Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension

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Abstract

Aims: To evaluate the efficacy and safety of balloon pulmonary angioplasty (BPA) in patients with non-operable chronic thromboembolic pulmonary hypertension (CTEPH) using the results of pulmonary endarterectomy (PEA) for operable patients as a reference, and annotate the role of BPA in the management of CTEPH.

Methods and results: Data from 53 CTEPH patients were collected retrospectively. Twenty-four operable patients underwent PEA, and 29 non-operable patients underwent BPA. Patients who underwent BPA showed improved mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output (39.4 ± 6.9 to 21.3 ± 5.6 mmHg, 763 ± 308 to 284 ± 128 dyn·s^{-1}·cm^{-5}, 3.47 ± 0.80 to 4.26 ± 1.15 L/min, respectively); patients who received PEA showed similar efficacy (44.4 ± 11.0 to 21.6 ± 6.7 mmHg, 781 ± 278 to 258 ± 125 dyn·s^{-1}·cm^{-5}, 3.35 ± 1.11 to 4.44 ± 1.58 L/min, respectively). The mortality rates of BPA and PEA patients were 3.4% and 8.3%, respectively.

Conclusions: The efficacy and safety of BPA for non-operable cases were similar to those achieved using PEA for operable cases. BPA could be an additional treatment option for non-operable CTEPH patients, and most CTEPH patients can be satisfactorily treated by BPA or PEA.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by stenosis and obstruction of the pulmonary artery (PA) with non-resolving organised thromboemboli, leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), right heart failure, and finally death[1-3]. Without treatment, the prognosis for patients with CTEPH is very poor, with a five-year survival rate of 10% in patients with a mean PA pressure (mPAP) >50 mmHg[4]. Pulmonary endarterectomy (PEA) is the gold standard for the treatment of CTEPH; however, up to 40% of CTEPH patients are judged non-operable owing to distal thromboembolism or comorbidities[5]. Although targeted medical therapy established for pulmonary arterial hypertension[6] may be effective in non-operable patients, its efficacy is limited and the associated mortality rate remains high[7-9]. Currently, no established treatment strategies improve the prognosis of patients with non-operable CTEPH.

In 2001, Feinstein et al reported that balloon pulmonary angioplasty (BPA) significantly improved symptoms and haemodynamics in non-operable CTEPH patients[10]; however, the efficacy and safety were not satisfactory. Recently, with refinements in the technique, some groups have demonstrated the efficacy and safety of BPA in non-operable patients[11-13]. BPA may become an alternative treatment strategy for non-operable patients; however, it is an emerging therapy, and there is no consensus about the role of BPA in the management of CTEPH.

The purpose of this study was to evaluate the efficacy and safety of BPA for non-operable patients, utilising the results obtained using PEA for operable patients as a reference. Additionally, we sought to examine the role and the indication for BPA as a treatment strategy for CTEPH. We did not attempt to discuss the differences in clinical efficacies between BPA and PEA, because the lesions targeted by BPA and PEA are different. We aimed to comment on the roles of BPA and PEA in the management of patients with CTEPH.

Methods

STUDY DESIGN

Between September 2001 and September 2013, a total of 59 patients were diagnosed with CTEPH at Kobe University Hospital. The diagnosis of CTEPH was established according to clinical guidelines[6], based on medical history, physical examination, chest radiography, echocardiography, computed tomography (CT) scan, lung ventilation-perfusion scintigraphy, right heart catheterisation (RHC), and pulmonary angiography (PAG). Six patients who did not consent to therapeutic intervention were excluded from the study. Finally, 53 patients with CTEPH were reviewed retrospectively.

From March 2011, our institute started performing BPA for non-operable patients. Between September 2001 and March 2011, 31 patients were diagnosed with CTEPH. Of these, 17 patients judged as operable underwent PEA, while 14 patients judged as non-operable were treated medically. From March 2011, 22 more patients were diagnosed as having CTEPH. Of these, seven patients underwent PEA and 15 underwent BPA. In total, 29 patients underwent BPA, including the 14 patients diagnosed

before March 2011, who received medical treatment, plus 15 of the patients newly diagnosed with CTEPH.

ASSESSMENT OF OPERABILITY

The assessment of operability was conducted by cardiologists and cardiovascular surgeons. The decision regarding operability was based on the criteria for PEA[14]. The distribution of thromboembolic lesions and intimal thickening of PA was evaluated using chest CT and PAG, and reviewed by cardiologists, cardiovascular surgeons, and radiologists. The main responsible lesions in the main trunk and those from the lobar to the segmental artery were defined as proximal, while the distal segmental to subsegmental lesions were defined as distal. Surgical accessibility to lesions was decided after consensus between experienced cardiovascular surgeons and cardiologists, and for this several factors were considered, including lesion distribution, intimal thickening at the lesions, and patient age that could affect the fragility of intima. Patients judged as operable underwent PEA, and those judged as non-operable were treated medically for at least three months and then underwent BPA. Patients provided written informed consent to undergo PEA or BPA.

BPA procedure

BPA was performed using techniques similar to those previously described[11]. We approached the PA through the right femoral (82.6%) or jugular (17.4%) vein using a 6 Fr long sheath (BRITE TIP® Interventional Sheath Introducer; Cordis/Johnson & Johnson, Bridgewater, NJ, USA) which was introduced via a 9 Fr sheath (Arrow-Flex®; Teleflex Medical, Durham, NC, USA). Heparin (5,000 U) was administered after the placement of the 9 Fr sheath and was added every hour to maintain an activated clotting time between 200 and 300 s. A 6 Fr guide catheter (Autobahn; Multipurpose, or Judkins right 4.0; NIPRO Corporation, Osaka, Japan) was inserted through the long sheath and was advanced to the target vessels. Based on PAG, a 0.014-inch guidewire (Cruise; Asahi Intecc, Tokyo, Japan) was passed across the target lesion. While selecting the target vessels, the lower lobe lesions were preferentially dilated because the pulmonary blood flow at this site was relatively high, thus lowering mPAP. The lumen diameter was measured using intravascular ultrasound (IVUS) (Eagle Eye® Platinum; Volcano Corp, Rancho Cordova, CA, USA). IVUS was also used to check whether the guidewire had crossed eccentrically to ensure that the PA had not ruptured while ballooning. In cases of severe stenosis, abrupt narrowing, or complete obstruction, initially a 2.0 mm balloon catheter was used to dilate the lesions. Subsequently, the lesions were dilated to an appropriate size using 2.0 mm to 9.0 mm balloon catheters depending on the diameters of the vessels (Bandicoot RX; St. Jude Medical, St. Paul, MN, USA; Shiden; Kaneka Medix, Osaka, Japan; Sterling Monorail®; Boston Scientific, Natick, MA, USA). To prevent PA injury, the maximum balloon size was slightly smaller than the actual vessel diameter. We treated one to six segmental to subsegmental arteries in each procedure according to mPAP, which is the main indicator of reperfusion pulmonary injury (RPI)[15]. The procedure was repeated twice

within one to two weeks in the course of one admission. BPA was performed for a total of one to six sessions to normalise mPAP. We used non-invasive positive pressure ventilation (NIPPV) to prevent RPI in the first 50 sessions at least 24 hours after BPA. In the last 36 sessions, NIPPV was used only if needed. Epoprostenol was used in some cases if mPAP was over 40 mmHg, and dobutamine was administered if the cardiac index was <2.0 L/min/m² up to three days after BPA. A chest CT was performed within six hours after BPA to evaluate RPI, which was indicated as a high-density area of the dilated segments. Haemodynamic data were obtained in all patients around seven days after BPA.

PEA procedure

PEA was performed using techniques similar to those established by the San Diego group[16,17]. Bilateral PEA was performed through a median sternotomy. Distal endarterectomy was conducted with intermittent circulatory arrest for a period limited to 20 minutes, while the central temperature was maintained at 16°C. Patients were provided with perioperative medical treatment using catecholamines, PDE3 inhibitors, epoprostenol or diuretics until recovery. We classified lesions based on the location and morphology at the time of operation, as previously defined[18]. Haemodynamic data were obtained around two weeks after PEA. Residual PH after PEA was defined as mPAP >25 mmHg.

Statistical analysis

Quantitative values are presented as mean±standard deviation. Differences in values were tested using the Student's t-test and the paired Student's t-test. Nominal data were expressed as numbers and percentages and were analysed using the χ^2 test. World Health Organization functional class (WHO-Fc) was presented as the median and number of patients in each class, and the differences were tested by the Mann-Whitney test. The level of statistical significance was set at p<0.05. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA).

Results

CLINICAL CHARACTERISTICS

The baseline characteristics of the study population are shown in **Table 1**. The mean age was significantly higher in the BPA group than in the PEA group. The median time from diagnosis to PEA or BPA was 113 days or 802 days, respectively. Most patients judged as non-operable had only distal lesions. Vasodilators were administered to 29.2% of patients who underwent PEA and 82.8% of patients who underwent BPA. **Table 2** shows the main reasons patients were judged as non-operable. We abandoned PEA and performed BPA in four patients who had proximal segmental lesions, because of severe COPD, the co-existence of cancer, advanced age, and a history of stroke.

PROCEDURES AND OUTCOMES OF BPA AND PEA

A total of 86 BPA sessions were performed in 29 patients (average 2.97 sessions per patient). The number of dilated vessels was

Table 1. Baseline characteristics.

Variable	BPA (n=29)	PEA (n=24)	p-value
Male (%)	7 (24.1%)	7 (29.2%)	0.695
Age	67.3±11.1	57.0±13.9	0.005
Lesion classification			
Proximal lesion (%)	4 (13.8%)	14 (58.3%)	0.001
Distal lesion (%)	25 (86.2%)	10 (41.7%)	0.001
Medication			
Endothelin receptor antagonist (%)	20 (69.0%)	7 (29.2%)	0.001
Phosphodiesterase-5 inhibitor (%)	10 (34.5%)	0 (0.0%)	0.002
Prostacyclin analogue (%)	1 (3.4%)	0 (0.0%)	0.354
Others (%)	0 (0.0%)	1 (4.2%)	0.270
Haemodynamic data			
Cardiac output (L/min)	3.47±0.80	3.35±1.11	0.672
Cardiac index (L/min/m²)	2.17±0.45	2.09±0.62	0.594
Systolic pulmonary artery pressure (mmHg)	68.6±13.5	76.7±19.9	0.098
Mean pulmonary artery pressure (mmHg)	39.4±6.9	44.4±11.0	0.061
Diastolic pulmonary artery pressure (mmHg)	22.1±5.8	24.4±10.7	0.335
Pulmonary vascular resistance (dyn·s⁻¹·cm⁻⁵)	763±308	781±278	0.844
Pulmonary capillary wedge pressure (mmHg)	8.1±3.3	13.1±7.3	0.003
Right atrium pressure (mmHg)	5.5±5.0	10.2±8.8	0.031
WHO functional class (I/II/III/IV)	3 (0/3/18/8)	3 (0/3/13/8)	0.798
Brain natriuretic peptide (pg/mL)	210±240	263±241	0.558
WHO: World Health Organization			

2.74 per session. All distal segmental and subsegmental lesions were accessible. The average balloon size used in BPA was 4.35±1.78 mm. The required contrast medium was 195±64 mL per session. Perioperative medical treatment with catecholamines or epoprostenol was performed in 21 sessions (24.4%). The median stay in intensive care unit after BPA was 2.96±1.59 days. **Figure 1** and **Moving image 1-Moving image 6** show representative PAGs, procedures, and IVUS footage of BPA. Blood flow of the PA improved dramatically after BPA.

A total of 24 patients underwent PEA. The mean duration of circulatory arrest, cardiopulmonary bypass, and surgery were 47.0±24.67 min, 235.9±44.3 min, and 424±151 min, respectively. An inferior vena cava filter was placed in 12 patients (50.0%).

Table 2. Main reasons for non-operability.

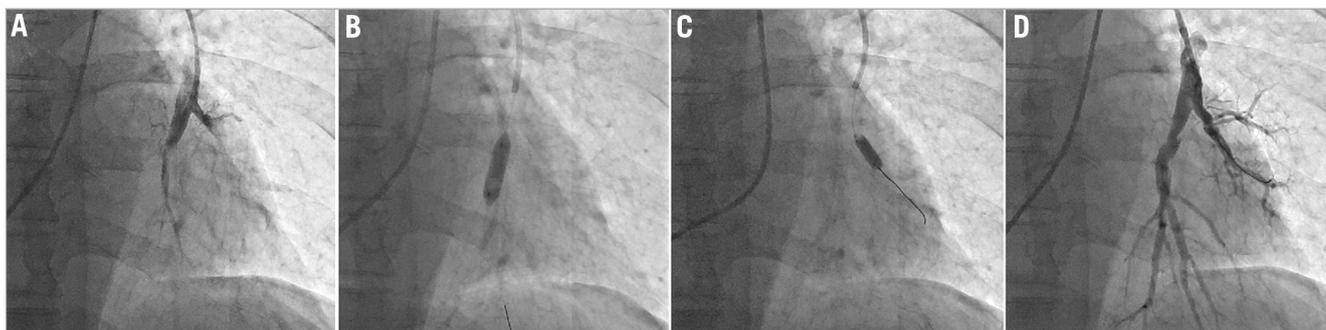| Variable	Patients, n (%)
Clot inaccessibility	13 (44.8)
Advanced age	6 (20.7)
Previous cerebrovascular diseases	2 (6.9)
Severe COPD	3 (10.3)
Post PEA	2 (6.9)
Comorbid to malignancy	3 (10.3)
COPD: chronic obstructive pulmonary disease; PEA: pulmonary endarterectomy	

Figure 1. *Representative pulmonary angiograms of the segmental pulmonary artery (left A10) from a patient who underwent BPA: before BPA (A) and after BPA (D). A pulmonary artery with abrupt narrowing is effectively dilated by a 5 mm balloon at 8 atm (B, C). BPA: balloon pulmonary angioplasty*

Perioperative medical treatment with catecholamines, PDE3 inhibitors, or epoprostenol was performed in 21 patients (87.5%). The mean duration of mechanical ventilation was 2.3±1.8 days, and the median stay in intensive care unit after PEA was 8.67±2.87 days. Intraoperative findings showed that 58.3% had surgical classification types I and II, and 41.7% had type III. There were no patients with type IV lesions. **Figure 2** shows representative PAG images before and after PEA and a thromboembolic specimen from the same patient.

Although medical vasodilator therapies did not significantly improve haemodynamics and symptoms in the BPA group, BPA dramatically improved the patients' haemodynamics and clinical status to a similar degree to PEA (**Table 3**, **Figure 3**). Exercise capacity and haemodynamics in both operable and

Figure 2. *Representative pulmonary angiograms from an operable patient before (A) and after (B) PEA, including each part of the lung. Thromboembolic specimen removed from the same patient (C). The disease type is Type III on both sides. PEA: pulmonary endarterectomy*

Table 3. Baseline and post-procedural results.

|		BPA (n=29)			PEA (n=24)		
		Baseline	**Post-procedure**	***p*-value**	**Baseline**	**Post-procedure**	***p*-value**
Haemodynamic data	Cardiac output (L/min)	3.47±0.80	4.26±1.15	<0.001	3.35±1.11	4.44±1.58	0.007
	Cardiac index (L/min/m^2)	2.17±0.45	2.69±0.63	<0.001	2.09±0.62	2.83±0.81	0.005
	Systolic pulmonary artery pressure (mmHg)	68.6±13.5	38.1±11.6	<0.001	76.7±19.9	34.6±10.7	<0.001
	Mean pulmonary artery pressure (mmHg)	39.4±6.9	21.3±5.6	<0.001	44.4±11.0	21.6±6.7	<0.001
	Diastolic pulmonary artery pressure (mmHg)	22.1±5.8	10.9±4.6	<0.001	24.4±10.7	12.1±3.5	<0.001
	Pulmonary vascular resistance (dyn·s^{-1}·cm^{-5})	763±308	284±128	<0.001	781±278	258±125	<0.001
	Pulmonary capillary wedge pressure (mmHg)	8.1±3.3	6.9±3.4	0.189	13.1±7.3	8.6±3.4	0.032
	Right atrium pressure (mmHg)	5.5±5.0	2.6±2.8	0.013	10.2±8.8	6.0±3.8	0.089
WHO functional class (I/II/III/IV)		(0/3/18/8)	(11/14/3/0)	<0.001	(0/3/13/8)	(13/7/2/0)	<0.001
Brain natriuretic peptide (pg/mL)		210±240	41±37	0.010	263±241	74±64	0.022
Six-minute walk distance (m)		295±95	397±117	<0.001	N.A.	N.A.	
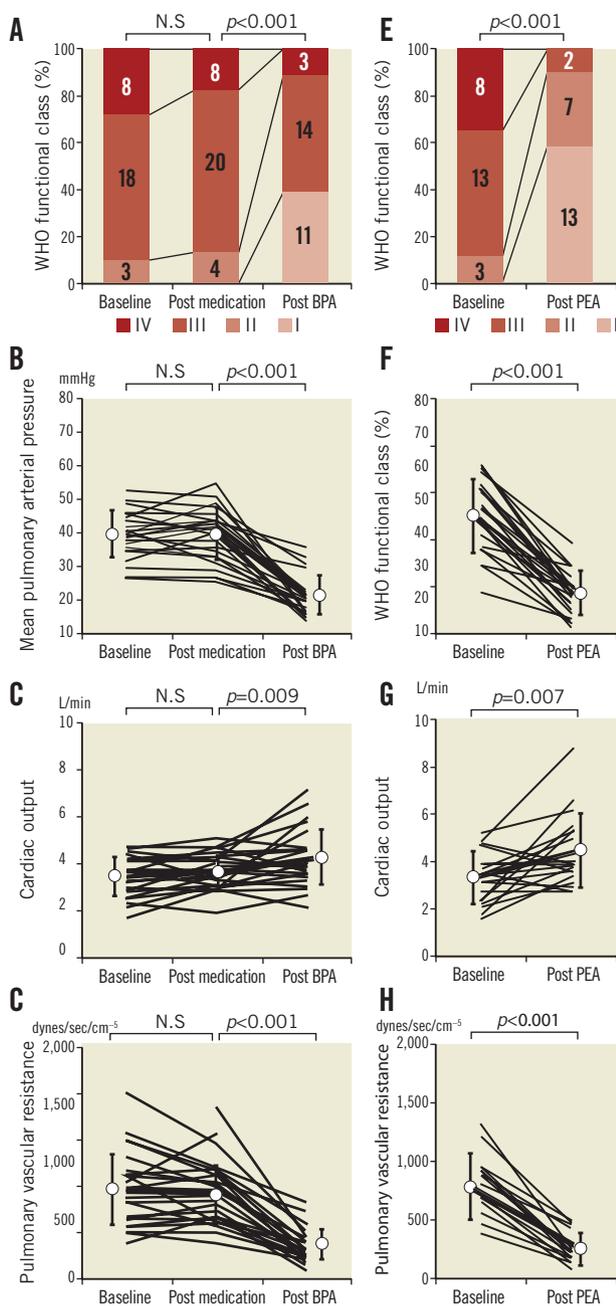
Figure 3. *Changes in WHO functional class and haemodynamics before and after vasodilator therapy and after balloon pulmonary angioplasty (A-D) and pulmonary endarterectomy (E-H). WHO functional class (A, D), mean pulmonary arterial pressure (B, F), cardiac output (C, G), and pulmonary vascular resistance (D, H). WHO: World Health Organization*

non-operable patients improved remarkably after treatment with BPA or PEA.

COMPLICATIONS OF BPA AND PEA

Complications due to BPA and PEA are presented in **Table 4**. RPI was the main complication of BPA and occurred in 64.0% of sessions, but 50.9% of the RPI cases were asymptomatic. Symptomatic

Table 4. Complications of balloon pulmonary angioplasty and pulmonary endarterectomy.

	BPA	PEA
Session-based analysis	**86 sessions**	**24 sessions**
Reperfusion pulmonary injury		
Severe haemoptysis, n (%)	3 (3.5)	3 (12.5)
Haemosputum or desaturation, n (%)	24 (27.9)	3 (12.5)
Only CT findings, n (%)	28 (32.6)	N.A.
Infection		
Ventilator associated pneumonia, n (%)	0 (0.0)	2 (8.3)
Mediastinitis, n (%)	0 (0.0)	1 (4.2)
Others, n (%)	2 (2.3)	1 (4.2)
Wire perforation, n (%)	4 (4.7)	0 (0.0)
Neurologic complications, n (%)	0 (0.0)	2 (8.3)
Pericardial effusion, n (%)	0 (0.0)	2 (8.3)
Bleeding, n (%)	0 (0.0)	1 (4.2)
Patient-based analysis	**29 patients**	**24 patients**
Persistent pulmonary hypertension, n (%)	4 (13.8)	4 (16.7)
Death, n (%)	1 (3.4)	2 (8.3)

RPI was associated with haemoptysis or haemoglobin desaturation. These patients required additional oxygen therapy, NIPPV, or intratracheal intubation. The use of NIPPV decreased to 58.1% in the more recent half of the sessions, that is, between September 2012 and September 2013, because it was not always necessary. Furthermore intratracheal intubation was not required in these patients. In case of wire perforation, we could control bleeding in all cases by ballooning the vessel at the proximal edge under low pressure. Wire perforation also decreased as the operators became more skilled in conducting the procedures. None of the patients required cardiopulmonary support. There was one in-hospital death related to infection resulting from central venous catheter use for epoprostenol administration.

Among those who underwent PEA, half of them had operative complications, including RPI, persistent PH, infection, and neurological complications. Two patients died 16 days and five days after PEA. Both patients had severe persistent PH and low cardiac output (CO) and required constant cardiopulmonary support. The in-hospital mortality rate of PEA was lower in cases reported between November 2006 and September 2013, and there was no in-hospital death among these patients.

Follow-up

In the BPA group, there was one death from malignant cancer during the follow-up for 1.15±0.81 years after the final sessions, and one in-hospital death as described above. None of the remaining 27 patients had re-exacerbation of symptoms. Twenty-three patients underwent RHC at 0.92±0.52 years after the final sessions and had mPAP of 22.5±5.7 mmHg, CO of 4.26±0.91 L/min, and PVR of 291±157 dyn·s^{-1}·cm^{-5}. The estimated right ventricular systolic pressure (RVSP) of 25 patients from follow-up echocardiography at

1.10±0.59 years remained almost equivalent from 38.4±8.5 mmHg to 37.2±10.1 mmHg. After the final BPA, the dose of medical therapy was reduced or was discontinued in seven patients (29.1%).

In the PEA group, all patients were alive during the follow-up for 4.69±3.60 years, except for two patients who had died perioperatively. Recently, five patients underwent follow-up RHC at 1.12±0.64 years after the PEA and had mPAP of 17.6±5.3 mmHg, CO of 3.86±0.41 L/min, PVR of 255±162 dyn·s^{−1}·cm[−5]. The RVSP of 18 patients after 3.93±3.57 years of follow-up was unchanged from 29.8±8.8 to 30.9±6.6 mmHg. One patient who had re-exacerbation of symptoms and pulmonary hypertension underwent BPA. **Figure 4** shows the survival curve of the BPA group and the PEA group by the Kaplan-Meier method.
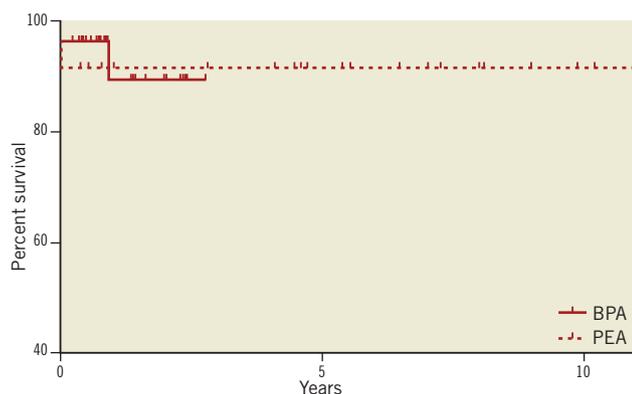

Figure 4. *The survival curve of the BPA group and the PEA group by the Kaplan-Meier method from the last procedures. Log-rank test, p=0.92.*

Discussion

This is the first study to describe the efficacy and safety of BPA for patients with non-operable CTEPH using the efficacy and safety achieved by PEA for operable patients as reference. BPA could effectively improve haemodynamics and exercise capacity in non-operable patients who could not get benefit with medical therapy, similar to those of PEA in operable patients. With regard to complications, the mortality rate of BPA was comparable to that in previous reports[11,19] and was not higher than that with PEA in this study or in other experienced centres[20]. The frequency of RPI with BPA and PEA was also comparable to those reported previously[11,21]. In BPA, only a few cases required intratracheal intubation and had a few other complications. Thus, although it cannot necessarily be said that BPA was a minimally invasive therapy, the efficacy and safety of BPA for non-operable patients were as satisfactory as those of PEA for operable patients. These results suggest that most CTEPH patients can be treated successfully with either BPA or PEA.

To decide the treatment strategy for CTEPH patients, it is most important to assess surgical operability; however, there is no universal consensus regarding operability. The indications for non-operability vary from 12% to 60.9% among different centres and countries[5].

Comorbidities are one of the main factors influencing the decision. COPD is a frequent comorbidity observed in 9.5% of CTEPH patients[5], and severe chronic lung disease is a contraindication for PEA. In the present study, two patients who were judged as non-operable owing to severe COPD were successfully treated with BPA. Furthermore a history of cerebrovascular disease is a risk factor for postoperative stroke and mortality[22,23]. We judged two patients as non-operable owing to their history of cerebrovascular disease. In addition, three patients with a history of cancer were considered to have non-operable CTEPH. Since evidence for the safety of PEA in cancer patients is still lacking, we opted for BPA instead of PEA to treat patients with concomitant cancer. Advanced age should be considered when assessing operability. Previous reports have shown good outcomes with PEA in patients aged up to 86 years[20]; however, age over 60 years is a known risk factor for in-hospital mortality after PEA[24]. In our study, there were two in-hospital deaths after PEA in patients who were over 75 years of age. In the BPA group, 80% of patients were over 60 years of age, but the procedures were performed safely. Based on these findings, patients judged as non-operable owing to comorbidity or advanced age can be good candidates for BPA.

Another critical factor in the assessment of operability is clot accessibility. A previous report has shown that approximately half of the cases are judged as non-operable owing to clot inaccessibility[5]. Generally, patients with surgical classification of disease types I and II have excellent outcomes; however, disease types III and IV are associated with higher perioperative mortality caused by an insufficient improvement of haemodynamics[17]. The San Diego group has reported that distal segmental and subsegmental lesions are fully accessible, but the outcomes are unsatisfactory[17,20]. In our study, 24.5% (13/53 patients) of CTEPH patients were judged as non-operable mainly owing to clot inaccessibility. In those patients, BPA effectively accessed distal lesions and improved the haemodynamics. BPA could be promising for surgically inaccessible CTEPH.

Residual PH is one of the adverse events after PEA that is related to in-hospital mortality, with an incidence of 5-35% after PEA[25,26]. In this study, four patients (16.7%) had residual PH. After hospital discharge, the midterm outcome of residual PH is good[27]; however, the long-term outcome remains unknown. Furthermore, it is suggested that these patients have "residual CTEPH", since the recurrence of CTEPH is very rare[28], and inadequate surgical clearance of embolic materials in distal branches can be associated with residual PH and worsening of outcomes[26,27,29]. In the present study, two patients in the BPA group had residual PH after PEA. PAG of both patients demonstrated residual embolic material in the distal PA. In these patients, haemodynamics and symptoms were satisfactorily improved by BPA. Since the risk of reoperation in cardiovascular diseases is high[30], BPA can be an alternative therapy in selected patients with residual PH.

Limitations

There are several limitations of this study. The main limitation is the retrospective observational nature of the study design, combined with

the fact that the number of patients was small, and the data were collected in a single centre. A multicentre, prospective study is needed for further evaluation to determine the role of BPA. Second, the long-term efficacy of BPA was not evaluated in this study; furthermore, unlike PEA, no study has reported the long-term efficacy of BPA. In addition, restenosis of the PA after BPA was not fully investigated, although in the short term there appeared to be no restenosis after BPA. The influence of small-vessel disease in CTEPH[2] on the outcome after BPA is also unknown. Further, long-term analysis will be needed to evaluate the true efficacy of BPA. Finally, the assessment of operability, especially surgical accessibility, remains challenging. Preoperative assessment with modern imaging modalities cannot be easily applied to the evaluation of disease type, and intraoperative assessment is the only way to assess the real type of disease or the accessibility to the dissection plane of the intima. Furthermore, the assessment of operability depends in part on the experience of the institution[5]. A consensus regarding the assessment of operability is needed in order to determine the role of BPA.

In this regard, BPA is still an experimental therapy and awaits a stronger position in the CTEPH therapy algorithm by the accumulation of clinical evidence. Nevertheless, BPA could provide an additional therapeutic option for CTEPH patients.

Conclusion

In conclusion, this is the first study to evaluate the efficacy and safety of BPA for non-operable CTEPH using as reference the efficacy and safety achieved by PEA for operable CTEPH. Most CTEPH patients can be treated satisfactorily with either BPA or PEA, and this treatment strategy combined with medical therapy, including riociguat, may notably improve prognosis in patients with almost all types of CTEPH.

Impact on daily practice

While pulmonary endarterectory (PEA) is the gold standard for a treatment of chronic thromboembolic pulmonary hypertension (CTEPH) patients, up to 40% of CTEPH patients are judged as non-operable due to distal thromboembolism or comorbidities. Although riociguat has recently been approved for treatment of CTEPH patients, its efficacy is still limited as compared to that of PEA. The present study demonstrated that the efficacy and safety of balloon pulmonary angioplasty (BPA) for non-operable CTEPH patients were similar to those achieved using PEA for operable cases and that, in daily practice, balloon pulmonary angioplasty could provide an alternative therapeutic option for non-operable CTEPH patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Dartevelle P, Fadel E, Mussot S, Chapelier A, Herve P, de Perrot M, Cerrina J, Ladurie FL, Lehouerou D, Humbert M, Sitbon O, Simonneau G. Chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2004;23:637-48.

2. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation.* 2006;113:2011-20.

3. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev.* 2010;19:59-63.

4. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm followup of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest.* 1982;81:151-8.

5. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jais X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011;124:1973-81.

6. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30:2493-537.

7. Jais X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, Hoeper MM, Lang IM, Mayer E, Pepke-Zaba J, Perchenet L, Morganti A, Simonneau G, Rubin LJ; Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. *J Am Coll Cardiol.* 2008;52:2127-34.

8. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, Tsui SS, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2008;177:1122-7.

9. Pepke-Zaba J, Jansa P, Kim NH, Naeije R, Simonneau G. Chronic thromboembolic pulmonary hypertension: role of medical therapy. *Eur Respir J.* 2013;41:985-90.

10. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation.* 2001;103:10-3.

11. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv.* 2012;5:748-55.

12. Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, Tamura Y, Ando M, Fukuda K, Yoshino H, Satoh T. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv.* 2012;5:756-62.

13. Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, Tatebe S, Miyamichi-Yamamoto S, Shimokawa H. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. *Circ J.* 2012;76:485-8.

14. Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Dartevelle P, Pepke-Zaba J, Jamieson SW, Lang I, Corris P. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:73S-80S.

15. Inami T, Kataoka M, Shimura N, Ishiguro H, Yanagisawa R, Taguchi H, Fukuda K, Yoshino H, Satoh T. Pulmonary edema predictive scoring index (PEPSI), a new index to predict risk of reperfusion pulmonary edema and improvement of hemodynamics in percutaneous transluminal pulmonary angioplasty. *JACC Cardiovasc Interv.* 2013;6:725-36.

16. Ando M, Okita Y, Tagusari O, Kitamura S, Nakanishi N, Kyotani S. Surgical treatment for chronic thromboembolic pulmonary hypertension under profound hypothermia and circulatory arrest in 24 patients. *J Card Surg.* 1999;14:377-85.

17. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, Channick RN, Fedullo PF, Auger WR. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg.* 2003;76:1457-62; discussion 1462-4.

18. Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, Jamieson SW. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg.* 2002;124:1203-11.

19. Suntharalingam J, Treacy CM, Doughty NJ, Goldsmith K, Soon E, Toshner MR, Sheares KK, Hughes R, Morrell NW, Pepke-Zaba J. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest.* 2008;134:229-36.

20. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, Fedullo PF, Jamieson SW. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg.* 2012;94:97-103.

21. Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Technique and outcomes of pulmonary endarterectomy surgery. *Ann Thorac Cardiovasc Surg.* 2008;14:274-82.

22. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg.* 2003;75:472-8.

23. Lapar DJ, Gillen JR, Crosby IK, Sawyer RG, Lau CL, Kron IL, Ailawadi G. Predictors of operative mortality in cardiac surgical patients with prolonged intensive care unit duration. *J Am Coll Surg.* 2013;216:1116-23.

24. Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Imanaka H, Kitamura S. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. *Ann Thorac Surg.* 2006;82:630-6.

25. Rahnavardi M, Yan TD, Cao C, Vallely MP, Bannon PG, Wilson MK. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review. *Ann Thorac Cardiovasc Surg.* 2011;17:435-45.

26. Jenkins DP, Madani M, Mayer E, Kerr K, Kim N, Klepetko W, Morsolini M, Dartevelle P. Surgical treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2013;41:735-42.

27. Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2011;141:383-7.

28. Mo M, Kapelanski DP, Mitruka SN, Auger WR, Fedullo PF, Channick RN, Kerr K, Archibald C, Jamieson SW. Reoperative pulmonary thromboendarterectomy. *Ann Thorac Surg.* 1999;68:1770-6.

29. Hartz RS, Byrne JG, Levitsky S, Park J, Rich S. Predictors of mortality in pulmonary thromboendarterectomy. *Ann Thorac Surg.* 1996;62:1255-9; discussion 1259-60.

30. Roselli EE, Pettersson GB, Blackstone EH, Brizzio ME, Houghtaling PL, Hauck R, Burke JM, Lytle BW. Adverse events during reoperative cardiac surgery: frequency, characterization, and rescue. *J Thorac Cardiovasc Surg.* 2008;135:316-23.

Online data supplement

Moving image 1. A representative pulmonary angiogram of the segmental pulmonary artery (left A10) before angioplasty.

Moving image 2. Image of passing a 0.014-inch guidewire across a lesion.

Moving image 3. Pulmonary angiogram just after dilatation with a 5 mm balloon at 8 atm.

Moving image 4. Pulmonary angiogram four months after the procedures.

Moving image 5. Representative intravascular ultrasound imaging before angioplasty.

Moving image 6. Intravascular ultrasound imaging just after angioplasty.