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Pulmonary Vascular Disease

Refined Balloon Pulmonary Angioplasty for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension

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Background—Although balloon pulmonary angioplasty (BPA) for inoperable patients with chronic thromboembolic pulmonary hypertension was first reported over a decade ago, its clinical application has been restricted because of limited efficacy and complications. We have refined the procedure of BPA to maximize its clinical efficacy.

Methods and Results—Sixty-eight consecutive patients with inoperable chronic thromboembolic pulmonary hypertension underwent BPA. We evaluated pulmonary artery diameters and determined the appropriate balloon size by using intravascular ultrasound. We performed BPA in a staged fashion over multiple, separate procedures to maximize efficacy and reduce the risk of reperfusion pulmonary injury. A total of 4 (2–8) sessions were performed in each patient, and the number of vessels dilated per session was 3 (1–14). The World Health Organization functional class improved from 3 to 2 ($P<0.01$), and mean pulmonary arterial pressure was decreased from 45.4±9.6 to 24.0±6.4 mm Hg ($P<0.01$). One patient died because of right heart failure 28 days after BPA. During follow-up for 2.2±1.4 years after the final BPA, another patient died of pneumonia, and the remaining 66 patients are alive. In 57 patients who underwent right heart catheterization at follow-up, improvement of mean pulmonary arterial pressure was maintained (24.0±5.8 mm Hg at 1.0±0.9 years). Forty-one patients (60%) developed reperfusion pulmonary injury after BPA, but mechanical ventilation was required in only 4 patients.

Conclusions—Our refined BPA procedure improves clinical status and hemodynamics of inoperable patients with chronic thromboembolic pulmonary hypertension, with a low mortality. A refined BPA procedure could be considered as a therapeutic approach for patients with inoperable chronic thromboembolic pulmonary hypertension.   (*Circ Cardiovasc Interv.* 2012;5:748-755.)

Key Words: peripheral vascular disease ■ pulmonary hypertension ■ reperfusion ■ revascularization

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) have a poor prognosis. Pulmonary endarterectomy can dramatically reduce pulmonary arterial pressure in selected patients with CTEPH to improve their prognosis.[1] However, not all patients can undergo pulmonary endarterectomy because of technical limitations.[2–4] Pulmonary endarterectomy for CTEPH with peripherally located organized thrombus is associated with less improvement in pulmonary hemodynamics and has a higher mortality in patients compared with those with proximal thrombi.[1] The latest guidelines for the diagnosis and treatment for pulmonary hypertension indicate that the selection of patients for pulmonary endarterectomy depends on the extent and location of the organized thrombi in relation to the degree of pulmonary hypertension and taking into consideration age and comorbidities.[5]

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Balloon pulmonary angioplasty (BPA) for a patient with CTEPH was first reported in 1988.[6] In 2001, Feinstein et al[7] reported the efficacy of BPA for a series of patients with CTEPH. Although this report showed a significant improvement in hemodynamics and exercise tolerance, these improvements were not as good as those of pulmonary endarterectomy. Moreover, 1 of 18 patients died from reperfusion pulmonary injury and right ventricular failure after BPA. The mortality rate of BPA is not superior to that of pulmonary endarterectomy. Pulmonary endarterectomy is an established treatment for CTEPH and the mortality rate was recently reported to be as low as 2.2%,[8] although it varies up to 14.3% depending on the institute.[9–11] More than 20 years after the first report of BPA, BPA is still not widely accepted as a therapeutic option for inoperable patients with CTEPH.

We have recognized 2 major problems that need to be resolved for improving the clinical efficacy of BPA. One problem is insufficient improvement in hemodynamics after the BPA procedure, and the other is the high incidence of potentially fatal complications, including reperfusion pulmonary injury and rupture of the pulmonary artery. We have refined the BPA procedure to improve its clinical efficacy. The major difference of our refined BPA procedure is the introduction of intravascular ultrasound (IVUS) to determine the optimal balloon size. IVUS has enabled us to determine the actual size of the target lesions, which leads to improved hemodynamic outcome and reduced risk of reperfusion pulmonary injury and rupture of the pulmonary artery. We studied the clinical efficacy of this refined BPA procedure with advanced care for inoperable patients with CTEPH.

Methods

Patient Selection

Sixty-eight consecutive patients with inoperable CTEPH who underwent BPA between November 2004 and September 2011 were enrolled in this study. BPA was performed after approval of the Institutional Review Board, and written informed consent was obtained from each patient before the procedure. A diagnosis of CTEPH was based on detailed medical history, a physical examination, chest radiography, a chest computed tomography (CT) scan, transthoracic echocardiography, lung ventilation-perfusion scintigraphy, right heart catheterization, and angiographic demonstration of multiple stenoses and obstruction of bilateral pulmonary arteries. Pulmonary angiography showed at least 1 of the following features: pouching defects; webs or bands, intimal irregularities, abrupt vascular narrowing, and complete vascular obstruction.[12] All patients were diagnosed as inoperable by experienced surgeons because of the location of thrombi and surgical accessibility, age, and comorbidities. All patients were in

World Health Organization (WHO) functional class III or IV despite medical treatment. None of the patients were excluded from undergoing BPA based on age restrictions or severity of hemodynamics.

Management Before BPA

All patients were administered epoprostenol to decrease pulmonary arterial pressure as much as possible. Epoprostenol was started at 1 ng/kg/min ≈5 days before the procedure and increased by 1 ng/kg/min each day to a maximum of 5 ng/kg/min by the day of BPA. If a patient was already on long-term epoprostenol therapy before BPA, the dosage was unchanged. All medications, including warfarin, were maintained, except for beraprost sodium, which was discontinued when the dosage of epoprostenol reached 2 ng/kg/min. If the cardiac index was <2.2 L/min/m^2, dobutamine at a dose of 2 to 3 μg/kg/min was administered before the procedure.

BPA Procedure

On the basis of the results of pulmonary angiography and perfusion scintigraphy, we selected in advance which branches of the pulmonary arteries to dilate. We targeted webs (Figure 1) or bands, abrupt vascular narrowing, or complete vascular obstruction (Figure 2). The lower lobe was targeted for the initial BPA in most cases. Targeted vessels were limited within 2 vessels in a single lobe of the lung in the initial BPA session to avoid the occurrence of severe reperfusion pulmonary injury. We placed a 9F indwelling sheath (Arrow-Flex; Teleflex, Durham, NC) into a vein (mainly into the internal jugular vein [n=65] and occasionally into the subclavian [n=1] or femoral vein [n=2]) and brought a 6F long sheath (Bright Tip Sheath Introducer; Cordis/Johnson & Johnson, New Brunswick, NJ) to the main pulmonary artery via the 9F sheath, using 0.035-inch wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan). Heparin (5000 U) was administered when the sheath was inserted, and 1000 U of heparin was added every hour during the procedure. We selected a branch of the pulmonary artery by a 6F guiding catheter (Mach 1 peripheral MP; Boston Scientific, Natick, MA) and performed angiography (Figure 1A and 1B). We crossed a 0.014-inch wire (Cruise; Asahi Intecc, Tokyo, Japan) to the targeted lesion and evaluated the lumen size of the vessel with IVUS (Eagle Eye Platinum; Volcano, San Diego, CA) (Figure 1C). Because organized thrombi are isoechoic, we used ChromaFlo (Volcano, San Diego, CA) computer software to clearly visualize and distinguish lumen and thrombi. We measured the vessel diameter at the site where thrombi occupied the lumen and the vessel was most severely stenosed. After determination of the vessel diameter with IVUS, we usually used a 2-mm balloon for the initial dilatation to avoid rupture and dissection of the pulmonary artery. We dilated the vessel by balloon catheters of appropriate size (2 to 4 mm, IKAZUCHI PAD, Kaneka, Osaka, Japan; 5 to 7 mm, Bandicoot RX, St. Jude Medical, St. Paul, MN and Aviator Plus, Cordis/Johnson & Johnson, New Brunswick, NJ; 8 mm, Sterling Monorail, Boston Scientific, Natick, MA). The appropriate size was determined according to the vessel diameter measured by IVUS. The maximal size was set not to >90% of the original size of the vessel diameter, considering tapering and shrinkage of pulmonary arteries owing to reduced flow before BPA. The balloon was inflated by hand until the indentation disappeared or until the balloon was fully expanded. After inflation, angiography and IVUS were performed to ascertain that the vessel was dilated sufficiently and did not rupture (Figure 1D, 1E, and 1F). Dilatation was repeated if it was not sufficient by evaluation with IVUS, pulmonary arterial flow did not improve angiographically, or the pressure gradient across the dilated site >10 mm Hg. The procedure was discontinued when oxygen desaturation was >4% or hemo sputum occurred.

In the following sessions, targeted vessels were also limited within a unilateral lung, until the mean pulmonary arterial pressure was decreased to <35 mm Hg. When mean pulmonary arterial pressure was <35 mm Hg, BPA could be performed in both lungs in 1 session. BPA was repeated at an interval of 5 to 14 days after the initial procedure. Additional BPA at an interval of 12 to 16 weeks after the procedure was recommended until mean pulmonary arterial pressure at the end of hemodynamic monitoring became <30 mm Hg.
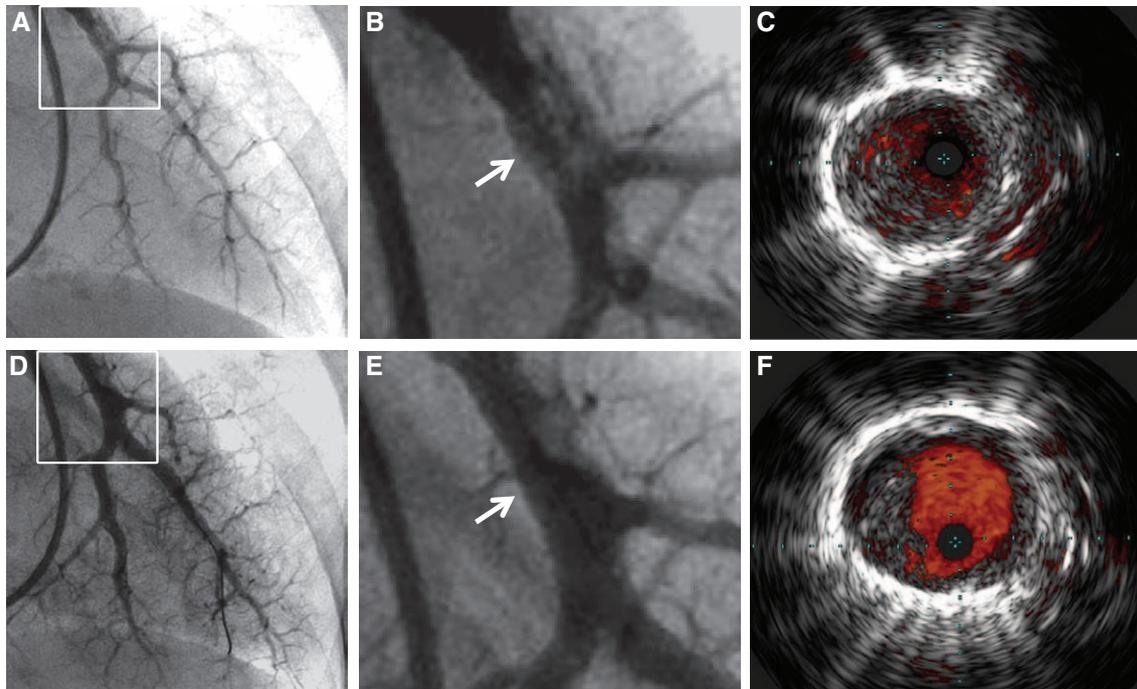
Figure 1. Representative angiographic and intravascular ultrasound (IVUS) images of balloon pulmonary angioplasty (BPA). **A**, Site of an intravascular web of the left pulmonary artery is indicated with a **square** on the angiogram. Peripheral arteries have shrunk because of a reduction in blood flow. **B**, A magnified image of a square in Figure 1A. An intravascular web is indicated with **arrows**. **C,** IVUS image (at the arrow in Figure 1B) shows organized thrombi, which occupy the lumen, and blood flow is limited in small channels. **D**, After a 5-mm balloon is dilated at 8 atm, an angiogram shows a dilated vessel and increased flow in the distal arteries after BPA. **E**, A magnified image of an intravascular web shown in Figure 1D. An intravascular web indicated with **arrows** is compressed and a vessel diameter of the distal artery is increased. **F**, IVUS image (at the arrow in Figure 1E). Thrombi are forced to 1 side and the lumen size is enlarged.

Management After BPA

We used noninvasive positive airway pressure ventilation at least 24 hours after BPA. Hemodynamics were continuously monitored with a Swan-Ganz catheter (Swan-Ganz CCOmbo V; Edwards Lifesciences, Irvine, CA) after the BPA procedure until noninvasive positive airway pressure ventilation could be weaned off. We performed a chest X-ray immediately after patients returned to the Cardiac Care Unit and performed a CT scan within 4 hours after BPA to check for increased density of the dilated segments. Epoprostenol and dobutamine were discontinued 3 days after a series of BPAs. Methylprednisolone (500 mg/day) was administered for 3 days to reduce reperfusion pulmonary injury after BPA.
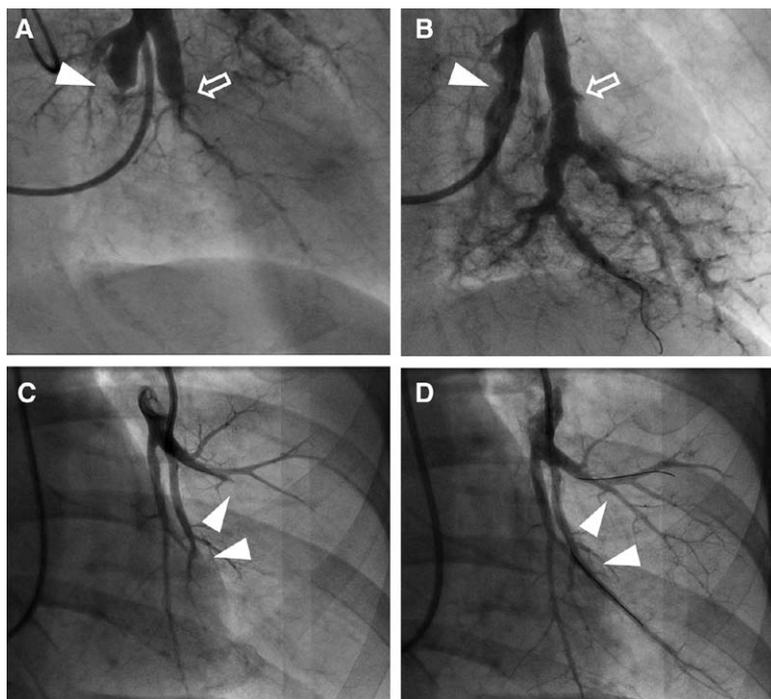
Figure 2. Representative pulmonary angiograms before and after balloon pulmonary angioplasty (BPA). **A**, Pulmonary angiogram shows abrupt vascular narrowing (**arrow**) and complete vascular obstruction (**arrowhead**) in the left lower arteries before BPA. **B**, After dilatation of target arteries with a 6-mm balloon at 6 atm, the lesions are successfully opened. **C**, Pulmonary angiogram shows complete vascular obstruction (**arrowhead**) in the left lower arteries before BPA. **D**, After dilatation of target arteries with a 2-mm balloon at 8 atm, the lesions are successfully opened.

Clinical Outcomes

Patients were followed up at least every 6 months after the final BPA. The effectiveness of BPA was evaluated by improvement of WHO functional class, hemodynamic parameters (systolic, diastolic and mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance), plasma levels of brain natriuretic peptide, and 6-minute walk distance before the first session of BPA, immediately after the final session of BPA, and at follow-up.

Statistical Analysis

Results are expressed as the mean±SD. Integers, including the number of sessions and balloons, are expressed as the median and range. Differences between variables measured at baseline and after BPA were tested by the paired *t* test. WHO functional class is expressed as the median and number of patients in each class, and changes in WHO functional class were evaluated using the Wilcoxon signed rank test. For assessing the difference among before, immediately after, and follow-up data, variables were analyzed by linear mixed modeling. Generalized linear mixed modeling was used to determine the learning curve for BPA, the incidence of complications between the initial 128 sessions (performed between November 2004 and October 2010), and the recent 127 sessions (performed between November 2010 and September 2011). All analyses were performed with IBM SPSS Statistics 20 (IBM, Armonk, NY). Statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics

Our study included 53 females (78%) and 15 males (22%) with inoperable CTEPH. The mean age was 62.2±11.9 years old, with a range of 38 to 82-years old at the time of first admission. Disease duration (the time between diagnosis and the first admission to our hospital) was 3.2±3.2 years. Baseline patient characteristics are shown in Table 1. All patients were in WHO functional class III or IV with a high pulmonary arterial pressure. All patients were treated with warfarin, supplemental oxygen therapy, and >1 pulmonary hypertension-targeted drug. In addition, 5 patients were transferred to our

hospital with intravenous infusion of dobutamine because of severe right heart failure.

BPA Procedure

The 68 patients underwent a total of 255 BPA sessions. A total of 4 (2–8) sessions were performed in each patient, and the number of vessels dilated per session was 3 (1–14). Preoperative application of epoprostenol only resulted in a slight decrease in mean pulmonary arterial pressure (to 42.3±8.1 mm Hg, $P<0.05$). After observation using IVUS and Chroma-Flo, balloons matched to the vessel diameters were selected. As a result, we used 3 (1–6) balloons in 1 session, and the number of different balloon sizes per vessel was 2 (1–3). Contrast medium of 160.2±57.2 mL/session was required. Patients underwent 2 (1–6) sessions during 1 admission. The percentages of targeted arteries in 150 arteries at the initial session and in 558 arteries in the total sessions are shown in Table 2. At the initial BPA, the lower lobe of a unilateral lung was the target in most cases and none of the arteries in the left upper lobe were targeted. Ultimately, BPA was performed in all segments and there were no inaccessible lesions. The relative reductions in mean pulmonary arterial pressure and absolute change in mean pulmonary arterial pressure were correlated with the number of segments of pulmonary arteries treated by BPA (Figure 3).

Outcomes of BPA

The changes in clinical parameters before and after BPA (within 1 week after the final session of BPA) are summarized in Table 1 and Figure 4. One patient died 28 days after the third session of BPA because of right-sided heart failure, who had been transferred from another hospital after 3 months of hospitalization because of dobutamine-dependent severe right heart failure. After BPA, severe reperfusion pulmonary injury developed and subsequent worsening of right-sided heart failure required percutaneous cardiopulmonary support, which could not be recovered. Among the other 67 patients, 64 patients (96%) were in WHO functional class I or II after BPA, while there were no patients in classes I

Table 1. Clinical and Hemodynamic Data Before and After BPA

	Before BPA (n=68)	After BPA (n=67)	*P* Value
WHO functional class (I/II/III/IV)	3 (0/0/49/19)	2 (11/53/3/0)	<0.01
Oxygen inhalation (L/min)	3.0±1.4	1.3±1.0	<0.01
6MWD, m	296±108	368±83	<0.01
BNP, pg/mL	330±444	35±55	<0.01
sPAP, mm Hg	81.3±16.9	42.3±11.9	<0.01
dPAP, mm Hg	24.3±7.1	13.4±4.8	<0.01
mPAP, mm Hg	45.4±9.6	24.0±6.4	<0.01
RAP, mm Hg	8.1±4.4	1.9±1.5	<0.01
CI, L/min/m²	2.2±0.7	3.2±0.6	<0.01
PVR, dyne sec/cm⁵	942±367	327±151	<0.01

Values other than WHO functional class are expressed as mean±SD. WHO functional class is presented as the median and number of patients in each class.

6MWD indicates 6-minute walk distance; BPA, balloon pulmonary angioplasty; BNP, brain natriuretic peptide; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; and WHO, world health organization.

Table 2. Distribution of Dilated Pulmonary Arteries at the Initial and Total Sessions

Right Lung Segment	Initial n (%)	Total n (%)	Left Lung Segment	Initial n (%)	Total n (%)
A1	1 (0.7)	44 (7.9)	A1+2	0 (0.0)	32 (5.7)
A2	2 (1.3)	40 (7.2)			
A3	1 (0.7)	32 (5.7)	A3	0 (0.0)	14 (2.5)
A4	3 (2.0)	27 (4.8)	A4	0 (0.0)	2 (0.4)
A5	8 (5.3)	30 (5.4)	A5	0 (0.0)	3 (0.5)
A6	2 (1.3)	6 (1.1)	A6	0 (0.0)	17 (3.0)
A7	13 (8.7)	30 (5.4)			
A8	32 (21.3)	48 (8.6)	A8	3 (2.0)	36 (6.5)
A9	33 (22.0)	48 (8.6)	A9	8 (5.3)	54 (9.7)
A10	40 (26.7)	54 (9.7)	A10	4 (2.7)	41 (7.3)

Initial indicates absolute number and percentage of targeted arteries in 150 arteries at the initial session; and total, absolute number and percentage of targeted arteries in 558 arteries in the total sessions.
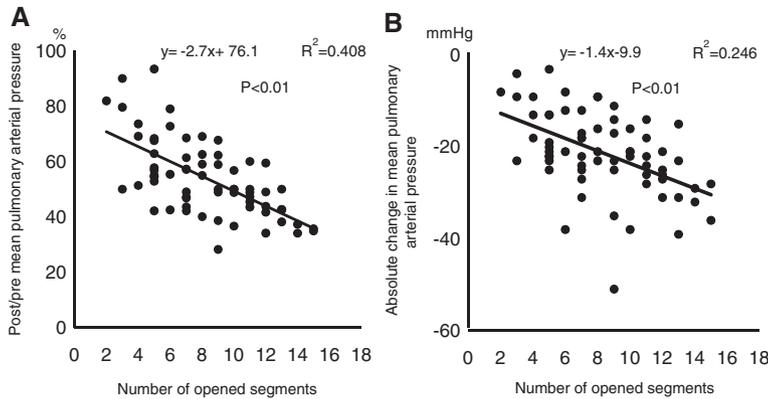
Figure 3. Correlation between the number of opened segments and the decrease in mean pulmonary arterial pressure. The relationships of reduction in mean pulmonary arterial pressure (**A**) and absolute change in mean pulmonary arterial pressure (**B**) with the number of segments of pulmonary arteries treated by balloon pulmonary angioplasty are shown. Values reflect the number of segments opened in all of the sessions, and the changes in pulmonary arterial pressure indicate changes from baseline to the last session. The more segments were dilated, the larger the decrease in mean pulmonary arterial pressure.

and II before BPA. Clinical and hemodynamic variables were remarkably improved after BPA. Six-minute walk distance and brain natriuretic peptide levels were significantly improved. Overall, mean pulmonary arterial pressure was significantly decreased ($P<0.01$) with an increased cardiac index after BPA, whereas there was no temporal change in systolic blood pressure (108.7±15.9 and 106.1±14.1 mm Hg). In addition, oxygenation was improved in all patients after BPA. The amount of oxygen to maintain peripheral oxygen saturation >95% was significantly decreased from 3.0±1.4 to 1.3±1.0 L/min ($P<0.01$).

Follow-up

During follow-up for 2.2±1.4 years after the final BPA, 1 patient died of pneumonia and the remaining 66 patients

are alive. Fifty-seven patients underwent right heart catheterization at 1.0±0.9 years (0.3–7.0 years) after the final BPA. In these patients, mean pulmonary arterial pressure was 24.0±5.8 mm Hg at follow-up and improved hemodynamics were maintained (Figure 4). Angiographically, the pulmonary arteries where BPA was performed were even larger in diameter at follow-up (Figure 5). The improved hemodynamics were maintained even after significant reduction of medications for pulmonary hypertension. All of the 4 patients on long-term epoprostenol therapy before BPA were able to completely discontinue epoprostenol. The percentage of patients on other oral medications was significantly reduced (endothelin receptor antagonist: from 52% to 37%, $P<0.05$; phosphodiesterase-5 inhibitor: from 40% to 28%, $P<0.05$). At initial admission, all patients
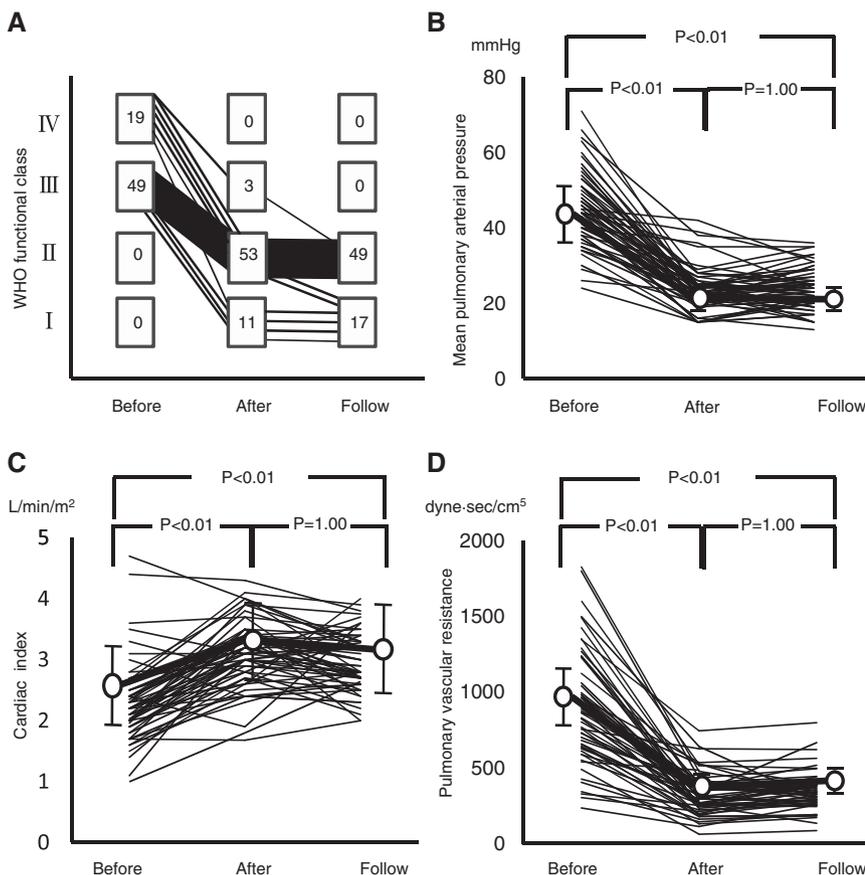
Figure 4. Change in parameters after balloon pulmonary angioplasty (BPA). Parameters before BPA (n=68), immediately after BPA (after) (n=67), and at follow-up (follow) (n=66 for **A** and 57 for **B**–**D**) were compared. World Health Organization (WHO) functional class (**A**), mean pulmonary arterial pressure (**B**), cardiac index (**C**), and pulmonary vascular resistance (**D**) were significantly improved immediately after BPA, and the improvement was maintained at follow-up.
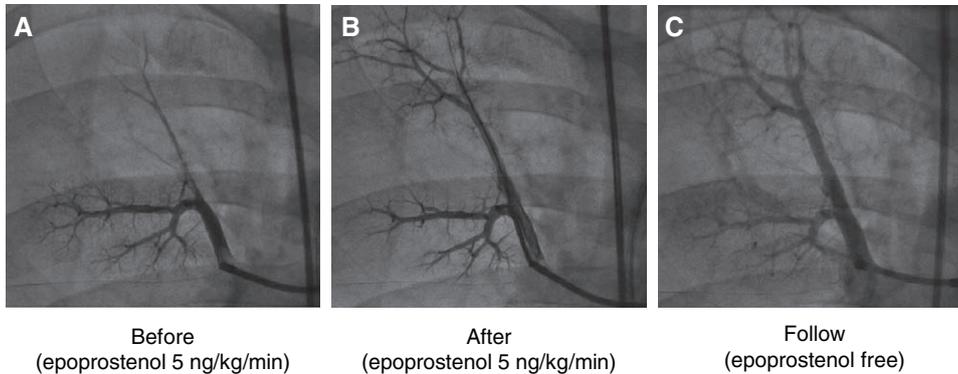
Figure 5. Representative pulmonary angiograms before balloon pulmonary angioplasty (BPA), after BPA, and at follow-up. Pulmonary angiograms before BPA (**A**), immediately after BPA (**B**), and at 1.5 years after the final BPA (**C**) are shown. The dose of epoprostenol was 5 ng/kg/min before and immediately after BPA. At follow-up, pulmonary arteries were dilated despite epoprostenol being discontinued.

required supplemental oxygen, whereas 26 patients were able to discontinue oxygen inhalation.

Complications Related to BPA

Reperfusion pulmonary injury was the major complication after BPA. It was confirmed by 3 methods, in the order of severity: hemo sputum; chest radiographic opacity in dilated segments and worsening of hypoxemia; or increased density of the dilated segment as shown by a chest CT scan taken 4 hours after BPA without any symptoms (Table 3). Patients were counted based on the methods by which pulmonary reperfusion injury was found and listed for only once. Chest-CT-only patients had chest CT findings without any other symptoms. When a patient had hemo sputum and radiographic findings, the patient was counted in the hemo sputum group. Intratracheal intubation was required in 3 patients with hemo sputum and 1 patient with increased radiographic opacity in a chest X-ray. Therefore, the incidence of severe reperfusion pulmonary injury that required intratracheal intubation was 6%. Among them, percutaneous cardiopulmonary support was required in 2 patients. One patient fully recovered and another patient died 28 days after BPA because of right-sided heart failure. None of the patients with reperfusion pulmonary injury detected only by chest CT required intratracheal intubation. Pulmonary artery perforation with a guide wire occurred in 5 patients, and 2 of them required emergent transcatheter

coil embolization. The frequency of reperfusion pulmonary injury, particularly injury manifesting as hemo sputum, was significantly lower during the most recent half of our experience (127 procedures) than during the first half of our experience (128 procedures) (*P*<0.01, Table 3). Further details are provided in the online-only Data Supplement.

No other procedural complications were experienced during BPA. There was no acute kidney injury caused by contrast medium. Interstitial pneumonitis in 1 patient and interstitial nephritis in 2 patients occurred after BPA. Non-steroidal anti-inflammatory drugs and radio-contrast medium were suspected to be the cause of these complications. All patients recovered after steroid pulse therapy.

Discussion

We found that our refined and comprehensive BPA strategy improved hemodynamics and clinical status of symptomatic patients with minimal serious adverse events. This is the first clinical trial to document that refined BPA can be a therapeutic option in inoperable patients with CTEPH who have no other treatment options.

The prognosis of CTEPH has been reported to be poor when mean pulmonary arterial pressure is >30 mm Hg,[13,14] and therefore, previously reported pulmonary arterial pressure after BPA >30 mm Hg should be insufficient.[7] To achieve a sufficient decrease in mean pulmonary arterial pressure without increasing the risk of reperfusion pulmonary injury, pulmonary artery rupture, and perforation, it is necessary to achieve adequate dilation by selecting the appropriate size of balloons. In previous reports, balloon size was determined according to angiographic findings.[6,7] In our study, we evaluated pulmonary artery diameters by using IVUS, which provides information regarding the true size of the pulmonary artery lumen and wall thickness.[15] Furthermore, we selected a target artery by a soft-tipped 6F guiding catheter, which enabled us to select the smaller branches of pulmonary arteries with a reduced risk of causing dissection of arteries compared with a 7F custom made catheter used in a previous report.[7] We also used a thinner wire (0.014-inch) and a low profile balloon catheter, which potentiated the opening of completely obstructed lesions, with a lower risk of perforation. In a previous report,[7] a 7F pigtail catheter was modified by removing most of the curled tip. Our procedure requires only commercially available devices, and this procedure can be performed anywhere. We repeated these procedures until

Table 3. Complications Related to BPA

	Diagnositic Criteria	Total	First 128 Sessions	Most Recent 127 Sessions	*P* Value
Reperfusion pulmonary injury	Hemo sputum	40	27	13	
	Chest X-ray or desaturation	36	19	17	
	Chest CT only	145	82	63	
	Total	221	128	93	<0.01
Pulmonary artery perforation		5	4	1	1.00

Data indicate the number of sessions. The incidence of complications was compared between the first 128 sessions (performed between November 2004 and October 2010) and the most recent 127 sessions (performed between November 2010 and September 2011).

CT indicates computed tomography.

a sufficient amount of stenoses were dissolved. The more segments were dilated, the larger the decrease in pulmonary arterial pressure was achieved. As a result, we succeeded in decreasing mean pulmonary arterial pressure by >20 mm Hg to achieve <25 mm Hg (Table 1).

Reperfusion pulmonary injury is the leading complication of pulmonary endarterectomy, and the incidence is reported to be 16% to 22%.[2,16] In our study, the incidence of clinically apparent reperfusion pulmonary injury was similar to that of a previous report (60% versus 61%).[7] With advanced examination, we found subclinical reperfusion pulmonary injury in 34% of patients, which indicated that occurrence of reperfusion pulmonary injury was essentially unavoidable in BPA. Feinstein et al[7] reported that development of reperfusion pulmonary injury is correlated with mean pulmonary arterial pressure before BPA >35 mm Hg. The reperfused area is anticipated to be exposed to a high perfusion pressure after BPA, resulting in severe reperfusion pulmonary injury. We expected that epoprostenol could dilate pulmonary arteries in the segments where BPA is not performed[17,18] and minimize the effect of pulmonary arterial pressure associated with pulmonary artery reperfusion. However, in our fully medicated patients, preoperative application of epoprostenol reduced mean pulmonary arterial pressure only by ≈3 mm Hg and a reduction <35 mm Hg could not be attained. We empirically used methylprednisolone to reduce pulmonary edema according to the procedure of pulmonary endarterectomy.[2] However, methylprednisolone failed to reduce lung injury after pulmonary endarterectomy,[19] and therefore, we stopped routinely using it after completion of this study. We attempted noninvasive positive airway pressure ventilation for at least 24 hours after BPA. Current studies suggest that noninvasive positive airway pressure ventilation does not show effectiveness in patients with acute lung injury.[20,21] We did not observe any difference in the frequency of reperfusion pulmonary injury compared with that reported by Feinstein et al.[7]

To reduce the size of the area of reperfusion pulmonary injury, we attempted to not dilate >2 vessels at the initial BPA and performed it in a staged fashion over multiple, separate procedures, as previously suggested.[7] In total, we performed more BPA sessions per patient compared with a previous report (4 [2–8] versus 3 [1–5] sessions/patient).[7] Performing BPA in limited vessels within a single lobe would reduce the extent of reperfusion pulmonary injury. With our best efforts, the incidence of severe reperfusion pulmonary injury that required intratracheal intubation was reduced to 6% compared with 17% reported in a previous study.[7] Notably, the incidence of complications was significantly reduced in recent sessions (Table 3), although we did not change other pharmacological prophylaxis to reduce reperfusion pulmonary injury. This finding indicated that the incidence of reperfusion pulmonary injury largely depended on the proficiency of operators performing BPA.

Considering the fact that reperfusion pulmonary injury is unavoidable in BPA despite best efforts, postprocedural intensive monitoring of hemodynamics and oxygenation is necessary, even if the patient appears to be free from pulmonary injury after BPA. On the other hand, a routine CT scan after BPA may be unnecessary, because no patients with pulmonary injury detected only by a CT scan required intratracheal intubation or percutaneous cardiopulmonary support.

Pulmonary endarterectomy is the only potentially curative treatment for CTEPH.[5,22] Although the University of California, San Diego pulmonary endarterectomy team has been publishing excellent outcomes, they are not applicable worldwide because of the complex surgical technique and requirement of experience. It was recently reported from Europe and Canada that over one third of patients are assessed as inoperable, with a large variation between countries (from 12.0% versus 60.9%).[4] Histopathological studies have confirmed the existence of small vessel changes in CTEPH, similar to those of idiopathic pulmonary arterial hypertension, and vasodilative agents have been attempted in patients with inoperable CTEPH.[23,24] Some of these therapies may play a role in improving exercise capacity in CTEPH to some extent, but a retrospective analysis of patients with CTEPH demonstrated that medical therapy has a minimal effect on hemodynamics.[25] All patients in our study were diagnosed as inoperable and suffered from increasing disability in spite of at least 1 specific drug to treat pulmonary hypertension at other experienced hospitals. Most of our patients were too old to undergo lung transplantation, and some of them were already in the end stage of right-sided heart failure. Considering the high mortality of these patients when untreated[13] and the difficulty of pulmonary endarterectomy, an alternative therapeutic option is required. Our data demonstrated that refined BPA successfully removed stenoses in distal arteries to obtain a substantial decrease in pulmonary arterial pressure in these patients. Therefore, our refined BPA procedure could be a treatment option for patients with inoperable CTEPH. Although the present results indicated the efficacy of BPA, it is clear that there is a learning curve in performing this procedure. To demonstrate sufficient safety and efficacy, acquirement of the BPA technique and experience of BPA are necessary, as well as comprehensive management of patients requiring expertise in pulmonary vascular diseases and respiratory and critical care medicine. In addition, our patient numbers are still too small to conclude that BPA is an alternative therapeutic option for inoperable patients with CTEPH. Therefore, further studies and clinical trials should be performed.

Limitations

There are some limitations to this study. We do not have results of long-term follow-up of >7 years. There might be cases with restenosis or persistent pulmonary hypertension after BPA similar to that found in patients after pulmonary endarterectomy. To date, we have not experienced patients with angiographically documented restenosis after BPA. Second, a randomized and controlled direct comparison of BPA and medical therapy is necessary, and cost analysis is required because of the long duration of hospitalization with repeated BPA.

Disclosures

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SUPPLEMENTAL MATERIAL

(1) Reperfusion pulmonary injury

Supplemental Methods

We assessed the site where reperfusion pulmonary injury occurred and how long the pulmonary injury lasted. Univariate logistic regression analysis (using a $P < 0.05$) was used to evaluate associations between clinically apparent reperfusion pulmonary injury and factors of baseline characteristics, laboratory data, and parameters related to BPA procedure.

Supplemental Results

Reperfusion pulmonary injury occurred at the area where pulmonary arteries were dilated. Reperfusion injuries found on chest X-ray disappeared in a median of 4 days. None of the parameters analyzed, including maximum inflation pressure (14 atm in all sessions) and the inflation time (2 seconds in all sessions), were associated with the occurrence of clinically apparent reperfusion pulmonary injury (Supplemental Table).

Patients with extreme pulmonary hypertension manifest a higher rate of postoperative reperfusion edema after pulmonary endarterectomy[1]. We pay special attention as described below when pulmonary arterial pressure is high, and this could be the reason why none of the hemodynamic parameters was significantly associated with the occurrence of clinically apparent reperfusion pulmonary injury.

(2) Learning curve

In the first 128 and the most recent 127 procedures, there were 42 and 26 initial procedures, respectively. More initial procedures were included in the first 128 procedures. However, there was no significant association in the occurrence of pulmonary injury and initial session vs. follow-up session. We attempted to avoid injury of the pulmonary artery by passing the

targeted lesion without vigorously pushing the guide wire or balloon catheter, and by placing the wire tip within the angiographically visible area, along with evaluating accurate diameters with IVUS throughout the targeted lesion and inflating the balloon just at the targeted lesion. Because there was a large amount of swinging of the tip of the guiding catheter along with the heart beat, placing and holding a guiding catheter at the appropriate position is most difficult, but it is important to complete these simple and ordinary tasks. After a learning curve, we were able to safely select each segmental pulmonary artery by the guiding catheter and place the tip of the catheter at the appropriate site just proximal to the targeted lesions coaxially.

Supplemental Table. Baseline characteristics and procedure-related parameters had no association with clinically apparent reperfusion pulmonary injury

	Odds ratio (95% confidence interval)	P
Baseline characteristics		
Sex	1.03 (0.52-2.02)	0.89
Age	1.02 (0.99-1.05)	0.07
Body mass index	0.99 (0.90-1.08)	0.46
6-minute walk distance	0.99 (0.99-1.00)	0.09
Baseline laboratory data		
Brain natriuretic peptide	0.99 (0.98-1.00)	0.08
White blood cell counts	1.00 (1.00-1.00)	0.75
Hemoglobin levels	0.93 (0.73-1.19)	0.09
Platelet counts	0.98 (0.94-1.03)	0.46
Creatinine levels	2.20 (0.52-0.94)	0.29
Uric acid levels	1.01 (0.88-1.06)	0.45
C-reactive protein	0.86 (0.65-1.13)	0.29
Baseline hemodynamic parameters		
Systolic systemic blood pressure	1.01 (0.97-1.01)	0.79
Right atrial pressure	1.06 (0.99-1.13)	0.12
Systolic pulmonary arterial pressure	1.01 (0.97-1.01)	0.79
Mean pulmonary arterial pressure	0.99 (0.92-1.05)	0.67
Cardiac index	0.97 (0.87-1.07)	0.51
Pulmonary vascular resistance	0.99 (0.98-1.00)	0.29

BPA procedure-related parameters

Initial vs. follow-up sessions	1.15 (0.47-2.81)	0.41
Maximum diameter of balloon/session	0.88 (0.74-1.05)	0.16
Number of balloon inflation/session	1.01 (0.97-1.04)	0.74
Number of dilated vessels/session	0.98 (0.80-1.18)	0.81
Number of balloons/session	1.07 (0.94-1.22)	0.29

BPA: balloon pulmonary angioplasty.

Supplemental Reference

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