Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a progressive disease of increasing pulmonary vascular resistance because of chronic thromboembolism in the pulmonary arteries that leads to pulmonary hypertension (PH), right-sided heart failure, and a grave prognosis. Several studies have demonstrated the efficacy of medical therapies using anticoagulation and pulmonary vasodilators, including several newly developed agents. The most powerful conventional therapeutic strategy for CTEPH is invasive surgical pulmonary endarterectomy (PEA). Surgical therapy is indicated when the thromboembolic lesions are located in the proximal pulmonary arteries or lobar branches. Thus, there are some patients in whom PEA is not indicated; furthermore, some patients continue to suffer from severe PH despite treatment with PEA.

**Background**—Chronic thromboembolic pulmonary hypertension leads to pulmonary hypertension and right-sided heart failure. The purpose of this study was to investigate the efficacy of percutaneous transluminal pulmonary angioplasty (PTPA) for the treatment of chronic thromboembolic pulmonary hypertension.

**Methods and Results**—Twenty-nine patients with chronic thromboembolic pulmonary hypertension underwent PTPA. One patient had a wiring perforation as a complication of PTPA and died 2 days after the procedure. In the remaining 28 patients, PTPA did not produce immediate hemodynamic improvement at the time of the procedure. However, after follow-up (6.0 ± 6.9 months), New York Heart Association functional classifications and levels of plasma B-type natriuretic peptide significantly improved (both P<0.01). Hemodynamic parameters also significantly improved (mean pulmonary arterial pressure, 45.3 ± 9.8 versus 31.8 ± 10.0 mm Hg; cardiac output, 3.6 ± 1.2 versus 4.6 ± 1.7 L/min, baseline versus follow-up, respectively; both P<0.01). Twenty-seven of 51 procedures in total (53%), and 19 of 28 first procedures (68%), had reperfusion pulmonary edema as the chief complication. Patients with severe clinical signs and/or severe hemodynamics at baseline had a high risk of reperfusion pulmonary edema.

**Conclusions**—PTPA improved subjective symptoms and objective variables, including pulmonary hemodynamics. PTPA may be a promising therapeutic strategy for the treatment of chronic thromboembolic pulmonary hypertension.

**Clinical Trial Registration**—URL: http://www.umin.ac.jp. Unique identifier: UMIN000001572. 

**Key Words:** chronic thromboembolic pulmonary hypertension, pulmonary hypertension, percutaneous transluminal pulmonary angioplasty, reperfusion pulmonary edema
WHAT IS KNOWN

- Surgical pulmonary endarterectomy is the most powerful interventional therapeutic strategy for chronic thromboembolic pulmonary hypertension.
- Limited studies have shown that percutaneous transluminal pulmonary angioplasty can improve subjective symptoms and pulmonary hemodynamics of the patients with chronic thromboembolic pulmonary hypertension.

WHAT THE STUDY ADDS

- This study suggests that percutaneous transluminal pulmonary angioplasty can treat the distal narrow lesions that cannot be reached by pulmonary endarterectomy with tolerable complications.
- Percutaneous transluminal pulmonary angioplasty may be a promising therapeutic strategy for the treatment of chronic thromboembolic pulmonary hypertension.

Methods

Study Subjects
In this study, 29 patients (age, 62.3 ± 11.5 years; 23 women, 6 men) with CTEPH who visited the Keio University Hospital and Kyorin University Hospital in Japan from January 2009 to December 2011 were enrolled. Their disease duration was 3.7 ± 3.6 years (range, 0.5–15 years). They were diagnosed with CTEPH by the demonstration of organized pulmonary thromboembolism using contrast-enhanced lung computed tomography, perfusion lung scintigraphy, and pulmonary angiography. However, one 74-year-old female patient had complications from PTPA (a wiring perforation) and died 2 days later. Thus, the study analyzed the therapeutic efficacy of PTPA in the remaining 28 patients (age, 61.9 ± 11.5 years; 22 women, 6 men). All patients provided their informed consent, and PTPA treatment was approved by the institutional review boards of the hospitals.

Examinations
Patients underwent right-sided heart catheterization just before and after PTPA, and at follow-up examinations. The timing of the follow-up right-sided heart catheterization after the last PTPA procedure was essentially at 1 to 3 months, 6 months, 12 months, and every 1 year thereafter. Right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary capillary wedge pressure were measured at the right-sided heart catheterization. Cardiac output (CO) was determined using the Fick technique. Although mean PAP was measured in the main trunk of the pulmonary artery, proximal to the stenoses further down the pulmonary arterial tree, pulmonary capillary wedge pressure was measured peripherally, distal to all the stenoses of the pulmonary arteries, so as to accurately measure pulmonary capillary wedge pressure. Furthermore, plasma B-type natriuretic peptide (BNP) levels were measured before PTPA and at the same time as the follow-up right-sided heart catheterization.

Medications
PH medications at baseline in the 29 enrolled patients were as follows: bosentan (228 ± 47 mg, 14 patients); ambrisentan (7.5 ± 3.5 mg, 2 patients); sildenafil (55 ± 13 mg, 20 patients); tadalafil (30 ± 12 mg, 4 patients); oral beraprost (96 ± 33 μg, 5 patients); and oral sustained release beraprost (312 ± 84 μg, 10 patients). All 29 patients were also treated with coumadin. Changes in medication until the last follow-up catheterization included the following: addition of ambrisentan (5 mg, 1 patient); addition of tadalafil (40 mg, 1 patient); bosentan increased from 125 to 250 mg (1 patient); sildenafil increased from 30 to 60 mg (1 patient); oral beraprost decreased from 120 to 60 μg (1 patient); and 187.5 mg bosentan and 60 μg beraprost discontinued (1 patient). Among the 28 patients whose follow-up hemodynamic data were obtained, the PH medication of 22 patients remained unchanged until the time of the last follow-up catheterization, whereas diuretics were decreased in 3 patients and increased in 2 patients until the last follow-up. Epoprostenol, treprostinil, and iloprost were not used in any of the patients.

Indication for PTPA
The inclusion criteria of this study were adult patients with CTEPH who could understand the PTPA procedure and possible complications and give informed consent of their own free will. Both the PEA and PTPA procedures were explained to the patients and the discussion included the possible complications of PTPA (based on the previous report by Feinstein et al) and the therapeutic benefits and operative risks of PEA, the latter given by an experienced PEA surgeon in some cases. Then, PEA was recommended on the basis of evidence-based medicine in patients whose main lesions were central lesions and whose operative risks were expected to be typical of the procedure. Our study basically selected patients with almost all of their pulmonary thromboembolic lesion existing in the lobar, segmental, and subsegmental pulmonary arteries. The target lesions for PTPA in the present study were mostly ones that would have also been amenable to PEA. PTPA targets basically the same lesions (lobar, segmental, and subsegmental lesions) as PEA, except for cases whose lesions exist in the main trunks of the pulmonary arteries. Thus, our study selected patients who rejected PEA or for whom we suggested PTPA was more appropriate than PEA because of their high age or poor physical condition. Additionally, our study included patients who had already undergone PEA but had residual PH because of lesions which could not be removed with PEA. Meanwhile, our exclusion criteria were patients who were expected to be impossible to keep on the treatment table during the PTPA procedure because of mental disorders, those with active infectious diseases, and those who had serious complications, such as hepatic disease, kidney disease, hemorrhagic tendency, and poorly controlled diabetic mellitus and hypertension.

PTPA Procedure
Catheters were inserted through the femoral vein or the right jugular vein. If the patients had a filter in the inferior vena cava, the right jugular vein was selected. A balloon wedge pressure catheter was inserted into the main pulmonary artery tract and replaced by a long Spring Guide Wire, and an 8 or 9 French long sheath was inserted into the main pulmonary artery tract. A 7 or 8 French guide catheter was inserted through the long sheath and a 0.014 inch guide wire was inserted through the target lesion. The target lesions were dilated using a 1.5 to 9.0 mm monorail or over-the-wire balloon catheter. The balloons were inflated by hand for 15 to 30 seconds until they were fully expanded. One to 6 lesions were targeted in each procedure.

Before the procedure, coumadin was replaced by heparin, and a continuous intravenous infusion of 2 μg kg⁻¹ min⁻¹ dobutamine was started a day before the procedure so as to prevent exacerbation of right-sided heart failure because of the extra load of the PTPA procedure and contrast agent. The dobutamine dosage was gradually tapered after the procedure and stopped in a few days.

Statistical Analysis
All data are presented as mean±SD. Comparisons of hemodynamic parameters and plasma BNP at baseline and after follow-up were made using the Student paired t test. Comparison of hemodynamic parameters just before and after PTPA procedures was made by a.
Angiography and Computed Tomography Images of PTPA

Representative pulmonary angiography showing the pulmonary blood flow before, during, and after the PTPA procedure is shown in Figure 1, and representative images of contrast-enhanced lung 3-dimensional computed tomography at baseline and after follow-up are shown in Figure 2. The contrast-enhanced lung computed tomography image before PTPA shows stenosis or occlusion of most of the pulmonary arteries without visualization of most of the peripheral capillary vessels. However, after follow-up, most of the pulmonary arteries are visualized along with the peripheral capillary vessels.

Baseline Characteristics and Changes in Hemodynamics

The baseline characteristics of 29 patients enrolled in the study are shown in Table 1. In the 28 patients whose follow-up hemodynamic data were obtained, the average number of target vessels per procedure was 3.6 ± 1.4, the average number of PTPA procedures per patient was 1.8 ± 0.9, and the average number of target vessels per patient was 6.5 ± 3.0. The average observation period from the first PTPA procedure to the last follow-up conducted on each patient was 6.0 ± 6.9 months.

A comparison of the hemodynamics between baseline and follow-up is presented in Figure 3. Right-sided heart catheterization demonstrated a significant improvement in the hemodynamic parameters (mean RAP, 5.9 ± 4.9 versus 3.5 ± 1.7 mm Hg; mean PAP, 45.3 ± 9.8 versus 31.8 ± 10.0 mm Hg; and CO, 3.6 ± 1.2 versus 4.6 ± 1.7 L/min, baseline versus follow-up, respectively; all P < 0.05).

A comparison of the hemodynamics between baseline and follow-up in those patients who did not receive any augmentation of their targeted PH therapy during the follow-up period demonstrated a significant improvement in their hemodynamic parameters (mean RAP, 5.4 ± 4.4 versus 3.5 ± 1.7 mm Hg; mean PAP, 43.3 ± 8.2 versus 30.6 ± 8.2 mm Hg; and CO, 3.8 ± 1.2 versus 4.6 ± 1.7 L/min, baseline versus follow-up, respectively; all P < 0.05). In contrast, comparison of the hemodynamics between baseline and follow-up in the 4 patients who received augmented targeted PH therapy demonstrated only a significant improvement in mean PAP (mean RAP, 9.3 ± 6.9 versus 3.5 ± 1.9 mm Hg, P > 0.05; mean PAP, 57.0 ± 11.9 versus 39.0 ± 17.6 mm Hg, P > 0.05; and CO, 2.4 ± 0.5 versus 4.2 ± 1.4 L/min, P > 0.05; baseline versus follow-up, respectively).

The effect of age on the efficacy of PTPA was assessed using a linear model which found that effects of age and baseline mean PAP were significant (P = 0.03 and P = 0.007, respectively). The estimated least squares mean change from baseline for mean PAP in the 3 age groups were −7.7 (95% CI, −12.7 to −2.6), −16.3 (95% CI, −21.2 to −11.5), and −16.0 (95% CI, −21.1 to −11.0), for patients >70 years, 60 to 69 years, and <60 years, respectively. This result suggests that
the efficacy of PTPA in elderly patients is at least comparable with that in a younger population.

Acute hemodynamic effects of PTPA are shown in Table 2. There was little or no change in the hemodynamic parameters, such as mean RAP, mean PAP, and CO, from just before the PTPA procedure compared with just after PTPA.

Changes in NYHA Functional Class and Plasma BNP
NYHA functional class and plasma BNP were also compared between baseline and follow-up. The NYHA functional classification was significantly improved after PTPA (P<0.01; Figure 4A). Although BNP data from 3 patients were missed at follow-up, plasma BNP was significantly decreased after PTPA in the remaining 25 patients (306±271 vs 98±197 pg/mL, baseline versus follow-up, respectively; P<0.01; Figure 4B).

Complications of PTPA
As mentioned previously, 1 patient had a wiring perforation as a complication and died 2 days after the PTPA procedure, therefore the mortality rate associated with PTPA was 3.4% in this study.

A total of 51 PTPA procedures were performed on the remaining 28 patients. A dissection in 1 of the targeted pulmonary arteries occurred just after balloon dilatation in 1 procedure. The dissection did not expand and the hemodynamics did not change. Thus, the dissection was left untouched. In another procedure, an extravascular leak occurred just after balloon dilatation. The extravascular leak was stopped by a prolonged low-pressure dilatation of the balloon. There were no appreciable procedural complications in the other 49 procedures.

Of a total of 51 procedures, 27 procedures (53%) resulted in reperfusion pulmonary edema. For the first PTPA procedure, 19 of 28 enrolled patients (68%) had reperfusion pulmonary edema. Thus, 70% of the procedures that had reperfusion pulmonary edema were first procedures. One patient with severe pulmonary edema needed intubation and artificial ventilation after the first procedure, along with a percutaneous cardiopulmonary support device for 5 days. Two patients with moderate pulmonary edema needed biphase positive airway pressure with high-concentration oxygen inhalation after their first procedure. Three other patients with pulmonary edema after their first procedure needed elevated concentrations of oxygen administrated via an oxygen mask to keep arterial saturation at an optimum level for a few days until they recovered. Other patients with pulmonary edema needed nasal administration of elevated levels of oxygen for a few days after their first procedure. After the second PTPA procedure, 7 patients developed pulmonary edema and needed nasal administration of oxygen for a few days without intubation or biphase positive airway pressure. After the third or fourth PTPA procedure, 2 patients had pulmonary edema and needed nasal administration of oxygen for a few days.

We compared the baseline hemodynamics of patients with reperfusion pulmonary edema after their first procedure (n=19) with those without pulmonary edema (n=9). The mean RAP and PAP at baseline were not significantly different between those patients with and without pulmonary edema (mean RAP, 6.0±4.3 vs 8.2±5.2 mm Hg; mean PAP, 50±8.2 vs 43.0±12.8 mm Hg), with versus without pulmonary edema, respectively; both P>0.05; Figure 5A and 5B). However, baseline CO was significantly lower in patients with pulmonary edema, although there was no significant difference (346±285 versus 139±161 pg/mL, with and without pulmonary edema, respectively; P>0.05). In the 28 enrolled patients, 3 patients had a baseline NYHA functional class of II, 16 patients had a class of III, and 9 patients had a class of IV. All 9 patients with a baseline NYHA functional class of IV had pulmonary edema after their first procedure.

Discussion
This study demonstrates that (1) PTPA is clinically effective for the treatment of CTEPH, although this study population

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<td>B-type natriuretic peptide, pg/mL</td>
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**Table 1. Baseline Characteristics of Patients**

**Figure 3.** Hemodynamic changes at follow-up after percutaneous transluminal pulmonary angioplasty. Mean RAP (A), mean PAP (B), and CO (C) improved significantly at follow-up. *P<0.01 vs baseline. RAP indicates right atrial pressure; PAP, pulmonary arterial pressure; and CO, cardiac output.
is a small and highly selected group; (2) PTPA does not produce immediate hemodynamic improvement at the time of the procedure and a certain amount of time is required before the maximal therapeutic effect on functional ability and hemodynamics is measurable; and (3) patients with severe clinical signs and/or severe hemodynamics at baseline have a high risk of reperfusion pulmonary edema after PTPA.

In the present study, the NYHA functional classification and all the hemodynamic parameters improved significantly after PTPA. BNP levels, indicating right heart overload, also improved significantly after PTPA. These results suggest that PTPA is clinically effective for the treatment of CTEPH. In a previous study by Feinstein et al, demonstrating the efficacy of balloon pulmonary angioplasty, the mean PAP was 42±12 mm Hg at baseline and improved to 33±10 mm Hg after balloon pulmonary angioplasty of 6.0±3.0 target vessels per patient. Similarly, in this study, the mean PAP at baseline was 45.3±9.8 mm Hg and improved to 31.8±10.0 mm Hg after PTPA of 6.5±3.0 target vessels per patient. These findings suggest that our study demonstrates an equivalent therapeutic efficacy in comparison with the results of the previous report by Feinstein and colleagues. In addition, in our study there was little or no change in hemodynamic parameters from just before PTPA to just after PTPA. This result demonstrates that PTPA does not produce an immediate therapeutic effect at the time of the procedure, although all of the hemodynamic parameters had significantly improved after ~6 months of follow-up. Therefore, these findings suggest that a certain amount of time is required after PTPA before maximal therapeutic effect on functional ability and hemodynamics is measurable. Additionally, these findings suggest that the repair and adaptive mechanisms after PTPA may be different to those seen after surgical PEA, and that the time course to clinical improvement, likewise, may be different. Combined with the fact that the degree of therapeutic effect in our study was almost the same as in the previous study by Feinstein and colleagues, which had an ~36 month observation period, these findings may raise the possibility that the therapeutic effect of PTPA is not recognized immediately after PTPA, but is seen after ~6 months, and the effect continues until ~36 months after PTPA.

In this study, reperfusion pulmonary edema was recognized in 53% of PTPA procedures, and 68% of the enrolled patients had reperfusion pulmonary edema with their first procedure. In the previous report by Feinstein et al, pulmonary edema was recognized in 11 of 18 enrolled patients (61%). Reperfusion pulmonary edema may be the most important complication of pulmonary angioplasty. Furthermore, PEA can remove the majority of lesions in 1 procedure, whereas PTPA cannot treat most of the lesions at once. Each lesion which is dilated by PTPA is still under high pulmonary arterial pressure, which may explain why the incidence of reperfusion lung injury after PTPA is higher than lung injury at any medical center doing PEA surgery. In this study, we compared the baseline characteristics of those patients with and without reperfusion pulmonary edema after their first PTPA procedure. Baseline CO was significantly lower in the patients who developed reperfusion pulmonary edema. Furthermore, baseline BNP levels and NYHA functional class demonstrated the presenting clinical severity of the patients who developed reperfusion pulmonary edema. These results suggest that patients with severe clinical signs and/or severe hemodynamics at baseline have a high risk of reperfusion pulmonary edema after PTPA, and that we should perform PTPA carefully in such patients. If more details relating to reperfusion pulmonary edema are analyzed and useful predictors of reperfusion pulmonary edema can be identified in a future study, the risk of reperfusion pulmonary edema after PTPA could be largely avoided and PTPA may become a safe and common therapeutic strategy for CTEPH.

The most powerful conventional therapeutic strategy for CTEPH is invasive surgical PEA. In centers with experience in PEA, perioperative mortality is <5%. In our study, there was 1 death among 29 enrolled patients, which means that the mortality rate associated with PTPA (3.4% in this study) might be in the same range as that of PEA in the experienced centers. Furthermore, the target lesions for PTPA in the present study were mostly the ones that would have also been amenable to PEA, suggesting that PTPA may be an alternative to PEA in otherwise operable patients. Nevertheless, PH

Table 2. Acute Hemodynamic Effects of PTPA

<table>
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<th>Just Before PTPA LS mean±SE</th>
<th>Just After PTPA LS mean±SE</th>
<th>P-value</th>
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<tr>
<td>CO, L/min</td>
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</table>

A total of 51 procedures were performed in 28 patients (1 patient with percutaneous death was excluded as the hemodynamic parameters of this patient were influenced by the complication of the wiring perforation). Among the 51 procedures, right-sided heart catheterizations were not performed just after PTPA in 2 instances. In addition, CO values were missing in another 3 procedures because blood gas measurements just after PTPA were not performed and, therefore, CO could not be calculated. CO, cardiac output; LS mean, least squares mean; PAP, pulmonary arterial pressure; PTPA, Percutaneous Transluminal Pulmonary Angioplasty; RAP indicates right atrial pressure; and SE, standard error.

Figure 4. Changes in the NYHA functional class (A) and plasma BNP (B) at follow-up after percutaneous transluminal pulmonary angioplasty. NYHA functional class significantly improved from baseline to follow-up (P<0.01). BNP (n=25) also improved at follow-up (P<0.01 vs baseline). BNP, B-type natriuretic peptide; and NYHA indicates New York Heart Association.
medication was continued in many of the enrolled patients or even intensified in some because we considered that PH medication should be continued if residual PH existed even after PTPA. In contrast, it is usually unnecessary to continue PH medication after PEA surgery. These findings suggest that the efficacy of PTPA may not be equal to that of PEA. Therefore, a large multicenter study is required in the future to compare the therapeutic efficacy, mortality, and complications of PTPA and PEA performed in experienced centers.

The percentage improvement in mean PAP between baseline and follow-up was 29% in those patients who did not receive any additional PH therapy, 32% in 4 patients who had augmented targeted PH therapy during the follow-up period, and 30% in all of the study patients. These findings suggest that the component of improvement attributable to medical therapy is likely to be small. In this study, the baseline hemodynamics of patients who had augmented targeted PH therapy post-PTPA were more severe than those patients who did not receive additional targeted PH therapy. Thus, these findings suggest that catheter-based balloon angioplasty, or PEA, should be considered at an earlier stage because augmentation of targeted PH therapy postprocedure does not seem to cause much improvement in hemodynamics for patients with severe baseline hemodynamics.

The distribution of patient ages differed between this study and the study by Feinstein et al.,\(^\text{18}\) with our study reporting more information on elderly patients. The percentage of patients in our study who were >70 years old was 37% (10 of 29 patients) compared with 11% (2 of 18 patients) in the Feinstein study.\(^\text{18}\) Our limited results suggest that catheter-based balloon angioplasty, or PEA, should be considered at an earlier stage because augmentation of targeted PH therapy postprocedure does not seem to cause much improvement in hemodynamics for patients with severe baseline hemodynamics.

Finally, based on our current experiences, the additional benefits of PTPA may be that (1) PTPA can treat the distal narrow lesions which cannot be reached by PEA; (2) PTPA is a less-invasive procedure which does not need general anesthesia; and (3) PTPA can become widespread in the future because institutions which have abundant experience in patient care for PH and catheter interventions, such as percutaneous coronary intervention, may be able to perform PTPA after a sufficient training of catheter-interventional operators.

There are several limitations to this study. (1) The average observation period was not very long. Additionally, restenosis and long-term survival after PTPA is unclear from this study. To investigate the 5- or 10-year therapeutic efficacy of PTPA and whether there is some recurrence of thromboembolic lesions, a longer observation period is necessary. (2) The number of patients was relatively small. A study based on a longer observation period following a greater number of patients is needed to confirm our results on a long-term basis. (3) The medications of ≥75% of the study patients were unchanged during the follow-up period, however, the possibility that changes in medications influenced hemodynamics and both objective and subjective functional assessment after PTPA cannot be denied. Therefore, a prospective study in a population of patients whose medication is not changed during the observation period is necessary to demonstrate the efficacy of PTPA. (4) In this study, dobutamine was used periprocedurally. However, the role of pretreatment prophylactic dobutamine is unclear and its efficacy is not substantiated. Its use in this study remains confounding influence.

In conclusion, PTPA improved subjective symptoms and pulmonary hemodynamics with tolerable complications, although the study population was a small and highly selected group. PTPA did not produce any immediate hemodynamic improvement at the time of the procedure and a certain amount of time is required before maximal therapeutic effect on functional ability and hemodynamics is measurable. Patients with severe clinical signs and/or severe hemodynamics at baseline have a high risk of reperfusion pulmonary edema after PTPA. PTPA may be a promising therapeutic strategy for the treatment of CTEPH.

**Acknowledgments**

We thank the “Conference for Pulmonary Arterial Intervention (Conference of Percutaneous Transluminal Pulmonary Angioplasty)” held in Sendai, Japan in 2010 and 2011 for widening our development of strategies and indications for catheter-based interventions in pulmonary arteries in patients with chronic thromboembolic pulmonary hypertension.

**Disclosures**

None.

**References**

Percutaneous Transluminal Pulmonary Angioplasty for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

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