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ORIGINAL RESEARCH

Efficacy and Safety of Balloon Pulmonary Angioplasty for Patients With Chronic Thromboembolic Pulmonary Hypertension and Comorbid Chronic Obstructive Pulmonary Disease

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BACKGROUND: Balloon pulmonary angioplasty (BPA) is a promising treatment modality for nonoperable chronic thromboembolic pulmonary hypertension (CTEPH). However, BPA for atypical CTEPH with concurrent chronic obstructive pulmonary disease (COPD) remains controversial owing to the risk of exacerbation of ventilation-perfusion mismatch. We aimed to evaluate the efficacy and safety of BPA for CTEPH with moderate or severe COPD.

METHODS AND RESULTS: Data from 149 patients with CTEPH, who underwent BPA from March 2011 to June 2021, were retrospectively analyzed. Patients were divided based on COPD comorbidity: the COPD group (n=32, defined as forced expiratory volume in 1 second/forced vital capacity <70% and forced expiratory volume in 1 second <80% predicted) and the non-COPD group (n=101); patients with mild COPD (n=16) were excluded. Hemodynamic and respiratory parameters were compared between the groups. Hemodynamics improved similarly in both groups (reduction in pulmonary vascular resistance): −55.6±29.0% (COPD group) and −58.9±21.4% (non-COPD group); *P*=nonsignificant. Respiratory function and oxygenation improved in the COPD group (forced expiratory volume in 1 second/forced vital capacity [61.8±7.0% to 66.5±10.2%, *P*=0.02] and arterial oxygen partial pressure [60.9±10.6 mm Hg to 69.3±13.6 mm Hg, *P*<0.01]). Higher vital capacity (*P*=0.024) and higher diffusing capacity for lung carbon monoxide (*P*=0.028) at baseline were associated with greater improvement in oxygenation in the multivariable linear analysis. Lung injury per BPA session was 1.6% in the COPD group.

CONCLUSIONS: The efficacy and safety of BPA for nonoperable CTEPH in patients with comorbid COPD were similar to those in patients without COPD. Oxygenation and forced expiratory volume in 1 second/forced vital capacity improved in patients with COPD. BPA should be considered in patients with CTEPH with concurrent COPD.

Key Words: balloon pulmonary angioplasty ■ chronic obstructive pulmonary disease ■ chronic thromboembolic pulmonary hypertension

See Editorial by Cheng and Conrad.

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study to focus on balloon pulmonary angioplasty (BPA) for atypical chronic thromboembolic pulmonary hypertension (CTEPH) with concurrent chronic obstructive pulmonary disease (COPD).
- The efficacy and safety of BPA in patients with COPD were similar to those in patients without COPD; hemodynamics nearly normalized despite comorbid COPD.
- BPA improved oxygenation and forced expiratory volume in 1 second/forced vital capacity without exacerbation of the ventilation-perfusion mismatch.

What Are the Clinical Implications?

- Most patients with stable COPD do not have pulmonary hypertension or exhibit mild pulmonary hypertension; therefore, factors related to CTEPH contribute considerably to pulmonary hypertension in patients with CTEPH and concurrent COPD. BPA could be considered as an effective and safe treatment method for these patients.
- Moderate-to-severe COPD is one of the causes of nonoperability of CTEPH even if the type is deemed operable, However, BPA can be safely performed in CTEPH with moderate-to-severe COPD because it is minimally invasive.

Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
BPA	balloon pulmonary angioplasty
CTEPH	chronic thromboembolic pulmonary hypertension
DLCO	diffusing capacity for lung carbon monoxide
PaO_2	arterial oxygen partial pressure
PAP	pulmonary arterial pressure
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
VC	vital capacity

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and obstruction of the pulmonary arteries caused by nonresolving, organized thromboemboli, leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), and right heart failure.[1–3] CTEPH is categorized within Group 4 in the updated clinical classification of PH proposed at the 6th World Symposium on PH in Nice, France in 2018.[4] Without treatment, the prognosis for patients with CTEPH is very poor, with a 5-year survival rate is 10% in patients with a mean pulmonary artery pressure (mean PAP) >50 mm Hg.[5] Pulmonary endarterectomy (PEA) is the gold standard treatment for operable CTEPH. Balloon pulmonary angioplasty (BPA), an endovascular procedure to widen narrowed or obstructed pulmonary arteries, has emerged as an alternative treatment option for patients with nonoperable CTEPH.[6–8] Interventional treatments including PEA, BPA, or both, and the concurrent use of soluble guanylate cyclase stimulators dramatically improved hemodynamics, which translated into excellent survival in both operable and nonoperable CTEPH in the modern medical management era.[9]

Chronic obstructive pulmonary disease (COPD), characterized by persistent respiratory symptoms and airflow limitation caused by airway and alveolar pathologies, is a relatively common disease with a prevalence of 9% to 10% in the population aged >40 years.[10] Patients with COPD often exhibit mild PH, and only a few patients with COPD (1%–3%) have severe PH with mean PAP >40 mm Hg.[11] PH because of lung disease and/or hypoxia is categorized within Group 3 in the aforementioned classification of PH. Moreover, COPD is one of the associated medical conditions of CTEPH.[12]

The efficacy and safety of BPA for nonoperable CTEPH could be promising; however, many reports supporting the efficacy of BPA have targeted typical CTEPH. The efficacy and safety of BPA for atypical CTEPH with lung disease still remain controversial. We aimed to evaluate the efficacy of BPA for CTEPH in patients with comorbid moderate or severe COPD.

METHODS

The study protocol was approved by the ethics committee of Kobe University Hospital (approval number: B210255) and complied with the Declaration of Helsinki. All enrolled patients were provided with the option to opt out if they did not wish to participate in the study. Written informed consent was waived because the data were collected retrospectively. The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients and Study Design

This retrospective observational study was conducted in consecutive patients who underwent BPA at Kobe University Hospital (Kobe, Japan) from March 2011 (commencement of our BPA program) to June 2021. All patients were diagnosed with CTEPH according to established clinical guidelines,[4,13] and

judged as nonoperable at a multidisciplinary meeting including experienced BPA interventionists and PEA surgeons.

COPD is diagnosed when the forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) is <70% after the inhalation of a bronchodilator, and exclusion of other diseases which could cause obstructive impairment. The severity of COPD was assessed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria:[14] Stage I: mild COPD, FEV1 ≥80% predicted; Stage II: moderate COPD, 50% ≤FEV1<80% predicted; Stage III: severe COPD, 30% ≤FEV1<50% predicted; and Stage IV: very severe COPD, FEV1<30% predicted.

Clinical assessments including hemodynamic characteristics assessed by right heart catheterization, respiratory function tests, arterial blood gas analysis, functional status based on the New York Heart Association functional class, and exercise capacity using the 6-minute walk test (6MWT) and cardiopulmonary exercise test were performed at baseline (ie, at the time of CTEPH diagnosis) and re-evaluated at 3 months after the last BPA session. These examinations were performed under the same conditions of oxygen inhalation (room air, if possible) and treatment for COPD with inhalant bronchodilators in each patient. In this study, we excluded patients with mild COPD (stage I of GOLD classification) to avoid ambiguous results. The COPD group was defined as FEV1/FVC <70% and FEV1<80% predicted. Patients who underwent rescue BPA for life support, patients without baseline respiratory function data, and patients without re-evaluation (3 months after the last BPA) by right heart catheterization were also excluded.

The primary objective of this study was to assess the hemodynamic change in mean PAP and PVR in CTEPH with comorbid COPD compared with CTEPH without COPD who underwent BPA. The secondary efficacy end point included the improvement in oxygenation and respiratory function parameters, New York Heart Association functional class, BPA-related complications, exercise capacity using cardiopulmonary exercise test, and long-term survival.

BPA Procedure

We performed BPA using techniques similar to those previously described.[15,16] We approached the pulmonary arteries through the right femoral vein using a 6-French guiding sheath (Parent Plus; Medikit Terumo, Tokyo, Japan). A 6-French guiding catheter (Profit, Multipurpose, or Judkins right and left 4.0; Goodman, Nagoya, Aichi, Japan) was inserted through the guiding sheath into the target vessels. A 0.014-inch guide wire (Athlete Bpahm; Japan Lifeline, Tokyo, Japan) was passed across the target lesion. A 2.0-mm balloon catheter was initially used to dilate the lesions. Subsequently, 2.0- to 9.0-mm balloon catheters were chosen to dilate the lesions to the appropriate size, depending on the vessel diameter and hemodynamic severity of each patient. Two BPA sessions were performed at 4- or 5-day intervals during a single hospital admission. Additional BPA sessions were repeated until all the accessible lesions were considered treated, regardless of normalized mean PAP.

Cardiopulmonary Exercise Test and Respiratory Function Test

Cardiopulmonary exercise test was performed using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan) according to the American Thoracic Society guidelines.[17] One minute of upright rest was followed by 4 minutes of unloaded pedaling and progressive workload increments (5 or 10 W/min), until symptom-limited maximum tolerance was reached. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation were measured continuously using breath-by-breath analysis (Cpex-1; Inter-Reha, Tokyo, Japan). Peak VO_2 was defined as the average VO_2 data collected during the last 30 seconds of peak exercise. Ventilatory efficiency during exercise was expressed as the slope of ventilation versus VCO_2, over the linear component of the plot.[18]

Respiratory function of FEV1, FVC, percentage of vital capacity (%VC), and the diffusing capacity of lung carbon monoxide (DLCO) were assessed using a spirometer (Autospirometer S21; Minato medical Co., Osaka, Japan), within ≈2 days following right heart catheterization. Arterial blood gas analyses for oxygen saturation, and arterial oxygen partial pressure (PaO_2) and mixed venous oxygen saturation in the pulmonary artery were performed during right heart catheterization in room-air conditions.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 26.0 (IBM, Armonk, NY, USA) and GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA). Continuous variables were expressed as mean±SD. Differences in continuous variables such as age, 6MWT distance, hemodynamic data, and respiratory function or oxygenation parameters, were compared using the paired Student *t*-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables such as sex, New York Heart Association functional class, and treatments were expressed as numbers and percentages and were compared using the χ^2 test for independence or using Fisher exact test when the expected counts were <5. For survival analysis, the date of the first session of BPA was used as the starting point to

determine the length of survival. The cut-off date was July 31, 2021. The Kaplan–Meier method was used to estimate the overall survival at each interval. Univariate and multivariable analyses based on the linear regression model were constructed to assess adjusted relationships between improvement in oxygenation (PaO_2) after BPA and baseline clinical characteristics including age, hemodynamic data, and respiratory function or oxygenation parameters in the COPD group. In a multivariable regression model, respiratory-related variables considered to be clinically associated with improvements in oxygenation (baseline %VC, FEV1/FVC, percent predicted diffusing capacity for lung carbon monoxide [%DLCO], and PaO2) as well as variables with P values <0.20 in univariate analyses served as candidate predictors in the model building procedure. Forward-backward stepwise variable selection (criteria: probability-of-F-to-enter ≤0.05, probability-of-F-to-remove ≥0.10) was used to identify predictors for the final multivariable model. The level of statistical significance was set at P<0.05 for all analyses.

RESULTS

Patient Population

During the study period, a total of 149 patients with nonoperable CTEPH underwent BPA with a mean of 4.0±1.2 sessions per patient and completed re-evaluation after a median of 3.6 (interquartile range, 3.1–4.4) months after the last BPA session. Most of the patients (n=139, 93.3%) were deemed nonoperable owning to distal lesions; 10 patients (6.7%) were nonoperable because of advanced age and/or comorbidities of COPD, malignant tumor, and cerebrovascular disease. Sixteen patients with mild COPD (GOLD stage I) were excluded. Of the 133 patients included in the analysis, 32 were classified in the COPD group, and 101 in the non-COPD group. In the COPD group, 24 patients (75%) were classified as GOLD stage II, 8 (25%) as GOLD stage III, and there were no patients in GOLD stage IV. The patient cohort is shown in Figure 1. Baseline characteristics of the COPD and non-COPD groups are summarized in Table 1. More patients in the COPD group had a smoking history than in the non-COPD group (75% versus 20%, respectively; P<0.001), and a shorter walking distance in the 6MWT (289±86 m versus 331±103 m; P=0.042). Eighteen of the 32 patients with COPD (56%) received inhalant bronchodilator therapy. Other baseline characteristics and medical treatment for PH in both the groups were similar.

Efficacy and Safety of BPA

Table 2 shows the efficacy of BPA on hemodynamic parameters, respiratory function and oxygenation, and exercise capacity in the COPD and non-COPD groups. Mean PAP decreased significantly in both groups (COPD: 36.1±9.6 mm Hg to 21.6±5.8 mm Hg; P<0.001, and non-COPD: 36.5±10.1 mm Hg to 19.3±3.9 mm Hg, P<0.001). PVR also decreased (COPD: 763±447 dyne/s per cm^{-5} to 281±186 dyne/s per cm^{-5}, P<0.001, and non-COPD: 726±383 dyne/s per cm^{-5} to 247±98 dyne/s per cm^{-5}, P<0.001). The decrease in mean PAP (–14.4±10.5 mm Hg versus –17.0±10.1 mm Hg, P=0.226) and the percent decrease in PVR (–55.6±29.0% versus –58.9±21.4%, P=0.495) in the COPD and the non-COPD groups, respectively, were nearly similar. The %VC did not improve in the COPD group; however, significant improvement was observed in the non-COPD group (90.6±16.0%

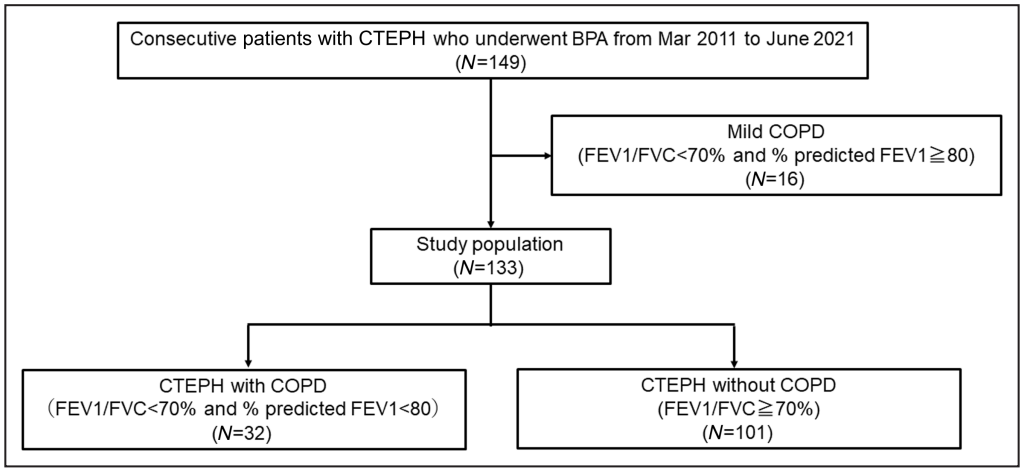

Figure 1. Patients study cohort.
BPA indicates balloon pulmonary angioplasty; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; FEV1, forced expiratory volume in 1 second; and FVC, forced vital capacity.

Table 1. Baseline Characteristics of the Patient Population

Variable	Overall population (n=133)	COPD group (n=32)	Non-COPD group (n=101)	*P* value*
Baseline characteristics				
Age, y	68±11	68±11	68±12	0.925
Men (n, %)	30 (23%)	8 (25%)	22 (22%)	0.707
BMI, kg/m^2	23.4±3.6	23.1±3.4	23.4±3.6	0.660
NYHA FC (I, II/III, IV) (%)	29/71	22/78	32/68	0.288
Previous DVT (n, %)	28 (21%)	9 (36%)	19 (19%)	0.264
Previous acute PE (n, %)	42 (32%)	9 (36%)	33 (33%)	0.633
Smoking (current past), (n, %)	44 (33%)	24 (75%)	20 (20%)	<0.001
Comorbidities				
Hypertension (n, %)	35 (26%)	7 (22%)	28 (28%)	0.513
Diabetes (n, %)	22 (17%)	6 (19%)	16 (16%)	0.700
Atrial fibrillation (n, %)	10 (8%)	3 (9%)	7 (7%)	0.448
Coronary artery disease (n, %)	5 (4%)	1 (3%)	4 (4%)	0.653
Malignant tumor (n, %)	22 (17%)	4 (13%)	18 (18%)	0.480
Exercise capacity				
6MWD (m)	320±101	289±86	331±103	0.042
Baseline SpO_2 (%)	94.5±2.7	94.0±3.1	94.6±2.5	0.284
Minimum SpO_2 (%)	86.6±5.2	85.0±6.3	87.1±4.7	0.039
Peak VO_2 in CPET (mL/min per kg)	12.9±4.2	13.2±3.7	12.8±4.3	0.672
Ventilation/VCO_2 slope in CPET	41.0±11.8	44.2±12.9	40.2±11.5	0.169
VD/VT in CPET	0.18±0.09	0.22±0.09	0.17±0.09	0.023
Ventilation max/MVV in CPET	0.61±0.22	0.79±0.25	0.57±0.19	<0.001
Inhalant bronchodilator				
ICS/LABA (n, %)		8 (25%)	0 (0%)	<0.001
LABA (n, %)		4 (13%)	0 (0%)	0.003
LAMA (n, %)		6 (19%)	0 (0%)	<0.001
Ambulatory oxygen therapy (n, %)	64 (48%)	16 (50%)	48 (48%)	0.809
PH medical treatment at baseline				
sGC stimulator (n, %)	65 (49%)	14 (44%)	51 (50%)	0.510
ERA (n, %)	21 (16%)	6 (19%)	15 (15%)	0.601
PDE5-i (n, %)	13 (10%)	6 (19%)	7 (7%)	0.058
Prostacyclin analog (n, %)	13 (10%)	3 (9%)	10 (10%)	0.617

Data are given as mean±SD. 6MWD indicates 6-minute walk distance; BMI, body mass index; CPET, cardiopulmonary exercise testing; DVT, deep venous thrombosis; ERA, endothelin-receptor antagonists; ICS, inhaled corticosteroid; LABA, long acting beta agonists; LAMA, long acting muscarinic antagonist; MVV: maximal voluntary ventilation; NYHA FC, New York Heart Association functional class; PDE5-i: phosphodiesterase type-5 inhibitors; PE, pulmonary embolism; sGC, soluble guanylate cyclase; SpO_2, percutaneous oxygen saturation; VCO_2, carbon dioxide production; VD/VT, dead-space gas volume to tidal volume ratio; and VO_2, oxygen uptake.

*Comparison between a chronic obstructive pulmonary disease group and a non-chronic obstructive pulmonary disease group.

to 94.7±15.7%, *P*=0,003). FEV1/FVC improved in the COPD group (61.8±7.0% to 66.5±10.2%, *P*=0.021); however, no improvement was observed in the non-COPD group. Oxygenation (PaO_2) improved significantly (60.9±10.6 mm Hg to 69.3±13.6 mm Hg, *P*=0.007, and 61.3±13.0 mm Hg to 70.1±11.3 mm Hg, *P*<0.001, in the COPD and non-COPD groups, respectively), and patients with ambulatory oxygen therapy decreased significantly in both groups. Exercise capacities based on the distance walked on the 6MWT and cardiopulmonary exercise testing also improved in both groups.

In the safety analysis, severe lung injury with hemoptysis requiring noninvasive or invasive mechanical ventilation occurred in 2 sessions (1.6% of all sessions in 32 patients) of BPA in the COPD group, and in 12 sessions (3.0% of all sessions in 101 patients) in the non-COPD group. The incidence of severe lung injury did not differ between the groups (*P*=0.535).

Survival

During a median follow-up period of 37.9 (interquartile range, 20.7–72.9) months, 2 of the 32 patients with COPD (6.3%) and 7 of the 101 patients with non-COPD

Table 2. Hemodynamic and Respiratory Function Results After BPA in Patients With CTEPH With COPD and Without COPD

Variable	COPD group (n=32)			Non-COPD group (n=101)		
	Baseline	After BPA	*P* value	Baseline	After BPA	*P* value
Hemodynamics						
Mean RAP, mm Hg	5.4±3.6	4.9±3.9	0.749	4.7±3.6	3.9±2.7	0.097
Systolic PAP, mm Hg	62.5±16.4	36.3±9.8	<0.001	65.2±19.2	32.7±7.8	<0.001
Diastolic PAP, mm Hg	22.0±7.1	13.1±4.6	<0.001	20.5±6.7	11.1±3.6	<0.001
Mean PAP, mm Hg	36.1±9.6	21.6±5.8	<0.001	36.5±10.1	19.3±3.9	<0.001
PAWP, mm Hg	8.1±3.0	9.2±3.2	0.048	8.0±3.5	8.4±3.5	0.369
Cardiac index, L/min per m^2	2.1±0.6	2.5±0.7	0.012	2.3±0.8	2.5±0.7	0.025
PVR, dyne/s per cm^{-5}	763±447	281±186	<0.001	726±383	247±98	<0.001
SvO_2 (%)	62.0±7.6	68±5.7	<0.001	64.6±8.6	69.0±5.3	<0.001
Absolute change of mean PAP		−14.4±10.5			−17.0±10.1	0.226*
% Decrease of PVR		−55.6±29.0			−58.9±21.4	0.495*
Respiratory functions and oxygenation						
%VC (%)	81.1±17.8	83.4±17.0	0.413	90.6±16.0	94.7±15.7	0.003
%FEV1 (%)	61.0±12.9	71.6±18.9	0.002	89.0±16.7	94.6±17.2	0.001
FEV1/FVC (%)	61.8±7.0	66.5±10.2	0.021	78.2±5.7	76.9±6.1	0.100
%DLCO (%)	58.2±13.0	53.4±13.4	0.031	67.3±16.2	63.6±17.0	0.175
SaO_2 (%)	90.8±4.6	92.9±4.9	0.002	91.0±4.7	94.1±2.9	<0.001
PaO_2 (mm Hg)	60.9±10.6	69.3±13.6	0.007	61.3±13.0	70.1±11.3	<0.001
$PaCO_2$ (mm Hg)	38.4±5.7	39.6±5.1	0.120	36.9±5.1	38.7±4.8	0.009
A-aDO_2 (mm Hg)	47.4±33.4	34.6±29.5	0.029	45.7±20.7	35.6±24.4	0.004
Ambulatory oxygen therapy (n, %)	16 (50%)	9 (28%)	0.006	48 (48%)	30 (30%)	<0.001
Cardiopulmonary exercise test						
6MWD	289±86	354±125	0.004	331±103	383±102	<0.001
Peak VO_2 in CPET (ml/min per kg)	13.2±3.7	16.2±4.7	0.015	12.8±4.3	16.2±4.6	<0.001
Ventilation /VCO_2 slope in CPET	44.2±12.9	30.9±5.3	<0.001	40.2±11.5	27.2±5.7	<0.001
VD/VT in CPET	0.22±0.09	0.17±0.07	0.032	0.17±0.09	0.14±0.09	0.018
Ventilation max/MVV in CPET	0.79±0.25	0.65±0.21	0.185	0.57±0.19	0.50±0.19	0.030

Data are given as mean±SD. Data are given as mean±SD. %DLCO indicates percent predicted diffusing capacity for lung carbon monoxide; %FEV1, percent predicted forced expiratory volume in 1 second; %VC, percent predicted vital capacity; 6MWD, 6-minute walk distance; A-aDO_2, alveolar-arterial difference for oxygen; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MVV, maximal voluntary ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; VCO_2, carbon dioxide production; VD/VT, dead-space gas volume to tidal volume ratio; and VO_2, oxygen uptake.

*Comparison between chronic obstructive pulmonary disease group and the non-chronic obstructive pulmonary disease group.

(6.9%) passed away. Both patients died of malignant tumor in the COPD group, and in the non-COPD group, 4 patients died of malignant tumor, and 3 died of pneumonia, sepsis, and severe aortic stenosis. No patients died of right heart failure or COPD. The 1- and 5-year survival rates of patients with COPD were 100% and 93.5%, compared with 98.0% and 93.0%, in patients with non-COPD (*P*=0.734 by the Cox–Mantel log-rank test) (Figure 2).

Predictors of Improvement in Oxygenation in Patients With COPD

Table 3 summarizes the results of linear regression analysis of the association between the clinical variables before BPA and the improvement in PaO_2 after BPA in patients with COPD. In univariate analysis, higher %VC, higher %DLCO, and lower PaO_2 at baseline were significantly associated. Four baseline respiratory variables (%VC, FEV1/FVC, %DLCO, and PaO2) served as the only candidate predictors in multivariable modeling based on clinical considerations, as no additional variables gave *P* value <0.20 in univariate analyses. After performing stepwise variable selection, %VC (adjusted *P*=0.024) and %DLCO (adjusted *P*=0.028) were retained in the final model. Higher %VC and %DLCO at baseline were associated with greater improvement in oxygenation after BPA (adjusted R-square=0.471). However, COPD severity such as FEV1/FVC was not associated in both analyses.

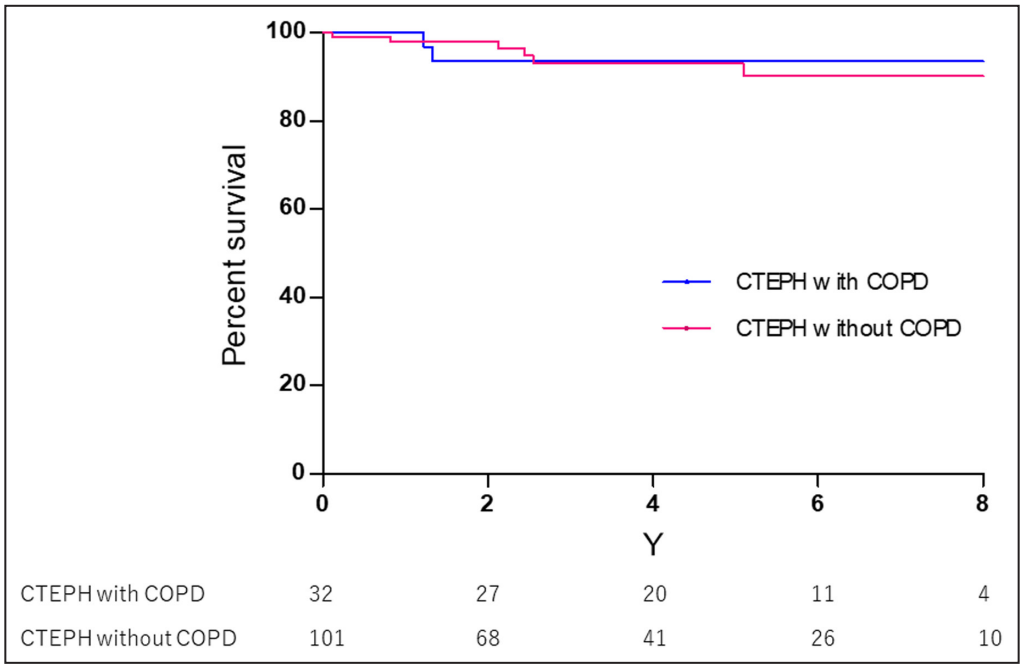

Figure 2. Kaplan–Meier estimates of 8-year survival in patients with chronic thromboembolic pulmonary hypertension (n=32) with concurrent chronic obstructive pulmonary disease (blue line) and patients with chronic thromboembolic pulmonary hypertension without chronic obstructive pulmonary disease (n=101) (red line); *P*=0.734 (Cox–Mantel log-rank test).
COPD indicates chronic obstructive pulmonary disease; and CTEPH, chronic thromboembolic pulmonary hypertension.

DISCUSSION

In this study, the efficacy and safety of BPA in patients with CTEPH and concurrent COPD were similar to those in patients without COPD. BPA also improved oxygenation and FEV1/FVC without exacerbation of ventilation-perfusion mismatch. BPA could be considered as an effective and safe treatment method for patients with nonoperable CTEPH and comorbid COPD.

COPD and CTEPH

CTEPH is categorized in Group 4, and PH because of lung disease including COPD is in Group 3 according

Table 3. Associations Between Improvement of Oxygenation After BPA and Each Clinical Parameter at Baseline in COPD

	Univariate				Multivariable			
Variable	Unstandardized B	SE of B	95% CI for B	*P* value	Unstandardized B	SE of B	95% CI for B	*P* value
Patient characteristics								
Age, y	−0.118	0.270	−0.670 to 0.434	0.666				
Respiratory parameters								
%VC (%)	0.323	0.158	0.001 to 0.646	0.049	0.368	0.154	0.051 to 0.684	0.024
FEV1/FVC (%)	0.338	0.425	−0.531 to 1.206	0.433				
%DLCO (%)	0.680	0.192	0.285–1.074	0.001	0.465	0.200	0.055 to 0.874	0.028
PaO_2 (mm Hg)	−0.877	0.233	−1.354 to −0.401	0.001				
Hemodynamics								
Mean PAP (mm Hg)	0.095	0.310	−0.538 to 0.728	0.760				
Cardiac index (L/min per m^2)	3.308	5.215	−7.343 to 13.959	0.531				
PVR (dyne/sec per cm^{-5})	−0.002	0.007	−0.016 to 0.012	0.755				

%DLCO indicates percent predicted diffusing capacity for lung carbon monoxide; %VC, percent predicted vital capacity; BPA, balloon pulmonary angioplasty; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO_2, partial pressure of arterial oxygen; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VCO_2, carbon dioxide production; and VO_2, oxygen uptake.

to the clinical classification of PH. PH because of COPD may develop because of the loss of vasculature resulting from hyperinflation and hypoxic vasoconstriction of the small pulmonary arteries.[19] However, most patients with stable COPD do not have PH or exhibit mild-to-moderate PH with an average mean PAP of 20.3±8.1 mm Hg, and the prevalence of severe PH (mean PAP>40 mm Hg) was low (2%–3%).[11] COPD is considered as one of the medical conditions associated with CTEPH; the comorbidity rate of CTEPH in COPD was 0.2%,[11] whereas the comorbidity rate of COPD in CTEPH was 10% to 23% in the international CTEPH registry.[20,21] Therefore, factors of Group 4 appear to contribute considerably to PH in patients with CTEPH and concurrent COPD. The treatment algorithm for CTEPH was updated at the 6th World Symposium on PH at Nice, France in 2018; after an assessment by a multidisciplinary CTEPH expert team; patients judged operable undergo pulmonary endarterectomy, patients judged nonoperable are treated with medical therapy with or without BPA. Interventional treatment including PEA for operable and BPA for nonoperable CTEPH have been established treatment strategies.[4] However, the efficacy and safety of interventional treatment for CTEPH with comorbid COPD had not been well evaluated. Kamenskaya et al reported the impact of comorbid COPD on the outcomes of PEA in a study involving 136 patients with operable CTEPH. In that study, 49 patients (23%) had COPD, and the presence of COPD was a significant negative risk factor for adverse PEA outcomes, including increased risk of complications, prolonged duration of hospitalization, the risk of residual PH, and the risk of in-hospital mortality in the early postoperative period of PEA.[20] Comorbid respiratory dysfunction can negatively impact the results of surgical intervention, and lead to poor PEA outcomes. Moderate-to-severe COPD is one of the causes of nonoperability, even if the type of the organized thrombus is deemed operable.[22] However, BPA is not contraindicated in patients with nonoperable CTEPH with moderate-to-severe COPD because it is minimally invasive. Our study demonstrated that the efficacy and safety of BPA for nonoperable CTEPH with comorbid COPD were similar to those in patients without COPD.

Oxygenation in Patients With COPD After BPA

Moreover, BPA improved oxygenation in patients with CTEPH and comorbid COPD (PaO_2: 60.9±10.6 mm Hg to 69.3±13.6 mm Hg, P=0.007). The exploratory study that assessed the short-term efficacy of riociguat (a soluble guanylate cyclase stimulator) for 22 patients with PH associated with COPD demonstrated a moderate decrease in PaO_2, despite hemodynamic improvement.[23] A small randomized controlled trial of bosentan (endothelin receptor antagonist) involving 30 patients with severe COPD demonstrated that PaO_2 decreased from 65.2 mm Hg to 58.8 mm Hg, alveolar-arterial oxygen difference increased from 31.4 mm Hg to 42.0 mm Hg, and the quality of life deteriorated significantly in patients treated with bosentan 4 weeks after initiation.[24] Pulmonary vasodilators have the potential risk of increasing ventilation-perfusion mismatch and worsening the oxygenation in patients with COPD. In the present study, elevated minute ventilation/carbon dioxide production (ventilation/VCO_2) in the cardiopulmonary exercise test, which is a marker of ventilatory inefficiency and reflects ventilation-perfusion mismatch,[25] and alveolar-arterial oxygen difference, which is a marker of ventilation-perfusion mismatch and lung diffusing capacity, also improved after BPA in patients with COPD (44.2±12.9 to 30.9±5.3; P<0.001, 47.4±33.4 mm Hg to 34.6±29.5 mm Hg; P=0.029, respectively). Various factors including dead space ratio, intrapulmonary shunt ratio, and microvasculopathy may be involved in oxygenation after BPA.[16,26,27] However, our data indicated that BPA could improve hemodynamics and oxygenation in patients with CTEPH and moderate or severe COPD without exacerbating the ventilation-perfusion mismatch.

The present study also demonstrated that higher %VC and higher DLCO at baseline were independently associated with the improvement in PaO_2 after BPA in patients with COPD; however, baseline FEV1/FVC was not. The severity of COPD was not associated with the improvement in oxygenation after BPA, whereas patients with CTEPH and comorbid COPD who had restrictive ventilatory impairment exhibited poor improvement in oxygenation after BPA.

Patients with COPD have lower DLCO compared with patients with non-COPD because of increased ventilation-perfusion mismatch or decreased alveolar gas exchange area attributable to hyperinflation. A lower DLCO was strongly associated with the severity, exacerbation risk, emphysema dominance, and COPD mortality according to a meta-analysis of 43 studies.[19] Several studies have reported the clinical implication of DLCO in patients with CTEPH. A lower DLCO was associated with poor outcomes in nonoperable CTEPH who were treated medically in a study involving 89 patients.[28] Lower baseline DLCO was associated with a higher in-hospital mortality in 136 patients with CTEPH who underwent PEA.[20] A low baseline DLCO was associated with BPA failure in a study of 101 patients in the French BPA registry.[29] Onishi et al reported that patients with CTEPH with lower DLCO had more severe PVR, which was disproportionate to lung perfusion blood volume quantified by dual-energy computed tomography.[30] A lower DLCO may suggest the existence of small vessel disease in CTEPH. Although it is widely recognized that small vessel disease may contribute

to the development and progression of CTEPH,[31,32] it remains a resistant and incurable condition even when near-normal hemodynamics are achieved, because it cannot be accessed by BPA. Oxygenation occurs in the distal pulmonary arterioles and capillaries; therefore, patients with COPD with low DLCO exhibited poor improvement in oxygenation even after BPA.

Another finding of this study is that BPA could improve FEV1/FVC in patients with COPD without increasing the dose of the bronchodilators. Takei et al reported that respiratory function including total lung capacity, functional residual capacity, and peak expiratory flow improved after BPA; however, residual volume, FEV1/FVC, and DLCO did not change in the study involving 55 patients. In that study, baseline FEV1/FVC was 87.3% (range, 83.1%–93.9%), which reflected preserved lung function.[33] Yanagisawa et al demonstrated that the pulmonary vascular obstruction score evaluated using computed tomography negatively correlated with %FEV1 in CTEPH, and mean PAP markedly decreased in the patients whose %FEV1 improved remarkably after PEA. They speculated that respiratory obstructive impairment may have an etiological relationship with vascular obstruction.[34] Our study demonstrated the possibility that impaired FEV1/FVC may be improved by BPA for CTEPH with comorbid COPD, although the precise mechanism remains unclear.

BPA should be recommended as a useful treatment option for patients with nonoperable CTEPH and comorbid COPD. The efficacy and safety were also demonstrated in patients with non-COPD, along with an improvement in FEV1/FVC.

Limitations

The main limitation of this study is its single-center, retrospective, observational nature. Therefore, the occurrence of some missing values was unavoidable and could have influenced the results in the multivariable regression model. Further, the cohort was relatively small. It cannot be denied that less experience with the procedure in the initial stages of our BPA program could have affected BPA outcomes. Moreover, the majority of the patients in the COPD group had moderate COPD, and patients with severe or very severe COPD were relatively few.

CONCLUSIONS

The efficacy and safety of BPA in patients with nonoperable CTEPH and concurrent COPD were similar to those in patients without COPD, and the hemodynamics nearly normalized despite comorbid COPD. BPA could also improve oxygenation and FEV1/FVC without exacerbation of ventilation-perfusion mismatch. In our experience, higher baseline DLCO was strongly associated with the improvement in oxygenation after BPA, however, the severity of COPD was not. BPA could be considered as an effective and safe treatment method for patients with nonoperable CTEPH and comorbid COPD.

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