure over 30 mmHg are poor,¹⁾ and medical therapies remain unsatisfactory.²⁻⁵⁾ Pulmonary endarterectomy (PEA) dramatically improves the hemodynamic status, quality of life (QOL), and moreover long-term survival,⁶⁻⁹⁾ and has therefore become accepted as the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH). Although distal type of disease location¹⁰⁻¹⁴⁾ and small vessel vasculopathy^{13,15,16)} are well-recognized as potent predictors of residual pulmonary hypertension, which often cause perioperative death,¹⁰⁾ the risk of perioperative mortality is still 4-10%.^{6,17,18)} It is therefore necessary to develop a strategy for PEA.

It is known that the amount of materials removed by PEA does not correlate with hemodynamic improvement. As shown in Figure 1, despite the small quantity of surgically removed materials, the patient showed surprising improvement of hemodynamics after PEA. Pulmonary angiography after PEA showed the disappearance of 'webs and bands' lesion and his-

topathological study identified many multiple recanalized lesions in surgical specimens. We therefore hypothesized that such specific histological features in surgical specimens are critical for predicting the outcome of PEA. In the present study, surgical specimens were examined histologically with the aim of elucidating factors that predict persistent or residual pulmonary hypertension after PEA.

METHODS

Patient selection and clinical data: Fifty-one consecutive patients with CTEPH who underwent PEA in our hospital between January 2003 and December 2007 were analyzed. All procedures were approved by the Human Subjects Institutional Review Board of the National Cardiovascular Center. Patient characteristics and clinical indices including hemodynamic parameters within 1 month before and after PEA were extracted from the medical records (Table I).

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Anatomical types of disease location: Photomacrography was performed on all PEA specimens at the time of surgery, and the samples were submitted to the Department of Pathology immediately. Patients who underwent PEA were retrospectively classified into proximal (San Diego type 1 or 2), segmental (San Diego type 3) and peripheral types (San Diego type 4) based on preoperative pulmonary angiography and gross findings of surgical specimens.^{11,12)}

Histopathological examination: The surgical specimens were fixed in 10% buffered formalin. The entire materials obtained from PEA were embedded in paraffin for histopathological study. Sections were prepared from the proximal to distal levels of all branches, and then stained with hematoxylin-eosin, Masson's trichrome, and elastica van Gieson stains. In this study, we focused on 3 characteristic histopathological findings that seem to predict surgical outcome. First, we examined the presence of multiple recanalized lesions. As shown in Figure 1, the appearance of webs or bands on the pulmonary artery angiograms may represent a large multiple recanalized thrombus. Microscopic analysis gives us detailed information about whether PEA has removed much smaller recanalized lesions, which could not be detected by angiograms. Second, the presence of a fresh or organizing thrombus that characterizes San Diego type 1 was examined. Third, the presence of atherosclerotic plaque with a necrotic core (cholesterol cleft) was examined, which is more frequently found in CTEPH patients than in patients with other types of pulmonary artery hypertension (such as plexogenic pulmonary hypertension).¹⁹⁾ A representative multiple recanalized lesion and atherosclerotic plaque are shown in Figure 2.

Definition of persistent or residual pulmonary hypertension: Jamieson and colleagues¹⁰⁾ reported that residual pulmonary hypertension with pulmonary vascular resistance (PVR) > 500

dynes-sec/cm⁵ after PEA affected the subsequent recovery course and postoperative mortality. Persistent or residual pulmonary hypertension was defined as a postoperative PVR of 500 dynes-sec/cm⁵ or above in this study. According to this definition, patients were classified into a good surgical outcome group (without persistent or residual pulmonary hypertension) and a poor surgical outcome group [with persistent or residual pulmonary hypertension or perioperative death (including in-hospital death)].

Statistical analysis: Statistical analysis was performed using JMP[®] 7 (SAS Institute Inc., Cary, NC, USA) statistical software. Fisher's exact test or chi-square test and unpaired Student's *t*-test were used to analyze categorical data and continuous data, respectively. Pearson's correlation test and linear regression analysis were used to assess the relation between the number of histopathological multiple recanalized lesions and the change in PVR after PEA. A *P* value less than 0.05 was regarded as statistically significant. Data are expressed as the mean ± standard deviation or percentage.

RESULTS

Patient characteristics and surgical outcome: The patient characteristics and clinical parameters are shown in Table I. The mean age was 52 ± 12 years (range: 191 to 72 years), with a slight female dominance (59%). Twenty-seven percent of the patients had a documented history of DVT.

The overall perioperative mortality rate was 3.9% (2/51 patients). Both patients who died could not be weaned from the extracorporeal cardiopulmonary device because of residual pulmonary hypertension. The right cardiac catheterization parameters before and after surgery were: mean right atrium pressure (RAP) 3.7 ± 3.3 and 2.4 ± 2.9 mmHg; mean pulmonary artery pressure (PAP) 46.6 ± 10.1 and 25.1 ± 13.7 mmHg; PVR 1142 ± 454 and 496 ± 363 dynes-sec/cm⁵, respectively. According to the above-mentioned definition, 31/51 patients (61%) belonged to the good surgical outcome group and more than half of them had PVR lower than 250 dynes-sec/cm⁵. The

Figure 1. Example of a patient showing improved hemodynamics despite a slight amount of tissue being removed by pulmonary endarterectomy. Although the surgery removed only a slight amount of material (**upper left**), the hemodynamic indices dramatically improved (**table**). Pulmonary angiography showed the disappearance of segmental webs and bands (**bottom left**; arrows). Many multiple recanalized lesions were found in the histopathological study (**upper right**: original magnification × 20, elastica van Gieson staining). CI indicates cardiac index, PAP, pulmonary artery pressure, PCWP, pulmonary capillary wedge pressure, PVR, pulmonary vascular resistance, and RAP, right atrium pressure.

Table I. Patient Characteristics

Patient background		
Age (years)	52.2 ± 12.2	
Male (%)	41.2	
History of DVT (%)	27.4	
Clinical parameter	before PEA	after PEA
mean RAP (mmHg)	3.7 ± 3.3	2.4 ± 2.9
mean PAP (mmHg)	46.6 ± 10.1	25.1 ± 13.7
CO (L/minute)	3.16 ± 0.99	3.75 ± 0.93
PVR (dynes-sec/cm ⁻⁵)	1142 ± 454	496 ± 363
BNP (pg/mL)	207 ± 217	68.6 ± 71.8
6MWD (m)	375 ± 102	429 ± 111

Data are mean ± SD or percentage. DVT indicates deep venous thrombosis; RAP, right atrial pressure; PAP, pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; BNP, brain natriuretic peptide; and 6MWD, 6 minutes walk distance. All clinical variables significantly improved after PEA.

Figure 2. Histopathological findings of surgical samples from pulmonary thromboendarterectomy. **a, b** and **c** show serial sections of a multiple recanalized lesion, which is an organized thrombus with multiple recanalization channels. **d** shows a large atherosclerotic plaque with cholesterol cleft and fresh mural thrombus. **e** is a higher magnification of the square in **d**. Original magnification $\times 20$ (**a, b, c, d**) and $\times 40$ (**e**), Hematoxylin eosin staining (**a**), Masson's trichrome staining (**b, d, e**), and elastica van Gieson staining (**c**).

Table II. Comparison by Presence of Residual Pulmonary Hypertension

Patient background	PVR < 500	PVR $\geq$ 500 or death	P
Age (years)	50.4 $\pm$ 13.9	55.5 $\pm$ 8.7	NS
Male (%)	58.1	15.0	< 0.01
Medical history of DVT (%)	25.8	30.0	NS
Disease location			
Proximal type (%)	73.0	27.0	< 0.01
Histopathologic finding			
Multiple recanalized lesions (%)	93.6	25.0	< 0.01
Fresh or organizing thrombus (%)	71.0	50.0	NS
Atherosclerotic plaque (%)	12.9	25.0	NS

Data are mean $\pm$ SD or percentage. DVT indicates deep venous thrombosis; PVR, pulmonary vascular resistance; and NS, not significant. Male gender, proximal disease location, and histological multiple recanalized lesions were significantly correlated with good surgical outcome (PVR < 500).

other clinical parameters before and after surgery were: BNP 207 ± 217 and 68.6 ± 71.8 pg/mL, 6MWD 375 ± 102 and 429 ± 111 m, respectively. All hemodynamic and clinical indices improved significantly after surgery ($P < 0.01$).

Anatomical disease location and surgical outcome in overall patients: Of 51 patients who underwent PEA, 73% (37/51) had the proximal type, 26% (13/51) the segmental type, and 2.0% (1/51) the peripheral type. Segmental disease was more frequent than in a past report from the United States,¹²⁾ while the distribution was similar to Japanese patients with CTEPH.⁶⁾ The changes in PVR (= preoperative PVR - postoperative PVR) were proximal type 722 ± 457 , segmental type $397 \pm$

Figure 3. Categorical diagram according to surgical outcome and disease location. Vertical and horizontal axes represent postoperative pulmonary vascular resistance and disease location type, respectively. **Upper panel** shows scatter plot of overall patients. Lower panel shows scatter plot of patients with (**left**) and without histological multiple recanalized lesions (**right**). The presence of multiple recanalized lesions predicts the surgical outcome with more accuracy.

Figure 4. Relation between change in pulmonary vascular resistance and the number of histopathological multiple recanalized lesions. Scattergram showing the relation between change in pulmonary vascular resistance (Δ PVR = preoperative PVR - postoperative PVR) and the number of histopathological multiple recanalized lesions. The fitted solid line shows significant correlation with the change in PVR and the number of histological multiple recanalized lesions ($R^2 = 0.10$, $P = 0.03$). The dashed lines represent 95% confidence intervals.

464, and peripheral type 206 (1 patient) dynes-sec/cm⁵, and were significantly correlated with disease location type.

Histopathological examination: Multiple recanalized lesions were observed in 67% (34/51) of the patients. The number and maximal diameter of the lesions were 4.6 ± 3.4 /patient and 3.6 ± 2.0 mm (range: 1.1 to 8.6 mm), respectively. Fresh or organizing thrombus and atherosclerotic plaque with a necrotic core were found in 63% (32/51 patients) and 18% (9/51 patients),

respectively.

Predictors of surgical outcome: Statistical tests showed that being male, proximal disease, and the presence of histopathological multiple recanalized lesions had a significant correlation with good surgical outcome. There were no differences between the two groups in the other histopathological findings (Table II). *Post hoc* analysis revealed that male patients had a significantly lower preoperative PVR than female patients, while the proximal type disease and the presence of multiple recanalized lesions were not significantly correlated to the preoperative PVR. Although the positive predictive value and negative predictive value of disease location for surgical outcome are 73% (27/37 patients) and 71% (10/14 patients), the values of combined predictors of both disease location and the presence of multiple recanalized lesions rise to 90% (26/29 patients) and 89% (8/9 patients), respectively (Figure 3).

DISCUSSION

The present study demonstrated that the presence of histopathological multiple recanalized lesions in surgical specimens is an additional predictor of good surgical outcome (PVR < 500). Since small pulmonary arteries partially anastomose with bronchial arteries, the peripheral pulmonary arteries are known to be patent. Moreover, multiple recanalized thrombi themselves may imply the predominance of fibrinolytic activity distal to the lesion. It is reasonable that histopathological analysis, which can diagnose more sensitively whether the removal of resistant lesions is successful or not, predicts hemodynamic status after surgery.

It is well known that the most common predictor of PEA outcome is disease location determined by preoperative pulmonary angiography, helical CT,^{20,21)} and intraoperative classification of thromboembolic disease. The present study in a Japanese population also revealed that the anatomical disease location is significantly correlated with surgical outcome. Moreover, the combined predictor consisting of both disease location and histopathological multiple recanalized lesions more precisely predicted the clinical course after PEA. The prediction of whether the hemodynamic status after PEA is stable or unstable is useful information when caring for a patient because it can help intensive care staff decide on the need for a cardiopulmonary support device without waiting for the recovery of cardiac function after surgery. Additionally, a recent study reported that optical coherence tomography can detect such small multiple thrombotic lesions.²²⁾ Examining where such multiple recanalized lesions are located may provide information concerning precise surgical accessibility before PEA. On the other hand, gender was also significantly correlated to the postoperative PVR. Since several previous reports suggested a higher preoperative PVR was correlated to the surgical outcome,^{23,24)} this could be explained by the *post hoc* analysis showing the preoperative PVR in males was significantly lower than in females. However, it is unclear why the PVR in male patients who underwent PEA was lower than that in female patients.

Based on these results, we statistically analyzed the relation between the number of multiple recanalized lesions and the change in PVR. Figure 4 shows the correlation reveals a significant linear correlation between them ($P = 0.03$) with a

low correlation coefficient ($R^2 = 0.10$). A possible explanation for the low correlation coefficient is that not only the number but also the diameter of the lesions, preoperative PVR, and removal of the other disease lesions such as complete obstruction and stenosis contributed to the postoperative change in PVR.

Limitations: First, only 51 PEA specimens were assessed, and this sample size is too small to allow a definitive conclusion. Furthermore, the subjects in the present study were all Japanese patients. It is uncertain whether this result can be generalized to other ethnic groups.

Second, the impact of small vessel vasculopathy distal to the multiple recanalized lesions remains unclear. Obviously the degree of small vessel vasculopathy distal to the lesion influences hemodynamic improvement after surgery. Further investigations are needed to clarify the relationship between small vessel vasculopathy and multiple recanalized lesions.

Clinical implication: Histopathological assessment of PEA specimens would provide a precise prediction of postoperative hemodynamic stability and surgical outcome earlier than the recovery in cardiac function after cardiac arrest. Furthermore, assessing the location of multiple recanalized lesions before surgery may assist with the development of a surgical strategy.

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