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RESEARCH ARTICLE

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Balloon pulmonary angioplasty for chronic thromboembolic pulmonary disease without pulmonary hypertension

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Abstract

Balloon pulmonary angioplasty (BPA) is beneficial for patients with chronic thromboembolic pulmonary disease (CTEPD) with pulmonary hypertension (PH). However, the clinical benefit of BPA for the patients with CTEPD without PH remains unknown. In this study, we aimed to evaluate the efficacy, safety, and long-term outcomes of BPA in patients with CTEPD without PH. We retrospectively analyzed the data from 84 CTEPD patients with mean pulmonary artery pressure (mPAP) < 25 mmHg and 39 CTEPD patients with mPAP ≤ 20 mmHg (without PH). Among the 39 patients with CTEPD without PH, 14 underwent BPA (BPA-treated group), and the remaining 25 received no treatment (untreated group). In the patients with CTEPD without PH, BPA led to improvements in symptoms, pulmonary vascular resistance (3.6 ± 1.6 to 2.6 ± 1.1 Wood units, $p < 0.001$), peak oxygen consumption (16.1 ± 4.0 to 18.8 ± 4.3 mL/kg/min, $p = 0.033$), minute ventilation versus carbon dioxide production slope (41.4 ± 12.2 to 35.1 ± 6.7, $p = 0.026$), and mPAP/cardiac output slope (7.0 ± 2.6 to 4.4 ± 2.0 mmHg/L/min, $p = 0.004$) and facilitated the discontinuation of home oxygenation therapy, with no serious complications. Kaplan–Meier analysis showed no significant difference in all-cause mortality between the untreated and BPA-treated groups. BPA may be a safe treatment option for the patients with CTEPD without PH that can alleviate symptoms, improve exercise capacity, and facilitate weaning from home oxygen therapy. Further prospective randomized trials are needed to confirm these findings.

KEYWORDS
balloon pulmonary angioplasty, chronic thromboembolic pulmonary disease, chronic thromboembolic pulmonary hypertension

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Chronic thromboembolic pulmonary disease (CTEPD) with pulmonary hypertension (PH), also known as chronic thromboembolic PH (CTEPH),[1,2] is a fatal pulmonary hypertensive disease caused by unresolved thromboembolic pulmonary obstruction.[3,4] Patients with mean pulmonary artery pressure (mPAP) < 25 mmHg, traditionally classified as chronic thromboembolic disease (CTED), experience dyspnea and exercise limitations.

The strategy for treating patients with symptomatic CTEPD with mild or no PH is only beginning to be addressed. Pulmonary endarterectomy (PEA), the gold standard treatment for CTEPH,[5,6] is considered effective in patients with CTED, with perioperative mortality rates of 0–0.9%.[7–9] Balloon pulmonary angioplasty (BPA), an alternative catheter-based treatment option for CTEPH,[10,11] has safely demonstrated beneficial effects in improving functional status and exercise capacity in patients with CTED.[12,13] Recent PH guidelines have lowered the diagnostic threshold for PH to an mPAP > 20 mmHg.[14] Nevertheless, the clinical benefit of BPA in patients with CTEPD with mPAP ≤ 20 mmHg (i.e., without PH) remains unknown. Therefore, this study aimed to clarify the clinical efficacy, safety, and long-term outcomes of BPA in patients with CTEPD without PH.

METHODS

Patient selection and measurements

In this single-center retrospective study, we included 84 patients diagnosed with CTEPD with mPAP < 25 mmHg who were admitted to the National Cerebral and Cardiovascular Center between November 2002 and October 2023. The absence of PH was defined as mPAP ≤ 20 mmHg according to the current guidelines.[14] The study protocol is shown in Figure 1. All patients underwent right heart catheterization (RHC), pulmonary angiography, and pulmonary perfusion scintigraphy. Adequate anticoagulation therapy was maintained before BPA for at least 3 months and was continued thereafter. The study protocol was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (R20075-3). Written informed consent was obtained from BPA-treated patients, and approval was granted through an opt-out option for patients who did not undergo BPA.

Measurements

RHC and clinical measurements were performed before the first BPA session at baseline and at least 3 months after the final session during the follow-up period. RHC was performed to measure mPAP, pulmonary arterial wedge pressure, mean right atrium pressure, cardiac output (CO) via the indirect Fick method, and pulmonary vascular resistance (PVR). Pulmonary arterial wedge pressure and mPAP were measured at the end of expiration. The cardiac index was determined using the indirect Fick method and corrected for the body surface area. Clinical assessments, including clinical parameters, brain natriuretic peptide level, and 6-min walk distance (6MWD), were performed simultaneously.

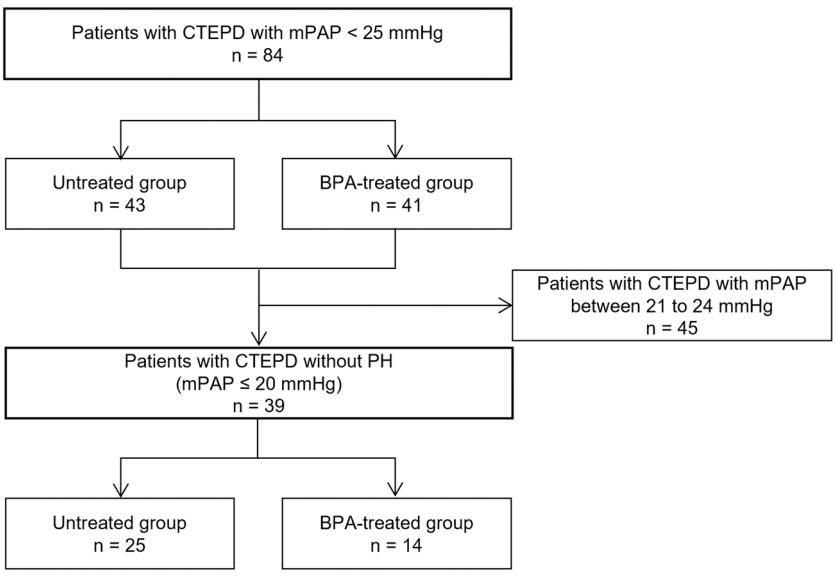

FIGURE 1 Protocol of this study. BPA, balloon pulmonary angioplasty; CTEPD, chronic thromboembolic pulmonary disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension.

Cardiopulmonary exercise tests (CPET)

The exercise ventilatory pattern at peak VO_2 was evaluated using the symptom-limited CPET during incremental exercise testing on an upright cycle ergometer, as previously reported.[15] The test started with a 2-min rest period, followed by a 1-min warm-up performed at 0-W intensity using the mask method. After the warm-up, the exercise intensity was increased continuously at a rate of 1.5–1 W every 6 s until exhaustion. VO_2, carbon dioxide production (VCO_2), and minute ventilation (VE) were measured using a gas analyzer (MINATO AE-310S; Minato Science Co., Ltd.). Peak VO_2 was determined at the highest exercise intensity.[16] Before the respiratory compensation point, the VE versus VCO_2 slope was measured as a linear relationship between VE and VCO_2.[17]

RHC and CPET

At a different time from the standard CPET, exercise RHC was performed as needed. Incremental symptom-limited CPET was performed in the supine position using a magnetically braked cycle ergometer, and RHC was performed using a 6-Fr double-lumen balloon-tipped flow-directed Swan–Ganz catheter via a transjugular approach. During cycling, the legs were elevated. The test comprised a 3-min rest period, followed by a 3-min warm-up at an ergometer setting of 0 W, and testing with a 20-W increase in exercise load every 3 min. During the exercise, VO_2, VCO_2, and VE oxygen consumption were measured using a gas analyzer (MINATO AE-310S; Minato Science Co., Ltd.). The heart rate and arterial blood pressure were recorded directly from the radial artery. PAP and pulmonary arterial wedge pressure during RHC were measured every 3 min. Arterial oxygen saturation in the radial artery and mixed venous oxygen saturation in the pulmonary artery were measured at rest and every 3 min. CO was determined using the direct Fick method. All measurements during exercise testing were performed without supplemental oxygen. The slope of the mPAP/CO was calculated from the multipoint plots of mPAP and CO using least-squares linear regression.

BPA PROCEDURE

Patients were considered inoperable if they had distal, surgically inaccessible thrombi or severe concomitant medical comorbidities at the discretion of the CTEPH team at our center that included cardiologists, radiologists, and surgeons. BPA was performed for inoperable patients, who had World Health Organization (WHO) functional class II or higher and peak VO_2 (% predicted) < 80%, mPAP/CO slope > 3.0, or were using home oxygen therapy. BPA was performed as described previously.[18,19] Target vessels were selected using preoperative contrast-enhanced computed tomography and pulmonary angiography. BPA was performed through the right femoral or internal jugular vein using a 6-F long sheath (BRITE TIP sheath introducer; Cordis). We selectively introduced a 6-F multipurpose guiding catheter (Mach1 Peripheral MP; Boston Scientific) or 6-F Ikari Left catheter (Terumo) with a soft-tipped 0.035-in. wire (Radifocus Guide Wire M; Terumo) into the target vessel. The target lesions were dilated with a balloon (Ikazuchi; KANEKA) using a 0.014-in. wire (B-Pahm; JAPAN LIFELINE Co.; or Cruise; Asahi Intec). The appropriate balloon size (2.0–4.0 mm) was selected based on the targeted vessel diameter measured on computed tomography in addition to angiographic findings. BPA was repeated until no more treatable lesions were detected angiographically. Complications included hemoptysis, wire perforation, reperfusion edema, pulmonary artery dissection, and periprocedural death.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and were compared using the Student's *t*-test, Wilcoxon rank-sum test, or Mann–Whitney *U* test. Categorical variables are expressed as counts and percentages and were compared using the χ^2 test. We analyzed the group of patients with CTEPD with mPAP < 25 mmHg and without PH (mPAP ≤ 20 mmHg). Kaplan–Meier analysis was used to assess the survival rate of any adverse events between the BPA-treated and untreated groups. The log-rank test was used for initial comparisons. All statistical analyses were performed using the SPSS version 29 software (IBM Corp.), and statistical significance was set at $p < 0.05$.

RESULTS

Patients' baseline characteristics

Baseline characteristics of the patients are presented in Table 1. Among 84 patients with CTEPD with mPAP < 25 mmHg, 39 had an mPAP ≤ 20 mmHg. Of

TABLE 1 Baseline characteristics.

Characteristics	Patients with CTEPD with mPAP < 25 mmHg	Patients with CTEPD without PH(mPAP ≤ 20 mmHg)
Number	84	39
Age, years	61.3 ± 14.4	58.0 ± 15.2
Female	55 (65%)	24 (62%)
Body mass index	23.1 ± 4.1	23.1 ± 4.6
BNP, pg/mL	19 [12.8, 49.0]	17 [11, 48]
6MWD, m	436.2 ± 105.8	451.8 ± 103.6
WHO functional class		
I	0	0
II	75 (89%)	38 (97%)
III	9 (10%)	1 (3%)
IV	0	0
%DLCO, %	77.6 ± 18.5	78.5 ± 16.3
Home oxygen therapy	18 (21%)	4 (10%)
Echocardiography		
RVDd, mm	31.0 ± 6.7	30.4 ± 5.7
TAPSE, mm	20.6 ± 3.6	21.2 ± 4.1
Tricuspid annulus s' velocity, cm/s	11.1 ± 2.2	11.2 ± 2.1
Treatment		
BPA	41 (48%)	14 (36%)
No-treatment	43 (51%)	25 (64%)
Risk factors and history		
Acute pulmonary embolism	30 (35%)	14 (36%)
Thrombophilic disorder	10 (12%)	3 (8%)
Cancer history	6 (7%)	3 (8%)
Mental disorder	9 (11%)	4 (10%)
Splenectomy	2 (2%)	2 (5%)
Hemodynamics		
mPAP, mmHg	19.9 ± 3.2	17.0 ± 2.5
PAWP, mmHg	6.1 ± 3.3	6.0 ± 3.6
RAP, mmHg	2.4 ± 2.1	2.3 ± 2.0
Cardiac index, L/min/m^2	2.4 ± 0.6	2.4 ± 0.7
PVR, Wood units	3.8 ± 1.7	3.0 ± 1.5
SaO_2, %	93.8 ± 4.6	94.6 ± 5.5
SvO_2, %	69.0 ± 6.8	71.6 ± 7.0

Note: Values are presented as mean ± SD, median [interquartile range] or *n* (%).

Abbreviations: 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CTEPD, chronic thromboembolic pulmonary disease; DLCO, diffusing capacity of lung for carbon monoxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrium pressure; RVDd; right ventricular end-diastolic diameter; SaO_2, atrial oxygen saturation; SvO_2, mixed venous oxygen saturations; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

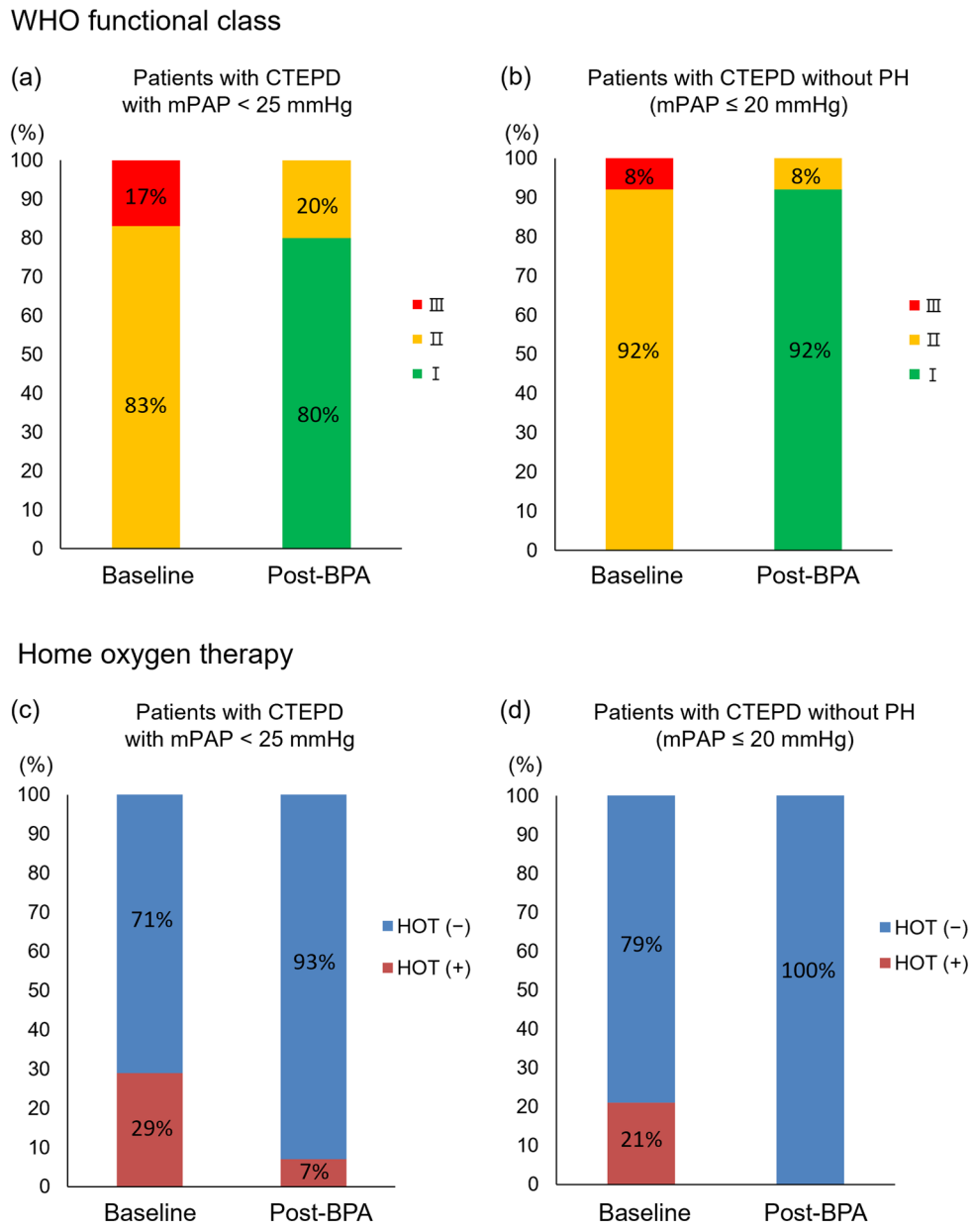

FIGURE 2 Comparison of the ratio of WHO functional class and HOT at baseline and post-BPA. (a) WHO functional class in patients with CTEPD with mPAP < 25 mmHg, (b) WHO functional class in patients with CTEPD without PH (mean PAP ≤ 20 mmHg), (c) HOT in patients with CTEPD with mPAP < 25 mmHg, (d) HOT in patients with CTEPD without PH (mPAP ≤ 20 mmHg). BPA, balloon pulmonary angioplasty; CTEPD, chronic thromboembolic disease; HOT, home oxygen therapy; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; WHO, World Health Organization.

these 84 patients with CTEPD, 41 underwent BPA, and the remaining 43 received no treatment. Within the group of 39 patients with CTEPD without PH, 14 underwent BPA, and the remaining 25 received no treatment. We compared the baseline characteristics between the untreated and BPA-treated groups in the entire cohort (Supporting Information S1: Table 1) as well as in the group of patients with CTEPD without PH (Supporting Information S1: Table 2).

Changes in parameters after BPA in patients with CTEPD with mPAP < 25 mmHg

All patients who underwent BPA received anticoagulation therapy before the initiation of BPA for more than 3 months, with a median anticoagulation duration of 16 months [interquartile range, 9–32 months]. The mean follow-up time after BPA was 4.5 months. In patients

TABLE 2 Comparison of clinical parameters and hemodynamics at baseline and follow-up after BPA in patients with CTEPD with mPAP < 25 mmHg.

Characteristics	Baseline ($n = 41$)	Follow-up ($n = 41$)	p Value
BNP, pg/mL	19.6 [12.8, 50.6]	20.0 [11.9, 35.4]	0.198
6MWD, *m*	437.5 ± 119.9	470.1 ± 124.8	0.038
%DLCO, %	78.0 ± 14.7	79.3 ± 16.3	0.356
Home oxygen therapy	12 (29%)	3 (7%)	0.010
WHO functional class			<0.001
I	0	33 (80%)	
II	34 (83%)	8 (20%)	
III	7 (17%)	0	
IV	0	0	
Hemodynamics ($n = 35$)			
mPAP, mmHg	20.0 ± 3.2	17.1 ± 2.9	<0.001
PAWP, mmHg	5.4 ± 2.9	6.0 ± 2.1	0.155
RAP, mmHg	2.3 ± 1.9	2.8 ± 2.0	0.108
Cardiac index, L/min/m^2	2.2 ± 0.4	2.4 ± 0.5	0.087
PVR, Wood units	4.4 ± 1.6	3.2 ± 1.3	<0.001
SaO_2, %	94.2 ± 3.4	96.0 ± 2.4	<0.001
SvO_2, %	68.6 ± 5.4	70.0 ± 5.0	0.069
CPET ($n = 23$)			
Peak heart rate, bpm	134.0 ± 29.7	142.7 ± 21.8	0.019
Peak work road, Watt	88.6 ± 32.1	102.9 ± 32.7	<0.001
Peak VO_2, mL/kg/min	16.3 ± 3.6	19.1 ± 4.2	<0.001
Predicted peak VO_2, %	69.9 ± 14.8	81.8 ± 15.3	<0.001
VE versus VCO_2 slope	40.9 ± 11.3	34.3 ± 6.1	<0.001
Exercise RHC ($n = 10$)			
mPAP/CO slope	6.4 ± 2.4	4.1 ± 1.8	<0.001
Peak mPAP, mmHg	47.1 ± 8.0	38.8 ± 7.2	0.001
Peak PAWP, mmHg	16.8 ± 4.2	19.2 ± 6.4	0.174
Peak PVR, Wood Units	3.5 ± 1.5	2.2 ± 0.9	0.026
Peak CO, L/min	8.9 ± 1.9	9.6 ± 2.3	0.202

Note: Values are presented as mean ± SD, median [interquartile range], or *n* (%).

Abbreviations: 6MWD, 6-min walk distance; BPA, balloon pulmonary angioplasty; BNP, brain natriuretic peptide; CO, cardiac output; CPET, cardiopulmonary exercise test; CTEPD, chronic thromboembolic pulmonary artery disease; DLCO, diffusing capacity of lung for carbon monoxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrium pressure; RHC, right heart catheterization; SaO2, atrial oxygen saturation; SvO2, mixed venous oxygen saturations; VE, minute ventilation; VCO2, carbon dioxide production; WHO, World Health Organization.

with CTEPD with mPAP < 25 mmHg who underwent BPA ($n = 41$), significant improvements in 6MWD (437.5 ± 119.9 to 470.1 ± 124.8 m, $p = 0.038$), WHO functional class ($p < 0.001$, Figure 2a), mPAP (20.0 ± 3.2 to 17.1 ± 2.9 mmHg, $p < 0.001$), PVR (4.4 ± 1.6 to 3.2 ± 1.3 Wood units, $p < 0.001$), and atrial oxygen saturation at rest (94.2 ± 3.4 to 96.0 ± 2.4%, $p < 0.001$) were observed from baseline to follow-up (Table 2). In addition, the proportion of patients requiring home oxygen therapy decreased from 29% at the initial assessment to 7% at the

TABLE 3 Comparison of clinical parameters at baseline and follow-up after BPA in patients with CTEPD without PH (mPAP ≤ 20 mmHg).

Characteristics	Baseline ($n = 14$)	Follow-up ($n = 14$)	p Value
BNP, pg/mL	17.1 [12.0, 60.0]	19.3 [11.0, 29.3]	0.338
6MWD, *m*	472.0 ± 123.3	492.0 ± 123.3	0.319
%DLCO, %	77.9 ± 10.6	79.2 ± 12.3	0.254
Home oxygen therapy	3 (21%)	0	0.067
WHO functional class			<0.001
I	0	13 (92%)	
II	13 (92%)	1 (8%)	
III	1 (8%)	0	
IV	0	0	
Hemodynamics ($n = 14$)			
mPAP, mmHg	16.4 ± 2.3	15.0 ± 3.4	0.537
PAWP, mmHg	4.6 ± 2.3	5.2 ± 2.3	0.167
RAP, mmHg	2.0 ± 1.7	3.2 ± 2.4	0.066
Cardiac index, L/min/m^2	2.2 ± 0.3	2.4 ± 0.5	0.114
PVR, Wood units	3.6 ± 1.6	2.6 ± 1.1	<0.001
SaO_2, %	95.9 ± 1.9	97.1 ± 2.1	0.057
SvO_2, %	69.9 ± 4.7	70.7 ± 4.9	0.597
CPET ($n = 10$)			
Peak heart rate, bpm	141.3 ± 29.6	143.7 ± 20.1	0.568
Peak work road, W	88.5 ± 39.0	98.7 ± 39.9	0.143
Peak VO_2, mL/kg/min	16.1 ± 4.0	18.8 ± 4.3	0.033
Predicted peak VO_2, %	68.0 ± 14.8	78.5 ± 12.5	0.028
VE versus VCO_2 slope	41.4 ± 12.2	35.1 ± 6.7	0.026
Exercise RHC ($n = 7$)			
mPAP/CO slope	7.0 ± 2.6	4.4 ± 2.0	0.004
Peak mPAP, mmHg	46.2 ± 9.6	37.0 ± 7.5	0.002
Peak PAWP, mmHg	17.2 ± 3.5	19.2 ± 7.6	0.414
Peak PVR, Wood units	3.7 ± 1.7	2.0 ± 0.8	0.020
Peak CO, L/min	8.3 ± 1.8	8.4 ± 1.5	0.768

Note: Values are presented as mean ± SD, median [interquartile range], or *n* (%).

Abbreviations: 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CO, cardiac output; CPET, cardiopulmonary exercise test; CTEPD, chronic thromboembolic pulmonary artery disease; DLCO, diffusing capacity of lung for carbon monoxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrium pressure; SaO_2, atrial oxygen saturation; SvO_2, mixed venous oxygen saturations; RHC, right heart catheterization; VCO2, carbon dioxide production; VE, minute ventilation; WHO, World Health Organization.

follow-up period ($p = 0.010$, Figure 2c). In CPET, improvement in the peak VO_2 (16.3 ± 3.6 to 19.1 ± 4.2 mL/kg/min, $p < 0.001$) and VE/VCO_2 slope (40.9 ± 11.3 to 34.3 ± 6.1, $p < 0.001$) was observed after BPA. In exercise RHC, a significant decrease in peak mPAP (47.1 ± 8.0 to 38.8 ± 7.2 mmHg, $p = 0.001$) and peak PVR (3.5 ± 1.5 to 2.2 ± 0.9 Wood units, $p = 0.026$) and improvement in the mPAP/CO slope (6.4 ± 2.4 to 4.1 ± 1.8 mmHg/L/min, $p < 0.001$) was observed after BPA.

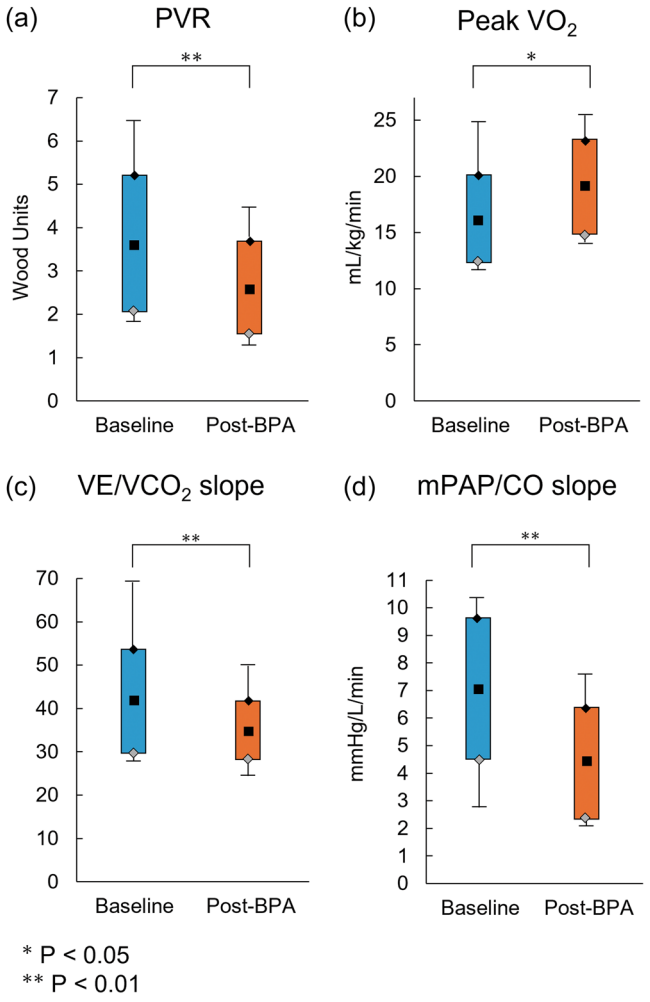

FIGURE 3 Comparison of clinical parameters at baseline and follow-up after BPA in patients with CTEPD without PH (mPAP ≤ 20 mmHg). (a) PVR, (b) Peak VO_2, (c) VE/VCO_2 slope, and (d) mPAP/CO slope. BPA, pulmonary balloon angioplasty; CO, cardiac output; CTEPD, chronic thromboembolic pulmonary disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; VCO_2, carbon dioxide production; VE, minute ventilation.

Changes in parameters after BPA in patients with CTEPD without PH (mPAP ≤ 20 mmHg)

Table 3 shows the changes in parameters after BPA in patients with CTEPD without PH ($n = 14$); the summary is presented in Figure 3. All patients who previously required home oxygen therapy were able to discontinue its use (Figure 2d); significant improvements in WHO functional class ($p < 0.001$; Figure 2b) and PVR (3.6 ± 1.6 to 2.6 ± 1.1 Wood units, $p < 0.001$) were observed. In CPET, the peak VO_2 increased (16.1 ± 4.0 to 18.8 ± 4.3 mL/kg/min, $p = 0.033$), and the VE/VCO_2 slope improved (41.4 ± 12.2 to 35.1 ± 6.7, $p = 0.026$). In exercise RHC, significant improvements in peak mPAP (46.2 ± 9.6 to 37.0 ± 7.5 mmHg, $p = 0.002$), peak PVR (3.7 ± 1.7 to 2.0 ± 0.8 Wood units, $p = 0.020$), and mPAP/CO slope (7.0 ± 2.6 to 4.4 ± 2.0 mmHg/L/min, $p = 0.004$) were observed after BPA.

Long-term outcomes between BPA-treated and untreated groups

During a median follow-up period of 48.9 months (interquartile range, 11.8–110.9 months), four patients (one in the BPA-treated group and three in the untreated group) experienced composite all-cause death. The cause of death was not related to cardiopulmonary comorbidities. No cases of hospitalization for worsening PH, decompensated right heart failure, or additional BPA procedures were reported. Kaplan–Meier analysis showed that the all-cause mortality was not significantly different between the untreated and BPA-treated groups in the overall cohort (Figure 4a) and in the group of patients with CTEPD without PH (Figure 4b).

BPA complications

Overall, two complications (1.3%) occurred in a total of 147 sessions, including one case of wire perforation and one case of hemoptysis. None of the complications were serious, and no instance of periprocedural death was reported. No complications were observed in the group of patients with CTEPD without PH.

DISCUSSION

Our study showed that (1) BPA was effective and safe in alleviating symptoms, reducing exercise intolerance, facilitating weaning from home oxygen therapy, and improving the degree of exercise PH in patients with CTEPD without PH and (2) the BPA-treated group showed no survival benefit over the BPA-untreated group. Therefore, BPA is considered a viable option for patients with CTEPD without PH to relieve symptoms, improve exercise intolerance, or discontinue home oxygen therapy.

BPA had significant beneficial effects in alleviating symptoms and improving exercise capacity in symptomatic patients with CTEPD without PH. Patients with CTED experience a degree of functional impairment similar to that of patients with CTEPH.[20] In an observational study including nine patients with CTED, PEA improved exercise capacity and hemodynamics,

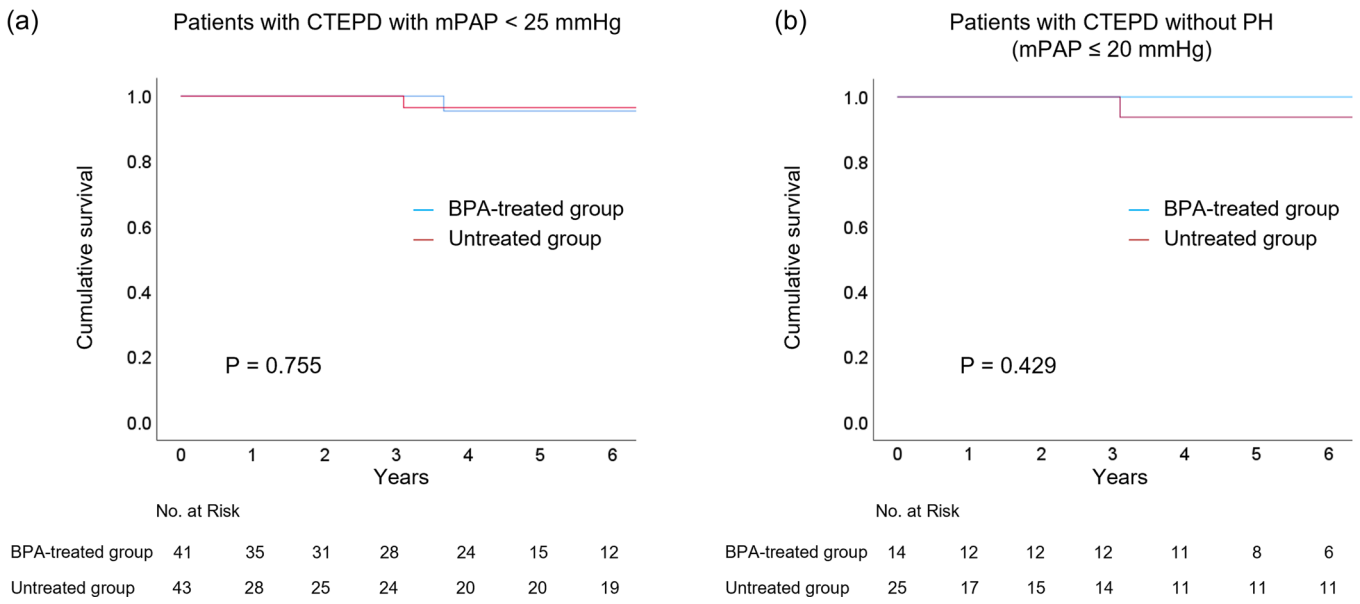

FIGURE 4 Kaplan–Meier analysis for all-cause mortality between BPA-treated and untreated groups. (a) Patients with CTEPD with mPAP < 25 mmHg. (b) Patients with CTEPD without PH (mPAP ≤ 20 mmHg). BPA, balloon pulmonary angioplasty; CTEPD, chronic thromboembolic pulmonary disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension.

and all the patients were reclassified to WHO FC I after PEA; their 6MWD had also improved.[9] PEA is a treatment option for patients with symptomatic CTED.[8,21] Previously reported findings on the beneficial effects of BPA on hemodynamics and other clinical parameters in patients with CTED[12,13] are consistent with our findings in patients with CTEPD without PH. The significant reduction in the need for home oxygen therapy after BPA is another clinically important indicator of improved quality of life. In addition, the lower complication rate of BPA in patients with CTEPD without PH observed in our study than that in previous studies on BPA for CTEPH[10,19,22] is reassuring. BPA may be a safe treatment option for patients with CTEPD without PH that can alleviate symptoms, improve exercise capacity, and facilitate weaning from home oxygen therapy.

BPA improved the degree of exercise PH and ventilatory efficiency in patients with CTEPD without PH. Recently, the role of exercise evaluation has become increasingly important in identifying PH in patients who do not exhibit PH at rest.[14,23] Recent guidelines have reintroduced the criteria for exercise PH, defined by the mPAP/CO slope between rest and exercise.[14] Increased pulmonary vascular load during exercise has previously been identified in patients with CTED,[9] and pulmonary vascular obstruction also profoundly affects right ventricular function during exercise.[24] In addition, patients with CTED have reduced ventilatory efficiency compared with healthy controls, partly owing to an increased dead space fraction,[25] which is correlated with disease severity. Some patients who undergo PEA continue to have limited exercise capacity despite normalization of resting PAP and PVR.[24] In the present study, exercise PH or ventilatory insufficiency was investigated to assess underlying hemodynamic abnormalities. Improvements in these parameters have been observed in patients with CTED after BPA,[12] consistent with our findings. The clinically beneficial effects of BPA in patients with CTEPD without PH, such as the improvement in symptoms and exercise capacity in the present study, may be due to the improvement in exercise PH or ventilatory insufficiency rather than the improvement in resting PH.

The present study showed no significant differences in the prognosis of patients with CTEPD without PH who did and did not undergo BPA. Borderline PH, classically defined as an mPAP of 19–24 mmHg, is a common and independent risk factor for adverse clinical outcomes in a large cohort of patients with underlying cardiopulmonary disease, particularly left heart dysfunction or parenchymal lung disease.[26] However, this study did not focus on CTEPD. The mortality of patients with CTEPD with mild or no PH over a median follow-up of 37 months was 8%, which was mainly due to comorbidities, particularly malignancy.[27] The cohort with mild or no PH did not demonstrate disease progression during the 3 years of follow-up based on noninvasive parameters. The natural course of CTEPD with mild or no PH did not worsen, and the prognosis remained favorable. The primary goal of BPA for patients with CTEPD

without PH may be to relieve symptoms rather than improve prognosis. As the long-term prognosis for CTEPD without PH is favorable even without treatment, considering the risk of complications, the decision to proceed with BPA in these patients should be made after a thorough assessment of the individual situation, such as the degree of symptoms, comorbidities, and clinical frailty.

The efficacy of BPA compared with PH-specific drugs was not evaluated in the present study because none of the patients were receiving PH-specific drugs. Riociguat, a soluble guanylate cyclase stimulator, significantly improves the 6MWD and reduces PVR in CTEPH.[28] Selexipag significantly improves PVR and other clinical hemodynamics in patients with CTEPH.[29] In patients with an mPAP of 25 mmHg or less, such oral medications may alleviate symptoms and improve exercise intolerance. Prescribing oral medications to patients with mPAP < 25 mmHg is not currently recommended due to insufficient evidence for this population. Larger-scale prospective studies on the efficacy of PH-specific medication as an alternative to BPA in patients with CTEPD with mPAP < 25 mmHg are needed.

This study had several limitations. First, this was a single center study, which may limit the generalizability of the results to other populations and clinical settings. Second, the retrospective nature of the analysis may have introduced bias related to patient selection and data collection. Finally, the lack of a randomized control group makes it difficult to attribute improvements solely to BPA, as other variables may have influenced the outcomes. Future multicenter, prospective studies with randomized control groups are warranted to validate our findings and further assess the long-term benefits and safety of BPA in this patient population.

In conclusion, BPA significantly alleviated symptoms, reduced exercise intolerance, facilitated the discontinuation of home oxygen therapy, and improved exercise PH in patients with CTEPD without PH. No serious complications were observed after BPA. No survival benefit was observed in the BPA-treated group over the BPA-untreated group. BPA may be a safe treatment option for patients with CTEPD without PH in alleviating symptoms, improving exercise capacity, and facilitating weaning from home oxygen therapy. Further prospective randomized trials are required to confirm these findings.

AUTHOR CONTRIBUTIONS

T. Kiko, R. Asano, and Ogo designed the study. H. Endo, N. Nishi, and H. Hayashi collected the data. T. Kiko, R. Asano, and T. Ogo analyzed the data. All the authors participated in the development of the manuscript, provided final approval for submission, and agreed to be accountable for the integrity of this work.

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CONFLICT OF INTEREST STATEMENT

T. Ogo reports lecture fees from Nippon Shinyaku Co., Ltd. during the conduct of the study and personal fees from Janssen Pharmaceutical K.K., Bayer Yakuhin, Ltd., Nippon Shinyaku Co., Ltd., GlaxoSmithKline K.K., Pfizer Japan Inc., and Mochida Pharmaceutical Co., Ltd., outside the submitted work. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (R20075-3).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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