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Efficacy of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension patients with pulmonary comorbidity

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) is an established treatment for inoperable chronic thromboembolic pulmonary hypertension (CTEPH), but its efficacy in CTEPH patients with a pulmonary comorbidity has not been well-studied. Here, we compared post-BPA outcomes between CTEPH patients with and without chronic pulmonary disease at baseline and analyzed predictors of BPA success.

Methods: From August 2017 to October 2022, 62 patients with inoperable CTEPH who underwent BPA were consecutively enrolled and grouped based on the presence of a pulmonary comorbidity at baseline. All patients underwent transthoracic echocardiography, pulmonary function tests, and right heart catheterization. Pre- and post-BPA data were evaluated to identify factors that influence the success of BPA.

Results: Among the 62 CTEPH patients, BPA was considered successful in 50 patients and unsuccessful in 12 patients. Responders to BPA had better exercise capacity and right heart function at baseline, but no differences in hemodynamic or respiratory function were detected between the groups. In CTEPH patients with chronic pulmonary disease (n = 14), BPA significantly improved mean pulmonary arterial pressure, pulmonary vascular resistance and right heart function parameters. Only CTEPH patients without chronic pulmonary disease (n = 48) exhibited significant improvement in 6-minute walk distance and respiratory function. Multivariate logistic regression analysis showed that pulmonary comorbidity at baseline was independently associated with the efficacy of BPA.

Conclusions: BPA provided significantly improvements in hemodynamics and right heart function in CTEPH patients, independent of pulmonary comorbidity at baseline. However, pulmonary comorbidity can negatively impact post-BPA outcomes.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is categorized within Group 4 in the updated clinical classification of pulmonary hypertension (PH)[1], which is characterized by stenosis and obstruction of pulmonary arteries due to persistent, chronic fibrotic clots [2–4]. As a progressive disease, CTEPH can lead to elevated pulmonary vascular resistance (PVR) and remodeling of pulmonary vessels and the right heart[4,5]. According to previous studies, the 3-year mortality rate among CTEPH patients who do not receive treatment may be as high as 90 %[6]. Pulmonary endarterectomy remains the preferred treatment method for CTEPH. However, this treatment is not suitable in all cases of CTEPH, because of its challenging and technical requirements. Over the past decade, balloon pulmonary angioplasty (BPA) emerged as an alternative treatment for inoperable CTEPH. Some expert centers have confirmed that BPA has an excellent long-term effect, providing significantly improvements in functional status, hemodynamics, and right ventricular (RV) geometry[7,8].

Recent publications indicated that CTEPH typically occurs in older individuals over the age of 50 years who also have basic pulmonary

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diseases, such as chronic obstructive pulmonary disease (COPD), tuberculosis, or lung tumors[9]. Respiratory comorbidities manifest as pulmonary parenchyma or interstitial injury, usually accompanied by impairment of the microvasculature and airways. According to the 2022 European Society of Cardiology/European Respiratory Society guidelines, PH caused by lung diseases and/or hypoxia is classified as Group 3 PH, and pulmonary arterial pressure is generally normal or only mildly elevated in this subgroup of patients. However, due to underlying airway and alveolar lesions, even non-severe PH negatively impacts symptoms and survival[10–12].

To data, many studies of BPA as treatment for CTEPH have only included patients with typical CTEPH, and thus, the current understanding of the efficacy of BPA for atypical CTEPH, particularly CTEPH with underlying lung disease, remains insufficient. Accordingly, the objectives of this study were to: 1) describe the prevalence of basic lung disease in a CTEPH cohort and evaluate its impact on the efficacy of BPA treatment; and 2) identify clinical variables and noninvasive diagnostic tools that can predict BPA success in these patients.

2. Material and methods

2.1. Study design

This was a single-center, retrospective observational analysis of consecutive adult CTEPH patients who underwent BPA procedures in our clinic between August 2017 and October 2022. Diagnoses of CTEPH were established based on clinical guidelines[1,5], and CTEPH was judged to be inoperable by a multidisciplinary team, comprising pulmonary endarterectomy surgeons, interventional cardiologists specializing in BPA, and physicians experienced in pharmacotherapy for PH. The baseline history of pulmonary disease among the enrolled population was obtained from medical records and included all long-term diseases such as COPD, emphysema, obstructive sleep apnea hypopnea syndrome (OSAHS), and pulmonary thuberculosis. The diagnosis of each pulmonary disease was defined according to established guidelines [13–16]. Patients were excluded if they: underwent rescue BPA for life support, had missing baseline or follow-up data, or had atrial fibrillation. After applying these exclusion criteria, a total of 62 patients were included in this study.

All procedures were conducted in compliance with the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics board of Beijing Chaoyang Hospital. Given the retrospective design of our study, the need for written informed consent of patients was waived.

2.2. Data collection

Prior to the first BPA procedure, patients underwent a series of preprocedural tests. The following clinical data were collected via an electronic medical record system: age, sex, body mass index (BMI), World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), Barthel index, N-terminal pro-brain natriuretic peptide (NT-proBNP) level, and D-dimer level. Pulmonary angiography and right heart catheterization (RHC) were performed to determine the degree of pulmonary vascular obstruction. A SwanGanz catheter was inserted via the internal jugular vein into the right inferior pulmonary artery. Hemodynamic measurements included pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), pulmonary arterial wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), and pulse oxygen saturation (SpO_2). All patients underwent routine pulmonary function tests (PFTs) before treatment and during follow-up, including bronchodilator test and pulmonary diffusion capacity tests. The absolute values and percentages of predicted values were recorded for the following parameters: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), diffusion capacity of lung carbon monoxide (DLCO), and carbon monoxide transfer coefficient (KCO). All patients underwent transthoracic echocardiography (TTE) examination using a Philips EPIQ 7C (Philips Healthcare, MA, USA) and a Doppler ultrasound machine equipped with an X5-1 probe (1–5 MHz). Cardiac structure and functional parameters were assessed based on the American Society of Echocardiography guidelines[17].

2.3. BPA procedure

All procedures were performed under local anesthesia. The standard procedure has been described previously in detail[18–20]. In brief, according to the Seldinger technique, an 8F femoral artery sheath was inserted via the femoral vein. After injection of heparin (1 mg/kg), a 5F pigtail contrast catheter was inserted into the main pulmonary artery. The width and length of the balloon were adjusted based on the type of lesion and degree of stenosis of the pulmonary artery as determined by angiography. Balloon catheters were advanced over a micro-guidewire through the stenosed or occluded pulmonary artery branches and gradually expanded. The patient's condition was monitored closely, and repeated dilation was performed as necessary.

2.4. Definition of BPA efficacy

At present, there continues to be no consensus on the definition of BPA efficacy. In line with previous studies[21,22], we used two hemodynamic parameters, mean PAP (mPAP) and PVR, determined according to the results of reevaluation RHC (more than 3 months after the last BPA session) to classify the study participants into two groups: 'BPA success' and 'BPA failure'. Successful BPA was defined as meeting at least one of the following criteria: (1) mPAP $\leq$ 30 mmHg; and (2) PVR decrease $\geq$ 30 %. Despite having sufficient BPA treatments (4–6 times or more), if upon reevaluation parameters still did not meet these criteria, the outcome of BPA was considered failure. For the BPA success group, data within 3 months of the BPA effectiveness time point were recorded. For the BPA failure group, data within 3 months of the last BPA procedure were recorded.

2.5. Statistical analysis

Data analyses were carried out using SPSS version 26.0 (IBM). The Shapiro–Wilk test was applied to determine the normality of the distribution of all data. Continuous variables are presented as mean $\pm$ standard deviation (SD) or as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Comparisons between the BPA success and failure groups were made using an independent-sample *t*-test, the Mann–Whitney *U* test, or the Pearson χ^2 test, as appropriate. Paired-sample t tests and Wilcoxon signed-rank test were used analyze the post- versus pre-procedural changes in variables, including hemodynamic data and clinical parameters. Univariate logistic regression was first performed to assess adjusted relationships between post-BPA improvement in hemodynamics and baseline clinical characteristics including age, respiratory function, and right heart functional parameters. Variables considered to be clinically significant associated with BPA outcomes (baseline mPAP, PVR, NT-proBNP and WHO-FC) as well as variables for which $P < 0.10$ on univariate analysis were selected as candidate predictors and included in a multivariable regression model (enter method). For all analyses, the level of statistical significance was set at $P < 0.05$.

3. Results

3.1. Baseline characteristics of study participants

The baseline patient characteristics are summarized in Table 1. A total of 62 patients (42 women; average age, 60.0 $\pm$ 11.9 years) with inoperable CTEPH who completed treatment with BPA procedures were enrolled in our analysis, including 9 (64.3 %) with COPD, 3 (21.4 %)

Table 1
Baseline characteristics of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) according to the outcome of BPA.

Variable	Overall Population (n = 62)	BPA Success Group (n = 50)	BPA Failure Group (n = 12)	*P* value*
No. of BPA sessions	3.7 ± 1.7	3.4 ± 1.5	5.2 ± 1.3	0.000
Age, y	60.0 ± 11.9	61.3 ± 9.7	54.5 ± 18.2	0.235
Female, n (%)	42 (68)	33 (66)	9 (75)	0.799
BSA, m^2	1.7 ± 0.2	1.7 ± 0.1	1.8 ± 0.3	0.250
WHO FC				0.179
I or II, n (%)	34 (55)	30 (60)	4 (33)	
III or IV, n (%)	28 (45)	20 (40)	8 (67)	
6WMD, mm	373.7 ± 88.2	388.2 ± 85.1	313.3 ± 76.8	0.002
NT-proBNP, pg/mL	1111.6 ± 1137.2	1088.6 ± 1167.2	1207.1 ± 1044.3	0.412
D-dimer, ng/ml	392.8 ± 408.6	411.2 ± 445.3	316.2 ± 186.1	0.762
Pulmonary comorbidity, n (%)	14 (23)	7 (14)	7 (58)	0.001
Pulmonary function tests				
FEV_1, %	87.1 ± 17.5	88.4 ± 17.8	81.7 ± 16.2	0.241
FEV_1/FVC, %	83.7 ± 9.3	83.4 ± 9.0	84.9 ± 11.0	0.880
D_{LCO}, %	73.6 ± 13.3	74.0 ± 12.7	72.0 ± 16.1	0.643
KCO, %	80.3 ± 16.9	80.2 ± 16.1	80.8 ± 20.8	0.909
Hemodynamics				
Systolic PAP, mm Hg	88.0 ± 18.4	87.2 ± 17.4	91.3 ± 22.5	0.972
Diastolic PAP, mm Hg	32.1 ± 8.7	31.8 ± 9.0	33.5 ± 7.7	0.543
Mean PAP, mm Hg	50.9 ± 10.4	50.4 ± 10.3	52.8 ± 11.3	0.695
PVR, Woods units	10.7 ± 4.1	10.7 ± 4.3	10.8 ± 3.7	0.556
PAWP, mm Hg	10.2 ± 4.7	10.3 ± 4.6	9.8 ± 5.4	0.754
CI, L/min/m^2	2.4 ± 0.7	2.5 ± 0.6	2.4 ± 0.9	0.498
SpO_2, %	90.4 ± 4.5	90.7 ± 4.3	89.3 ± 5.5	0.536
Echocardiography				
LVEF, %	65.4 ± 5.2	65.5 ± 5.3	65.1 ± 4.7	0.795
D_{MPA}, mm	33.2 ± 6.1	32.7 ± 5.6	35.1 ± 7.9	0.470
RVD, mm	46.6 ± 7.0	45.4 ± 6.3	51.3 ± 7.8	0.007
EI	1.4 ± 0.2	1.3 ± 0.2	1.5 ± 0.5	0.004
PASP, mmHg	90.7 ± 19.7	88.1 ± 19.2	101.6 ± 19.0	0.032
TAPSE, mm	14.7 ± 2.3	14.7 ± 2.8	14.7 ± 2.8	0.643
S'	9.7 ± 2.2	9.6 ± 2.1	10.1 ± 2.9	0.873
FAC, %	28.7 ± 9.5	29.9 ± 9.0	23.7 ± 10.1	0.040
RIMP	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.261

Abbreviations: BSA, body surface area; WHO FC, World Health Organization functional class; 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-b-type natriuretic peptide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; D_{LCO}, diffusing capacity of lung carbon monoxide; KCO, carbon monoxide transfer coefficient; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary artery wedge pressure; CI, cardiac index; SpO_2, percutaneous arterial oxygen saturation; LVEF, left ventricle ejection fraction; D_{MPA}, diameter of main pulmonary artery; RVD, right ventricular diameter; EI, eccentric index; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', peak systolic velocity of tricuspid annulus; FAC, fractional area change; RIMP, right ventricular index of myocardial performance.
Data are presented as mean ± SD or percentages.
*Comparison between BPA success and failure groups.

with emphysema, 1 (7.1 %) with OSAHS, and 1 (7.1 %) with pulmonary thuberculosis (Fig. 1). Most patients had severely compromised hemodynamics with a mPAP > 50 mmHg. During the study period, the baseline and final RHC data were obtained at a median of 6 days (IQR, 10 days) before and 2.7 months (IQR, 4.7 months) after the procedure, respectively. According to our strict classification rules, 50 (81 %) patients experienced outcomes classified as BPA success, and 12 (19 %) had outcomes classified as BPA failure. The average number of BPA sessions per patient was 3.7 ± 1.7 for all patients, and the number of sessions was higher in the BPA failure group than in the BPA success group (5.2 ± 1.3 vs 3.4 ± 1.5, $P < 0.01$).

No significant differences in demographic variables, WHO FC, laboratory test results, and hemodynamics at baseline were detected between the BPA success and BPA failure groups. However, the patients in the BPA failure group had a shorter 6MWD (313.3 ± 76.8 m versus 388.2 ± 85.1 m; $P = 0.002$). Additionally, the number of patients with a history of pulmonary comorbidity was significantly higher in the BPA failure group than in the BPA success group (58 % vs 14 %, $P < 0.01$). Moreover, the BPA failure group exhibited worse echocardiographic features, including more pronounced right ventricular dysfunction (FAC 29.9 ± 9.0 % versus 23.7 ± 10.1 %, $P = 0.04$) and morphology (RVD 45.4 ± 6.3 mm versus 351.3 ± 7.8 mm, EI 1.3 ± 0.2 versus 1.5 ± 0.5, all $P < 0.01$).

3.2. Changes in parameters with BPA treatment

Among the study cohort, patients were divided into groups based on the presence of pulmonary pathology at baseline: 48 without a pulmonary comorbidity and 14 with a pulmonary comorbidity. Table 2 illustrates the changes in parameters from baseline to follow-up in the groups of patients with and without a pulmonary comorbidity. As expected, PFTs indicated a more pronounced obstructive respiratory pattern in CTEPH patients with concomitant pulmonary pathology at baseline, with FEV_1 and FEV_1/FVC being significantly lower in those with a pulmonary comorbidity than in those without. After BPA treatment, in patients with pulmonary pathology, the FEV_1 improved from 89.5 ± 17.7 to 93.6 ± 17.4 ($P < 0.01$), and the KCO decreased from 80.6 ± 17.4 to 77.3 ± 14.3 ($P < 0.01$). However, no significant differences in respiratory function parameters were observed. More importantly, improvement in exercise capacity was observed based on the 6MWD (383.5 ± 86.8 m to 463.6 ± 63.3 m, $P < 0.01$) and laboratory parameters (reflected by NT-proBNP, 1105.8 ± 1165.1 to 245.6 ± 434.1 pg/mL, $P < 0.01$) in CTEPH patients without chronic pulmonary disease, whereas such changes were not observed in patients with a pulmonary comorbidity.

The hemodynamic data obtained from RHC showed improvement after BPA, regardless of concomitant pulmonary pathology, with statistically significant decreases observed for systolic PAP (sPAP), mPAP, and PVR (CTEPH without pulmonary comorbidity: sPAP 89.6 ± 15.9 to 59.3 ± 16.4 mmHg, mPAP 51.5 ± 9.5 to 33.8 ± 9.7 mmHg, PVR from 10.8 ± 4.4 to 5.6 ± 2.8 Woods units; CTEPH with pulmonary comorbidity: sPAP 82.6 ± 25.1 to 63.1 ± 19.8 mmHg, mPAP from 48.9 ± 13.3 to 38.9 ± 11.2 mmHg, PVR from 10.6 ± 3.1 to 7.6 ± 3.0 Woods units, all $P < 0.01$). On TTE, statistically significant reductions were observed in both anatomic and functional measurements (CTEPH without pulmonary comorbidity: RVD 46.5 ± 6.5 to 38.5 ± 5.5 mm, FAC 29.2 ± 9.8 % to 43.0 ± 9.2 %, and tricuspid annular plane systolic excursion [TAPSE] from 14.9 ± 3.0 to 18.0 ± 2.9 mm; CTEPH with pulmonary comorbidity: RVD 46.9 ± 8.7 to 41.3 ± 9.8 mm, FAC 27.2 ± 8.6 % to 35.4 ± 10.6 %, and TAPSE from 13.9 ± 2.1 to 15.9 ± 2.8 mm, all $P < 0.01$).

3.3. Predictors of BPA response

Normalized hemodynamics after BPA, defined as mPAP ≤ 30 mmHg or a PVR decrease ≥ 30 %, were observed in 50 patients (81 %). Table 3 shows the results of logistic regression analysis of associations between baseline variables before BPA and improvement in hemodynamics after BPA in patients with inoperable CTEPH. On univariate logistic analysis, age, 6MWD, WHO FC, pulmonary comorbidity, RVD, EI, and FAC from baseline to follow-up were significantly associated with BPA success with values of $P < 0.20$. In addition to these variables, NT-proBNP, mPAP, and PVR also were included in the subsequent multivariate analysis (enter method) based on their clinical significance. Considering the sample size and collinearity, these variables were not entered into the analysis simultaneously. The resulting 10 multivariable logistic models identified two variables as independently associated with BPA

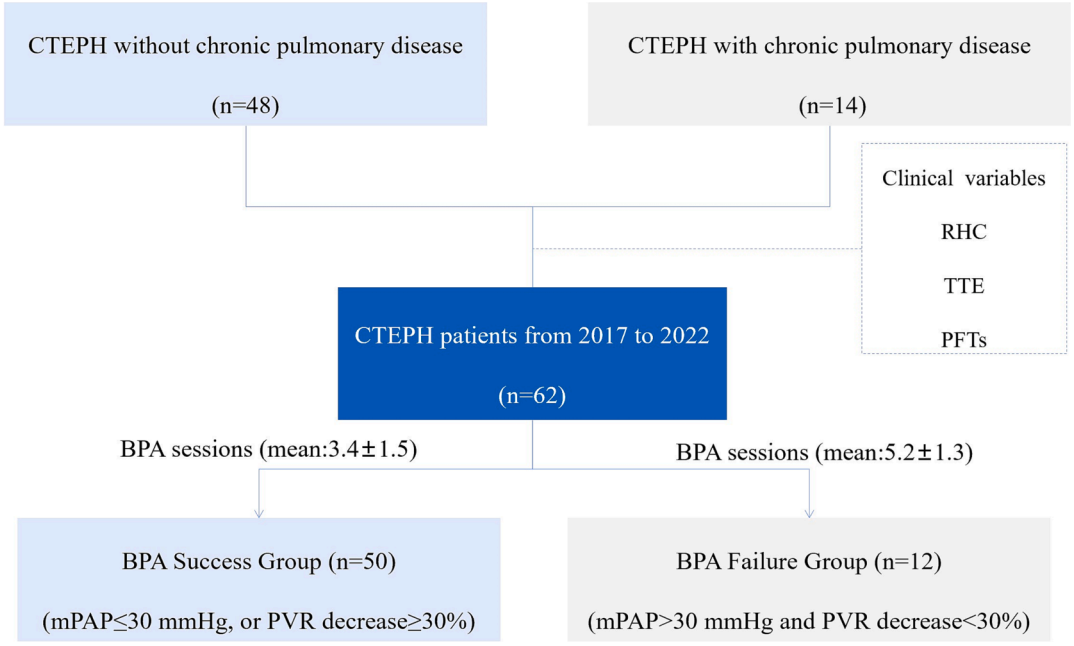

Fig. 1. Study cohort.Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; BPA, balloon pulmonary angioplasty; RHC, right heart catheterization; TTE, transthoracic echocardiography; PFTs, pulmonary function tests; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance.

efficacy: a longer 6MWD at baseline (odds ratio [OR]: 1.03, 95 % confidence interval [CI] 1.00–1.05, $P = 0.032$) was positively associated with BPA success and the presence of a pulmonary comorbidity was a significant negative risk factor for BPA failure (OR: 0.01, 95 % CI 0–0.27, $P = 0.008$). On the multivariate analysis, imaging parameters were not found to have a significant independent effect on the BPA outcome in patients with inoperable CTEPH.

4. Discussion

In this study, we analyzed parameter changes in CTEPH patients with chronic pulmonary disease in a real clinical setting, including parameters representing hemodynamics, exercise capacity, echocardiography, and respiratory function. The main findings our study are as follows: (1) BPA significantly improved hemodynamics and right heart function of CTEPH patients independent of the presence of chronic pulmonary disease; (2) approximately 15 % of patients with inoperable CTEPH experienced a poor response to BPA; and (3) chronic pulmonary disease has significant implications for the results of BPA treatment.

4.1. Pulmonary comorbidity in CTEPH

CTEPH is characterized by chronic thrombus obstruction in pulmonary vessels and is accompanied by secondary pulmonary vascular remodeling, leading to elevated PVR and PAP[23]. Due to ventilation/perfusion mismatch, airway abnormality, bypassing of blood, and hypoxemia in CTEPH, myocardial hypoxia intensifies, ultimately leading to progressive right heart failure[24]. In turn, underlying lung diseases, including parenchymal and interstitial involvement, can also lead to an increase in PAP, primarily due to airway/parenchymal remodeling and vascular remodeling, which is thought to be caused by hypoxia, inflammation and capillary loss[25,26].

In the international CTEPH registry, the rate of comorbid COPD among CTEPH patients ranges from 10 % to 23 %[27,28], and that in our research cohort was 13 %. Lung hyperinflation, caused by COPD, has been shown to adversely affect cardiovascular function, to be correlated with PH, and to lead to dyspnea and exercise intolerance[29]. We noted that CTEPH without pulmonary complications was accompanied by gas exchange disturbance, as evidenced by a decrease in baseline DLCO, but with normal ventilatory function. This is consistent with previous research findings, which suggests CTEPH patients have a certain degree of respiratory impairment[27,30]. On the other hand, the presence of chronic pulmonary disease is expected to worsen pulmonary ventilation and gas exchange parameters, due to the combined effects of an obstructive respiratory pattern and diffusion dysfunction. In terms of other parameters, only S' at baseline differed significantly between CTEPH patients with and without chronic pulmonary disease.

4.2. BPA efficacy

Although pulmonary endarterectomy is still the preferred treatment for patients with CTEPH, it is a challenging and technically demanding procedure[1]. BPA, as an endovascular procedure, has emerged as an alternative therapy for patients with inoperable CTEPH[31]. The efficacy of BPA for improving hemodynamics and exercise capacity is supported by increasing evidence, but no data or consensus are available regarding the therapeutic target after BPA in CTEPH. Some studies have emphasized the relationship between hemodynamics and prognosis [32,33]. A study in Japan reported outcomes of the first multicenter registry of patients undergoing BPA, and after a median of 4 procedures per person, the mPAP of 248 patients (81 %) had decreased to < 25 mmHg[34]. Yu Taniguchi et al suggested that the use of two hemodynamic parameters (mPAP and PVR) seems more appropriate for classifying patients as responders or poor responders to BPA. In their study, each patient underwent 5–6 procedures on average[21]. Therefore, in combination with our clinical practice experience, we defined "BPA failure" as the persistence of mPAP > 30 mmHg and a PVR decrease < 30 % after sufficient BPA treatments (4–6 times or more).

In the present study, significant improvements in hemodynamics were seen in CTEPH patients both with and without concomitant pulmonary pathology after BPA treatment, which is consistent with the findings of the study by Fujii et al[35]. Additionally, we found that right heart function was improved to varying degrees in both groups, whereas exercise capacity was improved only in CTEPH patients without underlying pulmonary disease. In our opinion, despite BPA treatment, compromised lung function may continue to impact exercise performance to some extent. On the other hand, PFT results for patients with cardiac pathology have attracted researchers' attention in recent years.

Table 2
Comparison of baseline and follow-up data between CTEPH patients with and without pulmonary comorbidity.

Variable	CTEPH without pulmonary comorbidity (n = 48)			CTEPH with pulmonary comorbidity (n = 14)		
	Before BPA	After BPA	*P* value*	Before BPA	After BPA	*P* value*
6MWD, m	383.5 ± 86.8	463.6 ± 63.3	0.000	340.0 ± 87.7	396.7 ± 111.5	0.064
NT-pro BNP, pg/mL	1105.8 ± 1165.1	245.6 ± 434.1	0.000	1131.5 ± 1076.9	719.8 ± 967.5	0.140
Pulmonary function tests						
FEV_1, %	89.5 ± 17.7	93.6 ± 17.4	0.007	78.8 ± 14.7	81.1 ± 18.4	0.525
FEV_1/FVC, %	85.1 ± 8.3	83.9 ± 8.2	0.196	79.2 ± 11.4	76.8 ± 13.3	0.181
D_{LCO}, %	74.6 ± 14.1	73.7 ± 13.4	0.375	70.1 ± 10.0	69.5 ± 8.6	0.649
KCO, %	80.6 ± 17.4	77.3 ± 14.3	0.003	79.3 ± 16.0	76.7 ± 12.1	0.208
Hemodynamics						
Systolic PAP, mmHg	89.6 ± 15.9	59.3 ± 16.4	0.000	82.6 ± 25.1	63.1 ± 19.8	0.004
Diastolic PAP, mmHg	32.2 ± 8.7	21.0 ± 7.5	0.000	31.8 ± 9.0	26.8 ± 8.3	0.069
Mean PAP, mmHg	51.5 ± 9.5	33.8 ± 9.7	0.000	48.9 ± 13.3	38.9 ± 11.2	0.005
PVR, Woods units	10.8 ± 4.4	5.6 ± 2.8	0.000	10.6 ± 3.1	7.6 ± 3.0	0.001
PAWP, mmHg	10.4 ± 4.1	9.5 ± 3.6	0.628	9.8 ± 6.4	8.7 ± 3.6	0.533
CI, L/min per m^2	2.5 ± 0.7	2.7 ± 0.5	0.073	2.2 ± 0.7	2.3 ± 0.4	0.258
SpO_2, %	90.6 ± 4.5	93.4 ± 3.1	0.000	89.7 ± 4.7	92.6 ± 5.3	0.075
Echocardiography						
D_{MPA}, mm	33.3 ± 5.6	31.2 ± 5.5	0.001	32.9 ± 8.0	33.9 ± 11.3	0.649
RVD, mm	46.5 ± 6.5	38.5 ± 5.5	0.000	46.9 ± 8.7	41.3 ± 9.8	0.011
EI	1.3 ± 0.2	1.2 ± 0.1	0.000	1.4 ± 0.2	1.2 ± 0.1	0.009
TAPSE, mm	14.9 ± 3.0	18.0 ± 2.9	0.000	13.9 ± 2.1	15.9 ± 2.8	0.020
S'	10.0 ± 2.3	11.6 ± 2.3	0.000	8.6 ± 1.7	10.0 ± 1.8	0.065
FAC, %	29.2 ± 9.8	43.0 ± 9.2	0.000	27.2 ± 8.6	35.4 ± 10.6	0.007
RIMP	0.7 ± 0.2	0.6 ± 0.1	0.000	0.8 ± 0.2	0.7 ± 0.3	0.388

Abbreviations: 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-b-type natriuretic peptide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; D_{LCO}, diffusing capacity of lung carbon monoxide; KCO, carbon monoxide transfer coefficient; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary artery wedge pressure; CI, cardiac index; SpO_2, percutaneous arterial oxygen saturation; D_{MPA}, diameter of main pulmonary artery; RVD, right ventricular diameter; EI, eccentric index; TAPSE, tricuspid annular plane systolic excursion; S', peak systolic velocity of tricuspid annulus; FAC, fractional area change; RIMP, right ventricular index of myocardial performance.
Data are presented as mean ± SD or percentages.
*Comparison between before and after BPA.

Indeed, due to interaction between the pulmonary and cardiovascular systems, many forms of dysfunction affecting one system also extend to affecting the other. Chronic pulmonary disease is very common in the adult population. However, the efficacy of interventional treatment for CTEPH with pulmonary comorbidity had not been well studied. In contrast with previous studies[35], our data did not show any changes in PFT parameters in patients with a pulmonary comorbidity. These discrepancies might partly be explained by the inclusion criteria used for the study population. Matsuoka et al reported, in a study of 132 CTEPH patients, that although hemodynamic parameters were nearly normalized after BPA, lung ventilation and diffusing capacity were unchanged or even worsened[19]. The existence of microvascular disease (small pulmonary vessel pathology) would influence local ventilation and perfusion matching as well as the capillary diffusing capacity, which is likely to contribute to the development and progression of CTEPH[36]. According to these results, performance of PFTs is essential for patients with CTEPH, to evaluate coexisting risk factors and optimize a combined therapeutic strategy, thereby improving patients' overall prognosis.

Table 3
Univariate and multivariate logistic regression analyses for association with normalized hemodynamics after BPA.

Variables	Univariate analysis		Multivariate analysis	
	OR [95 % CI]	*P* value	OR [95 % CI]	*P* value
Age	1.05[0.99,1.1]	0.087		
6WMD	1.01[1,1.02]	0.015	1.03[1,1.05]	0.032
WHO FC (I or II vs III or IV)	0.33 [0.09,1.26]	0.105		
NT-proBNP	1[1,1]	0.744		
Pulmonary comorbidity	0.12 [0.03,0.47]	0.003	0.01[0,0.27]	0.008
Mean PAP	0.98 [0.92,1.04]	0.490		
PVR	1[1,1]	0.936		
RVD	0.88[0.8,0.97]	0.013		
EI	0.01[0,0.31]	0.010		
TAPSE	1[0.79,1.25]	0.979		
FAC	1.08[1,1.17]	0.048		
S'	0.91[0.7,1.2]	0.506		
RIMP	0.16 [0.01,3.92]	0.260		

Abbreviations: OR, odds ratio; CI, confidence interval; 6MWD, 6-min walk distance; WHO FC, World Health Organization functional class; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RVD, right ventricular diameter; EI, eccentric index; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; S', peak systolic velocity of tricuspid annulus; RIMP, right ventricular index of myocardial performance.

4.3. Predictive factors for efficacy of BPA

Previous research revealed that respiratory disorders have a high predictive value for the outcome of CTEPH surgical treatment. In a study involving 136 patients with operable CTEPH, the presence of COPD was a significant negative risk factor for adverse pulmonary endarterectomy outcomes[27]. Likewise, in an analysis of the 3-year survival of patients with inoperable CTEPH, COPD also was found to have a negative impact [37]. However, the efficacy of interventional treatment for CTEPH with comorbid respiratory dysfunction had not been well evaluated. On univariate analysis in the present study (Table 3), several variables were significantly associated with BPA efficacy, whereas multivariate analysis identified only two independent predictors of BPA outcome: 6MWD and pulmonary comorbidity. The presence of chronic lung disease at baseline was a risk factor for failure to achieve the final therapeutic goals of BPA. Injury of the parenchyma and interstitium plays an important role in the pathophysiology and progression of CTEPH. PH is often induced by COPD, idiopathic pulmonary fibrosis, or chronic pulmonary thromboembolism. Pulmonary vascular remodeling is the main cause and is considered to occur via a combination of multiple mechanisms, including the effects of airflow limitation, hypoxemia, and inflammation [38]. Surprisingly, no baseline hemodynamic variables were identified as determinants of the outcome of BPA. Generally, the degree of

improvement in hemodynamics depends somewhat on the baseline condition. In our study cohort, the baseline hemodynamics were similar between the BPA success and failure groups. Moreover, the severity of hemodynamic dysfunction is not a contraindication for BPA.

While BPA improved hemodynamics, the morphological changes and contractile function of the RV also were significantly improved. Univariate analysis showed that RVD, EI, and FAC had predictive value; however, multivariate anlaysis results did not show a predictive role of echocardiographic parameters. We suggest the following possible reasons: 1) inadequate sample size; 2) the RV is formed by a highly complex three-dimensional structure and has different contraction modes: contraction from the RV free wall towards the interventricular septum, longitudinal contraction, and movement of the septum towards the RV cavity[39]. The parameters obtained from two-dimensional echocardiographic images are limited to a single motion mode, and their limitations in RV evaluation have been well described[17]. Advanced methods, including strain imaging, three-dimensional echocardiography, and cardiac magnetic resonance imaging can more sensitively reflect RV remodeling and overall systolic performance. In the future, based on this study, we will further incorporate more techniques and parameters to evaluate the efficacy of BPA in CTEPH patients with pulmonary comorbidity.

4.4. Clinical implications

Although BPA has achieved promising results for inoperable CTEPH, the indications and contraindications for BPA remain controversial. In the present study, we evaluated for the first time the efficacy of BPA in patients with and without pulmonary comorbidity, providing important insight into predictors of BPA efficacy. We must stress that our results do not imply that the presence of a respiratory comorbidity is a contraindication for BPA. As shown in Table 2, both hemodynamic function and echocardiographic right ventricular function were improved significantly after BPA in patients with chronic pulmonary disease. We suggest that these patients can be treated with individualized therapy for PH, which may include BPA. Overall, the future trend of CTEPH management should not only involve multidisciplinary collaboration among healthcare providers but also the comprehensive application of various treatment methods. Different surgical interventions, interventional therapies, and pharmacological treatments can complement each other in the treatment of inoperable CTEPH.

4.5. Study limitations

Several limitations of the present study should be acknowledged. Firstly, this was a retrospective, observational study with a limited number of patients treated in a tertiary center. Hence, selection bias cannot be excluded. Secondly, evaluation of right heart remodeling by two-dimensional single echocardiography has inherent limitations. Advanced imaging techniques (e.g., speckle tracking echocardiography and cardiac magnetic resonance) will be included for assessing RV performance in further prospective studies. Moreover, due to the nature of the study, the time interval between the final BPA session and the last evaluation was not close, and anticoagulation therapy during this period may have affected hemodynamic parameters. We chose a hemodynamic definition for BPA efficacy because it offered an objective parameter linked to prognosis. However, the sample size of the BPA failure group was too small to determine the causal relationship. Thus, the conclusions of this study must be further validated in larger populations before clinical application.

4.6. Conclusions

The results of the present study indicate that BPA can improve hemodynamic parameters and right heart function in CTEPH patients, independent of the presence of chronic lung disease at baseline. However, pulmonary comorbidity had a high predictive value for the prognosis of BPA for inoperable CTEPH. In clinical practice, the treatment strategy should be optimized to reduce the risk of adverse outcomes after BPA. Although BPA is a promising therapeutic option, further research is necessary to clarify the optimal treatment for atypical CTEPH.

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CRediT authorship contribution statement

Yeqing Wang: Data curation, Formal analysis, Investigation, Methodology, Supervison, Writing – original draft. **Dichen Guo:** Data curation, Validation. **Juanni Gong:** Resources, Visualization. **Jianfeng Wang:** Resources, Visualization. **Yuanhua Yang:** Conceptualization, Resources. **Xinyuan Zhang:** Resources, Visualization. **Huimin Hu:** Resources, Visualization. **Yaning Ma:** Resources, Visualization. **Xiuzhang Lv:** Conceptualization, Software, Supervision. **Yidan Li:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Software, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] N.H. Kim, et al., Chronic thromboembolic pulmonary hypertension, Eur. Respir. J 53 (2019), https://doi.org/10.1183/13993003.01915-2018.
[2] P. Dartevelle, et al., Chronic thromboembolic pulmonary hypertension, Eur. Respir. J 23 (2004) 637–648, https://doi.org/10.1183/09031936.04.00079704.
[3] M.M. Hoeper, E. Mayer, G. Simonneau, L.J. Rubin, Chronic thromboembolic pulmonary hypertension, Circulation 113 (2006) 2011–2020, https://doi.org/10.1161/CIRCULATIONAHA.105.602565.
[4] M. Humbert, Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology, Eur. Respir. Rev 19 (2010) 59–63, https://doi.org/10.1183/09059180.00007309.
[5] N. Galie, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur. Heart. J 37 (2016) 67–119, https://doi.org/10.1093/eurheartj/ehv317.
[6] A.B. Hartopo, L.K. Dinarti, A.S. Wahab, The challenge in diagnosis and current treatment of chronic thromboembolic pulmonary hypertension, Acta. Med. Indones 49 (2017) 183–191.
[7] Y. Taniguchi, et al., Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension, J. Heart. Lung. Transplant 38 (2019) 833–842, https://doi.org/10.1016/j.healun.2019.04.006.
[8] P. Brenot, et al., French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension, Eur. Respir. J 53 (2019), https://doi.org/10.1183/13993003.02095-2018.

[9] L. Deng, et al., Characteristics and long-term survival of patients with chronic thromboembolic pulmonary hypertension in China. Respirology (Carlton, Vic.) 26, 196-203, 10.1111/resp.13947 (2021).
[10] S.K. Medrek, A. Sharafkhaneh, A.M. Spiegelman, A. Kak, L.M. Pandit, Admission for COPD Exacerbation Is Associated with the Clinical Diagnosis of Pulmonary Hypertension: Results from a Retrospective Longitudinal Study of a Veteran Population, COPD 14 (2017) 484–489, https://doi.org/10.1080/15412555.2017.1336209.
[11] C.J. Lettieri, S.D. Nathan, S.D. Barnett, S. Ahmad, A.F. Shorr, Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis, Chest 129 (2006) 746–752, https://doi.org/10.1378/chest.129.3.746.
[12] R. Kessler, M. Faller, G. Fourgaut, B. Mennecier, E. Weitzenblum, Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care. Med 159 (1999) 158–164, https://doi.org/10.1164/ajrccm.159.1.9803117.
[13] D. Singh, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019, Eur. Respir. J 53 (2019), https://doi.org/10.1183/13993003.00164-2019.
[14] D.R. Subramanian, et al., Emphysema- and airway-dominant COPD phenotypes defined by standardised quantitative computed tomography, Eur. Respir. J 48 (2016) 92–103, https://doi.org/10.1183/13993003.01878-2015.
[15] N.C.C. Netzer, et al., Principles of practice parameters for the treatment of sleep disordered breathing in the elderly and frail elderly: the consensus of the International Geriatric Sleep Medicine Task Force, Eur. Respir. J 48 (2016) 992–1018, https://doi.org/10.1183/13993003.01975-2015.
[16] <肺结核诊断_WS_288—2017.pdf>.
[17] R.M. Lang, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr 28 (2015), https://doi.org/10.1016/j.echo.2014.10.003, 1–39 e14.
[18] K. Ejiri, A. Ogawa, S. Fujii, H. Ito, H. Matsubara, Vascular injury is a major cause of lung injury after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, Circ. Cardiovasc. Interv 11 (2018) e005884.
[19] Y. Matsuoka, et al., Assessment of oxygenation after balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension, Int. J. Cardiol 333 (2021) 188–194, https://doi.org/10.1016/j.ijcard.2021.03.002.
[20] Y. Taniguchi, H. Matsubara, Novelties in balloon pulmonary angloplasty, Respir. Med. Res 75 (2019) 26–28, https://doi.org/10.1016/j.resmer.2019.04.004.
[21] Y. Taniguchi, et al., Poor Subpleural Perfusion Predicts Failure After Balloon Pulmonary Angioplasty for Nonoperable Chronic Thromboembolic Pulmonary Hypertension, Chest 154 (2018) 521–531, https://doi.org/10.1016/j.chest.2018.03.059.
[22] Y. Zhang, et al., Heart-rate recovery at 1 min after exercise predicts response to balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension, Front. Cardiovasc. Med 9 (2022) 795420, https://doi.org/10.3389/fcvm.2022.795420.
[23] M. Delcroix, et al., ERS statement on chronic thromboembolic pulmonary hypertension, Eur. Respir. J 57 (2021), https://doi.org/10.1183/13993003.02828-2020.
[24] K. Fukushi, et al., Impaired respiratory function in chronic thromboembolic pulmonary hypertension: a comparative study with healthy control subjects, Ann. Am. Thorac. Soc 13 (2016) 1183–1184, https://doi.org/10.1513/AnnalsATS.201601-048LE.
[25] Y. Ni, Y. Yu, R. Dai, G. Shi, Diffusing capacity in chronic obstructive pulmonary disease assessment: A meta-analysis, Chron. Respir. Dis 18 (2021), https://doi.org/10.1177/14799731211056340, 14799731211056340.
[26] H. Olschewski, The challenge to decide between pulmonary hypertension due to chronic lung disease and PAH with chronic lung disease, Diagnostics. (basel) 11 (2021), https://doi.org/10.3390/diagnostics11020311.
[27] O. Kamenskaya, et al., Chronic obstructive pulmonary disease in patients with chronic thromboembolic pulmonary hypertension: Prevalence and implications for surgical treatment outcome, Clin. Respir. J 12 (2018) 2242–2248, https://doi.org/10.1111/crj.12898.
[28] J. Pepke-Zaba, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry, Circulation 124 (2011) 1973–1981, https://doi.org/10.1161/CIRCULATIONAHA.110.015008.
[29] P. Gagnon, et al., Pathogenesis of hyperinflation in chronic obstructive pulmonary disease, Int. J. Chron. Obstruct. Pulmon. Dis 9 (2014) 187–201, https://doi.org/10.2147/COPD.S38934.
[30] A.T. Low, A.R. Medford, A.B. Millar, R.M. Tulloh, Lung function in pulmonary hypertension, Respir. Med 109 (2015) 1244–1249, https://doi.org/10.1016/j.rmed.2015.05.022.
[31] M. Humbert, et al., ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, Eur. Respir. J 2022 (2022), https://doi.org/10.1183/13993003.00879-2022.
[32] K.P. Hug, et al., Serial right heart catheter assessment between balloon pulmonary angioplasty sessions identify procedural factors that influence response to treatment, J. Heart. Lung. Transplant 40 (2021) 1223–1234, https://doi.org/10.1016/j.healun.2021.06.011.
[33] C.B. Wiedenroth, et al., Complications of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: Impact on the outcome, J. Heart. Lung. Transplant 41 (2022) 1086–1094, https://doi.org/10.1016/j.healun.2022.05.002.
[34] A. Ogawa, et al., Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: Results of a Multicenter Registry, Circ. Cardiovasc. Qual. Outcomes 10 (2017), https://doi.org/10.1161/CIRCOUTCOMES.117.004029.
[35] H. Fujii, et al., Efficacy and safety of balloon pulmonary angioplasty for patients with chronic thromboembolic pulmonary hypertension and comorbid chronic obstructive pulmonary disease, J. Am. Heart. Assoc 12 (2023) e026466.
[36] G. Simonneau, A. Torbicki, P. Dorfmuller, N. Kim, The pathophysiology of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev 26 (2017), https://doi.org/10.1183/16000617.0112-2016.
[37] M. Delcroix, et al., Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry, Circulation 133 (2016) 859–871, https://doi.org/10.1161/CIRCULATIONAHA.115.016522.
[38] G. Armentaro, et al., Association between right ventricular dysfunction and adverse cardiac events in mild COPD patients, Eur. J. Clin. Invest 53 (2023) e13887.
[39] W. Li, et al., Balloon pulmonary angioplasty reverse right ventricular remodelling and dysfunction in patients with inoperable chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis, Eur. Radiol 31 (2021) 3898–3908, https://doi.org/10.1007/s00330-020-07481-6.