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Assessment of oxygenation after balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: The efficacy of balloon pulmonary angioplasty (BPA) in patients with inoperable chronic thromboembolic pulmonary hypertension would be promising. However, some patients showed residual dyspnea or symptoms, despite normalized hemodynamics. We aimed to clarify the clinical impact of oxygenation parameters on BPA outcome.

Method: Ninety-nine consecutive patients who underwent BPA from September 2011 to December 2019 were enrolled. We evaluated hemodynamics with right heart catheterization, arterial blood gas examination, New York Heart Association functional class (NYHA-FC), respiratory function tests, nocturnal oximetry, and exercise capacity (6-min walk test and cardiopulmonary exercise testing) at baseline and after BPA.

Result: Nearly normal hemodynamics was achieved after BPA (mean pulmonary artery pressure (PAP): 37.5 ± 10.0 to 20.6 ± 4.9 mmHg, $p < 0.01$). Oxygenation slightly improved (partial pressure of arterial oxygen; 61.5 ± 12.3 to 67.7 ± 12.7 mmHg, $p < 0.01$). Exertional desaturation remained unchanged (−8.1 ± 4.8 to −7.8 ± 5.1, $p = 0.59$), and this was associated with residual symptom (NYHA-FC ≥ 2) after BPA (OR 0.591, 95% CI 0.416–0.840, $p = 0.003$) in multivariate regression analyses. Lower vital capacity ($r^2 = 0.03$, $p = 0.01$), higher mean PAP ($r^2 = 0.08$, $p = 0.02$), and higher minute ventilation/carbon dioxide production (VE/VCO_2) slope ($r^2 = 0.18$, $p < 0.01$), the marker of ventilatory inefficiency, were correlated with exertional desaturation after BPA in multivariate linear analyses.

Conclusion: Although hemodynamics nearly normalized, oxygenation did not. Moreover, exertional desaturation remained unchanged. This might cause residual symptom after BPA. Residual pulmonary hypertension suggesting incurable arteriopathy, and higher VE/VCO_2 slope suggesting ventilation-perfusion mismatch might be related to exertional desaturation. Domiciliary oxygen therapy should be continued, if necessary.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and pulmonary artery obstruction with non-resolving, organized thromboemboli, leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), right heart failure, and death [1–3]. Surgical pulmonary endarterectomy (PEA) remains the gold standard of treatment for patients with operable CTEPH. However, roughly 40%–70% of CTEPH patients are inoperable due to distal lesions or the presence of comorbidities [4,5]. Recently, management of inoperable CTEPH has evolved with the availability of balloon pulmonary angioplasty (BPA), an endovascular procedure used to widen narrow or obstructed pulmonary arteries, which has emerged as an additional treatment option for these patients. The first case series, reported by Feinstein et al. in 2001, demonstrated a reduction in mean pulmonary artery pressure (mean PAP) of 9 mmHg, but its mortality rate was 5.6% [6]. With refinements in the technique, several reports, primarily from Japan in 2012, have succeeded in improving the efficacy and safety of BPA. Nearly normalized hemodynamics could be achieved and these hemodynamic improvements translate into

Abbreviations: BPA, Balloon pulmonary angioplasty; CPET, Cardiopulmonary exercise test; CTEPH, Chronic thromboembolic pulmonary hypertension; DLCO, Diffusing capacity for lung carbon monoxide; NYHA-FC, New York Heart Association functional class; PAP, Pulmonary arterial pressure; PaO_2, Oxygen partial pressure; PAH, Pulmonary arterial hypertension; PEA, Pulmonary endarterectomy; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; P_VO_2, Mixed venous oxygen saturation; SpO_2, Baseline peripheral capillary oxygen saturation; RHC, Right heart catheterization; VE/VCO_2, Minute ventilation/carbon dioxide production; VO_2, Oxygen uptake; 6-MWT, 6-min walk test.

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excellent survival in inoperable CTEPH [7–9]. BPA is a promising treatment strategy for most inoperable patients as segmental and subsegmental pulmonary arteries are accessible with BPA; the recent 2018 World Symposium on PH in Nice, France proposed and recommended PH-targeted medical therapy and BPA for inoperable cases at expert centers [10]. However, some patients showed residual dyspnea or desaturation in exercise despite normalized hemodynamics with unresolved oxygenation problems. Several reports showed that oxygenation was not normalized in most cases, although hemodynamic status was fully improved [8,11], or all accessible lesions were treated [12]. French data showed that about half the patients required continued ambulatory oxygen therapy after BPA [13]. The correlation between oxygenation and hemodynamic improvement in patients treated with BPA remains unclear. We aimed to clarify the clinical impact of oxygenation parameters on BPA outcome in patients with CTEPH.

2. Methods

This retrospective study complied with the Declaration of Helsinki. This study was approved by the ethics committee of Kobe University (approval number: B160007).

2.1. Patients

This observational study included all consecutive patients with inoperable CTEPH who underwent BPA at Kobe University Hospital between September 2011 and December 2019. In all patients diagnosed with CTEPH, the assessment of treatment strategies was made by a multidisciplinary team of experts, including experienced cardiologists and thoracic surgeons, as recommended by current guidelines of the European Society of Cardiology and the European Respiratory Society [14]. There was no clear criteria for indication or contraindication of BPA [15]; however, patient refusals, mild hemodynamics, extremely old age (>90 years), chronic kidney disease stages 4–5, and patients with malignancy with an expected prognosis of less than 6 months, were not offered BPA. Data were collected from hospital medical records. Routine medical assessment included hemodynamic characteristics assessed by right heart catheterization (RHC); lung functional tests; functional status with the New York Heart Association functional class (NYHA-FC); exercise capacity using the 6-min walk test (6-MWT) and cardiopulmonary exercise test (CPET); and nocturnal oximetry tests. These were collected at baseline during CTEPH diagnosis and re-evaluated after three months following the last BPA session as routine follow-up. These examinations were performed under the same condition for oxygen inhalation in each patient.

2.2. BPA procedure

The BPA procedure has been described in our previous reports [12,16,17]. We approached the femoral vein to insert a 6 French (Fr) guiding sheath into the main pulmonary artery. A 6 Fr guiding catheter (Profit®, Multipurpose, or Judkins right and left 4.0; Goodman, Nagoya, Aichi, Japan) was inserted through the peripheral guiding sheath and was advanced to the target vessels. Based on selective pulmonary angiography, a 0.014-in. guide wire (Athlete Bpahm®; Japan Lifeline, Tokyo, Japan) was passed across the target lesion. We treated six to 14 segmental or sub-segmental arteries in each procedure session according to the duration of the procedure (<2 h) and the amount of contrast media given. Two BPA sessions were performed at 4- or 5-day intervals during one hospital admission. Catheterization was repeated at an interval of 1 or 2 months, and additional BPA sessions were performed until all lesions considered possibly accessible were treated, regardless of normalized mean PAP.

2.3. Cardiopulmonary exercise test

CPET was conducted using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan) and performed using a method similar to that in our previous report, in accordance with the American Thoracic Society guidelines, within 2 days following RHC [18]. A 1-min upright rest was followed by 4 min of unloaded pedaling and then progressive workload increments (5 or 10 W/min) until symptom-limited maximum tolerance was reached. The rate of increase in the workload was empirically determined by the supervising physical therapist and physician, based on the patient's medical history and clinical data. The test lasted between 7 and 14 min (unloaded pedaling to peak exercise) for all patients. 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 s of peak exercise. Ventilatory efficiency during exercise was expressed as the slope of ventilation versus VCO_2 over the linear component of the plot of ventilation versus VCO_2 [19].

2.4. Respiratory function test

Respiratory function of percent vital capacity (%VC), forced expiratory volume percent in one second (FEV1.0%), and the diffusing capacity of carbon monoxide (DLCO) were assessed using a spirometer, approximately within 2 days following RHC. Blood gas analyses of oxygen saturation/arterial oxygen partial pressure (PaO_2) in the artery and pulmonary artery were performed during RHC in room air conditions.

Intrapulmonary shunt ratio was calculated with the following formula [20]. After hemodynamic evaluation during RHC, blood gas samples were obtained as well after oxygen loading with a reservoir mask (10 L/min for 5 min).

$$\text{Intrapulmonary shunt ratio} = \frac{Hb \times 1.36(1-SaO_2) + 0.003(P_AO_2 - PaO_2)}{Hb \times 1.36(1-S_VO_2) + 0.003(P_AO_2 - PvO_2)}$$

Hb, hemoglobin (g/dl); SaO_2, arterial oxygen saturation; P_AO_2, alveolar oxygen partial pressure; PaO_2, arterial oxygen partial pressure; S_VO_2, mixed venous oxygen saturation; P_VO_2, mixed venous oxygen partial pressure.

The nocturnal oximetry test was performed routinely using an oximetry monitor (SAS-2100, Nihon-Koden, Tokyo, Japan) during the night before RHC to evaluate oxygen saturation during sleep, the apnea hypopnea index (AHI), and the 3% oxygen desaturation index (3% ODI).

2.5. Statistical analysis

The data that support the findings of this study are available upon reasonable request from the corresponding author. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 26.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) according to variable distribution. Differences in continuous variables, such as age, 6-MWT distance, and hemodynamic or oxygenation parameters, were compared using the paired Student's *t*-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables, such as gender and NYHA-FC, were expressed as numbers and percentages and were compared using the χ^2 test for independence. Univariate and multivariate analysis based on the logistic regression model were used to examine the association of each variable (clinical and hemodynamic characteristics after BPA) with residual symptoms, and analysis based on the linear regression model were used to examine the correlation with exertional or nocturnal desaturation. For all analyses, the level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient population

Between September 2011 and December 2019, a total of 132 CTEPH patients underwent BPA who were determined as inoperable or residual PH after PEA, with a mean of 4.0 ± 1.5 sessions per patient after a median of 2.7 months (IQR: 1.2; 4.6 months) post diagnosis. Re-evaluation was done with RHC, CPET, and the lung function test after the last BPA had not been performed in 33 patients by the cut-off date; the efficacy analysis was evaluated in 99 patients. Average age was 66.0 ± 15.3 years old, 22 patients were male (22.2%). All patients received anticoagulants including warfarin ($n = 72$, 72.7%) or direct oral anticoagulants ($n = 17$, 17.2%). In those patients, 69 (69.7%) also received pulmonary arterial hypertension (PAH) drugs including endothelin receptor antagonist ($n = 17$, 17.2%), phosphodiesterase-5 inhibitor ($n = 18$, 18.2%) and soluble guanylate cyclase stimulator ($n = 45$, 45.5%).

3.2. Efficacy of BPA

Table 1 shows the efficacy of BPA on oxygenation, exercise capacity, and hemodynamic parameters in 99 patients. Re-evaluation of hemodynamics with RHC was performed after a median of 82.2 days (IQR: 67.3; 102.1 days) after the last BPA session. Nearly normalized hemodynamics could be achieved with mean PAP from 37.5 ± 10.0 mmHg to 20.6 ± 4.9 mmHg, $p < 0.01$; PVR from 744 ± 383 dyne/s/cm^{-5} to 261 ± 92 dyne/s/cm^{-5}, $p < 0.01$; and cardiac index from 2.27 ± 0.71 L/min/m^2 to 2.43 ± 0.62 L/min/m^2, $p = 0.03$. NYHA-FC improved from NYHA-FC I/II/III/IV; 6/ 18/ 67/ 9 (%) to 26/ 59/ 15/ 0 (%). Regarding oxygenation parameters, PaO_2 and SaO_2 improved (61.5 ± 12.3 mmHg to 67.7 ± 12.7 mmHg, $p < 0.01$; 90.8 ± 4.7% to 93.3 ± 4.6%, $p < 0.01$, respectively). Intrapulmonary shunt ratio and alveolar-arterial difference for oxygen (A-aDO_2) decreased (median of 0.43 to 0.33, $p < 0.01$; 44.0 ± 14.9 to 35.7 ± 18.4, $p < 0.01$, respectively). For the nocturnal oximetry test, AHI and 3% ODI did not improve (median of 14.5 to 20.6, $p = 0.09$; 26.7 ± 21.6 to 25.1 ± 19.7, $p = 0.63$). For the lung function test, %VC improved (89.1 ± 16.5% to 92.6 ± 15.4%, $p < 0.01$), FEV1.0% did not change (72.7 ± 9.6% to 72.9 ± 9.6%, $p = 0.79$), and %DLCO deteriorated (63.9 ± 16.3% to 59.3 ± 13.3%, $p < 0.01$).

Table 1
Hemodynamic and oxygenation parameters change before and after BPA ($n = 99$).

Variable	Baseline	After the last BPA	p value*
Baseline characteristics			
NYHA FC (I /II / III /IV) (%)	6/18/67/9	26/59/15/0	<0.01
Respiratory parameters			
VC (%)	89.1 ± 16.5	92.6 ± 15.4	<0.01
$FEV_{1.0}$ (%)	72.7 ± 9.6	72.9 ± 9.6	0.79
DLCO (%)	63.9 ± 16.3	59.3 ± 13.3	<0.01
SaO_2 (%)	90.8 ± 4.7	93.3 ± 4.6	<0.01
PaO_2 (mmHg)	61.5 ± 12.3	67.7 ± 12.7	<0.01
SvO_2 (%)	63.7 ± 7.7	66.8 ± 6.4	<0.01
A-aDO_2 (mmHg)	44.0 ± 14.9	35.7 ± 18.4	<0.01
Intrapulmonary shunt ratio ($n = 71$)	0.43 [0.19]	0.33 [0.19]	<0.01
Nocturnal oximetry test			
Minimum SpO_2 in sleep (%)	79.7 ± 6.2	80.6 ± 4.8	0.53
Desaturation in sleep (%)	−11.4 ± 4.2	−12.0 ± 4.8	0.47
AHI	14.5 [20.6]	20.6 [16.1]	0.09
3% ODI	26.7 ± 21.6	25.1 ± 19.7	0.63
Exercise capacity			
6MWT distance (m)	311 ± 97	360 ± 96	<0.01
Minimum SpO_2 during 6MWT (%)	85.4 ± 5.6	87.2 ± 5.2	0.03
Desaturation during 6MWT (%)	−8.1 ± 4.8	−7.8 ± 5.1	0.59
Peak VO_2 in CPET (ml/min/kg)	12.9 ± 3.9	16.0 ± 4.9	<0.01
VE/VCO_2 slope in CPET	41.9 ± 11.4	30.8 ± 8.3	<0.01
Baseline hemodynamics			
Mean RAP (mmHg)	4.8 ± 3.1	3.9 ± 2.8	0.20
Systolic PAP (mmHg)	64.8 ± 18.4	36.8 ± 11.9	<0.01
Diastolic PAP (mmHg)	21.5 ± 7.2	12.5 ± 4.5	<0.01
Mean PAP (mmHg)	37.5 ± 10.0	20.6 ± 4.9	<0.01
PAWP (mmHg)	8.6 ± 4.9	8.2 ± 3.3	0.63
Cardiac index (L/min/m^2)	2.27 ± 0.71	2.43 ± 0.62	0.03
PVR (dyne/s/cm^{-5})	744 ± 383	261 ± 92	<0.01

List of abbreviations: NYHA FC: New York Heart Association functional class; VC: vital capacity; $FEV_{1.0}$: forced expiratory volume in one second; DLCO: diffusing capacity for lung carbon monoxide; SaO_2: arterial oxygen saturation; PaO_2: partial pressure of arterial oxygen; SvO_2: mixed venous oxygen saturation; A-aDO_2: alveolar-arterial oxygen difference; SpO_2: percutaneous oxygen saturation; AHI: apnea hypopnea index; ODI: oxygen desaturation index; 6MWT: 6-min walk test; VO2: oxygen uptake; CPET: cardiopulmonary exercise testing; VE: ventilation; VCO_2: carbon dioxide production; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance.
Data are given as mean ± standard deviation or median [interquartile range].

3.3. Exertional and nocturnal desaturation

Fig. 1(a,b) demonstrates a temporal change of baseline peripheral capillary oxygen saturation (SpO_2) and minimum SpO_2 during the 6-MWT before BPA and after BPA (a), and those during sleep (b). Fig. 1 (c,d) demonstrates desaturation in the 6-MWT before BPA and after BPA (c), and those during sleep (d). Baseline SpO_2 and minimum SpO_2 during the 6-MWT improved after BPA (93.5 ± 2.7 to 94.9 ± 2.6%, $p < 0.01$; 85.4 ± 5.6% to 87.2 ± 5.2%, $p = 0.03$, respectively); however, desaturation in the 6-MWT was unchanged (−8.1 ± 4.8% to −7.8 ± 5.1%, $p = 0.59$). Baseline SpO_2 during sleep improved (91.1 ± 4.2 to 92.6 ± 3.1%, $p < 0.01$); however, minimum SpO_2 was unchanged (79.7 ± 6.2% to 80.6 ± 4.8%, $p = 0.53$). Desaturation during sleep also remained unchanged (−11.4 ± 4.2% to −12.0 ± 4.8%, $p = 0.47$).

3.4. Predictors of residual symptoms after BPA

Table 2 demonstrates the results of logistic regression analysis of clinical variables after BPA associated with residual symptoms (NYHA-FC ≥ 2). In the univariate analysis, lower DLCO, larger desaturation during 6MWT, lower 6-MWT distance, lower peak VO2 in CPET, higher mean PAP after BPA were significantly correlated with residual symptoms. In the multivariate analysis, larger desaturation during 6MWT (Odds Ratio [OR] 0.591, 95% CI 0.416–0.840, $p = 0.003$), lower 6-MWT distance (OR 0.983, 95% CI 0.968–0.999, $p = 0.034$), and lower peak VO2 in CPET (OR 0.724, 95% CI 0.572–0.917, $p = 0.007$) after BPA were independently correlated with residual symptoms (NYHA-FC ≥ 2).

The results of linear regression analyses of clinical variables after BPA associated with desaturation in 6-MWT are depicted in Table 3. In univariate analysis, lower %VC, lower %DLCO, higher mean PAP, higher PVR, and higher minute ventilation/carbon dioxide production (VE/VCO_2) slope after BPA were significantly correlated in the univariate analysis. In the multivariate analysis, lower %VC ($r^2 = 0.03$, $p = 0.01$), higher mean PAP ($r^2 = 0.08$, $p = 0.02$), and higher VE/VCO_2 slope ($r^2 = 0.18$, $p < 0.01$) after BPA were independently correlated with larger desaturation during 6-MWT. However, medical treatment was not correlated in either analyses. In the linear regression analyses of clinical variables correlated with nocturnal desaturation after BPA, higher VE/VCO_2 slope ($r^2 = 0.12$, $p = 0.03$) was significantly correlated in univariate analysis; however, no clinical variables were correlated in multivariate analysis.

4. Discussion

In this study, nearly normalized hemodynamics was achieved after BPA. Oxygenation also slightly improved, although it did not normalize. Moreover, exertional desaturation and nocturnal desaturation remained unchanged. Sustained exertional desaturation could be one

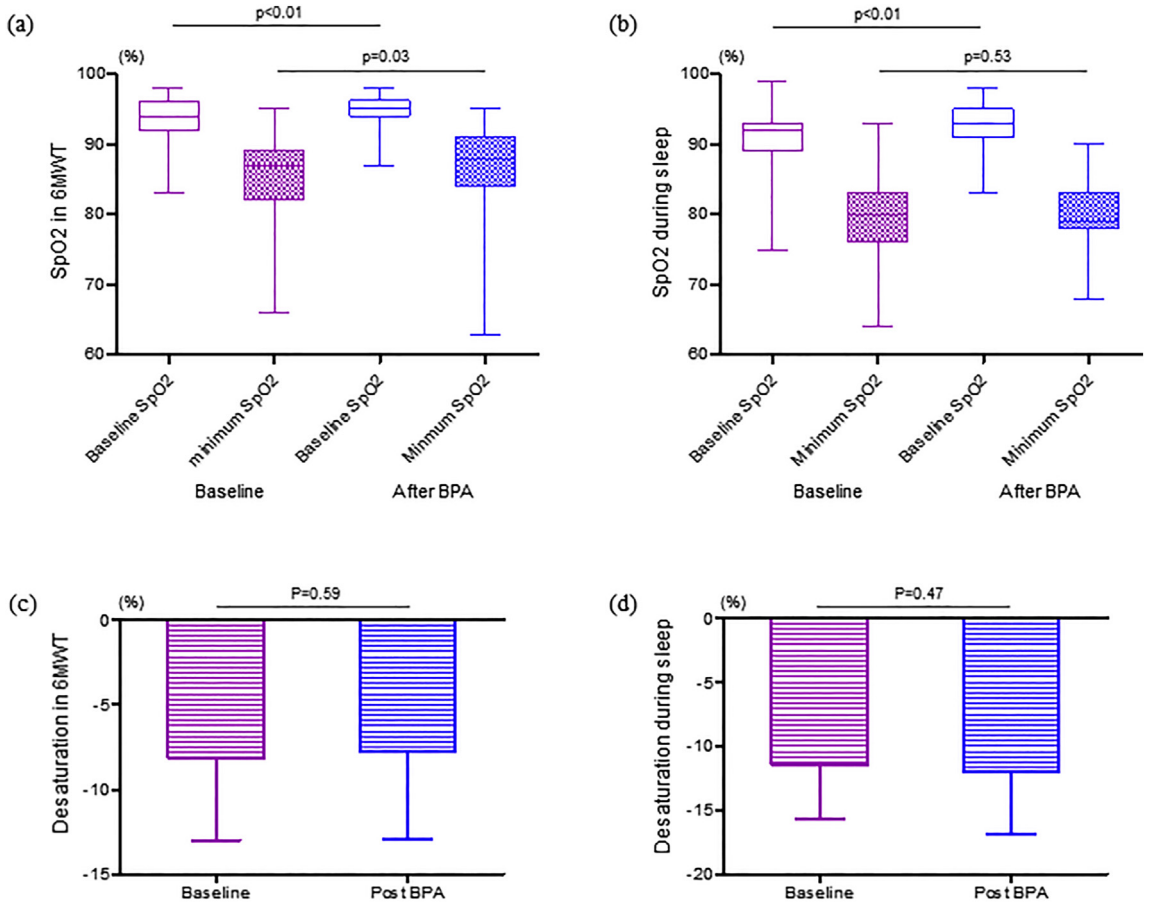

Fig. 1. Baseline peripheral capillary oxygen saturation (SpO_2) and minimum SpO_2 at baseline, after balloon pulmonary angioplasty (BPA): (a) during the 6-min walk test (6-MWT) and (b) during sleep. Desaturation at baseline, after BPA: (c) during the 6-min walk test (6-MWT) and (d) during sleep.

of the causes of exertional dyspnea or residual symptoms, despite nearly normalized hemodynamics after BPA.

Various factors are involved in residual hypoxia after BPA. Godinas et al. reported that gas exchange was more impaired in distal CTEPH than in PAH, which could be explained by more pronounced blood flow redistribution in CTEPH due to non-uniform vascular obstruction [21]. Minatsuki et al. reported, in a study of 23 patients, that dead-space ratios and intrapulmonary shunt ratios were elevated in CTEPH patients, and the former could be a marker for improved arterial oxygen saturation after BPA [11]. In a study of 24 patients, Aoki et al. demonstrated that decreased intrapulmonary shunt ratio after BPA is correlated with improved oxygenation [22]. Furthermore, there might be other possible factors related to hypoxia. Recent insights have revealed that apart from mechanical obstruction by organized thrombi in large and/or middle-sized pulmonary arteries, peripheral microvasculopathy (small pulmonary vessel disease) is also likely to contribute to the development and progression of CTEPH [23,24]. In a study of 23 operated patients, Jujo et al. reported that severe pulmonary arteriopathy was closely associated with persistent hypoxemia after PEA by pathological examination of lung biopsies. They also reported that hypoxemia could remain even after 1 year after PEA [25].

Oxygenation occurs in distal pulmonary arterioles or capillaries, inaccessible by interventional treatment. It has been reported that severe vascular remodeling remains even after successful BPA [26]. BPA can widen narrow or obstructed pulmonary arteries with a minimum diameter of 1.5 mm and a maximum of over 10 mm, and can improve blood flow to distal areas. The existence of microvasculopathy would cause disruption to pulmonary blood flow in the capillary bed, resulting in a local ventilation perfusion mismatch and impaired diffusing capacity at the capillary level. Indeed, DLCO, which is the marker for lung diffusing capacity and might indicate pronounced microvasculopathy [13,27], was unchanged or even worsened after BPA in this study. A-a DO_2 which is the marker of ventilation perfusion mismatch and lung diffusing capacity was also impaired. (44.0 ± 14.9 mmHg to 35.7 ± 18.4 mmHg, $p < 0.01$). BPA treatment can be used at the sub-segmental pulmonary arterial level, but it cannot be used at the capillary level, downstream of the pulmonary arterioles.

Another finding of this study is that desaturation remains in exercise or during sleep even after hemodynamics at rest were normalized. Desaturation of −8.1 ± 4.8% during 6-MWT (minimum SpO_2 of 85.4 ± 5.6%) at baseline, −7.8 ± 5.1% (minimum SpO_2 of 87.2 ± 5.2%) after BPA were observed. Even though minimum SpO2 improved significantly, exertional desaturation remained unchanged. In addition, a nocturnal desaturation of −11.4 ± 4.2% (minimum SpO_2 of 79.7 ± 6.2%) at baseline, −12.0 ± 4.8% (minimum SpO_2 of 80.6 ± 4.8%) after BPA was observed. We demonstrated that exertional desaturation is one of the causes of exertional dyspnea or residual symptoms after adequate BPA.

Exertional hypoxia is common in PAH. The pathophysiological abnormality of pulmonary vasculopathy or right ventricular failure during exercise may contribute to impaired cardiac output, ventilation/perfusion mismatching [28,29], and abnormal gas exchange. These factors result in reduced oxygen delivery to tissues, and increased lactate and VCO_2 levels. Nocturnal oxygen desaturation is also common in patients with PAH. Physiological alterations to the respiratory system which may lead to oxygen desaturation during sleep may occur in healthy subjects [30]; however, nocturnal hypoxia correlated with PH severity and right ventricular dysfunction [31,32]. Multiple underlying mechanisms may be involved in nocturnal hypoxia, including alterations in ventilation

Table 2
Univariate and multivariate logistic regression analysis of clinical variables associated with residual symptoms (NYHA-FC ≥ 2) after BPA.

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Patient characteristics (post BPA)						
Age (years)	1.024	0.989–1.061	0.179			
Gender (male)	1.500	0.498–4.519	0.471			
Medication	0.386	0.145–1.031	0.058			
Respiratory parameters (post BPA)						
VC (%)	0.977	0.946–1.010	0.173			
DLCO (%)	0.954	0.916–0.993	0.023			
SaO_2 (%)	0.911	0.791–1.048	0.192			
SvO_2 (%)	0.983	0.911–1.061	0.663			
Exercise capacity (post BPA)						
6MWT distance (m)	0.991	0.986–0.997	0.002	0.983	0.968–0.999	0.034
Desaturation during 6MWT (%)	0.733	0.611–0.880	0.001	0.591	0.416–0.840	0.003
Peak VO_2 in CPET (ml/min/kg)	0.860	0.767–0.965	0.011	0.724	0.572–0.917	0.007
VE/VCO2 in CPET	1.085	0.998–1.178	0.055			
Hemodynamics (post BPA)						
RAP (mmHg)	1.015	0.864–1.193	0.852			
Mean PAP (mmHg)	1.117	1.006–1.241	0.039			
Cardiac index ($L/min/m^2$)	0.636	0.283–1.430	0.274			
PVR ($dyne/s/cm^{-5}$)	1.001	0.996–1.006	0.697			

List of abbreviations: NYHA FC: New York Heart Association functional class; BPA: balloon pulmonary angioplasty; VC: vital capacity; DLCO: diffusing capacity for lung carbon monoxide; SaO_2: arterial oxygen saturation; SvO_2: mixed venous oxygen saturation; VO2: oxygen uptake; CPET: cardiopulmonary exercise testing; VE: ventilation; VCO_2: carbon dioxide production; RAP: right atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance.

perfusion [33], reduced functional residual capacity, reduced respiratory drive, and airway stability, leading to alveolar hypoventilation [34,35]. Exertional or nocturnal desaturation is also observed in CTEPH patients, despite the absence of parenchymal lung disease or sleep apnea [35].

This study demonstrates that exertional and nocturnal desaturation remains a resistant and incurable condition even though the hemodynamics were almost normalized. Several factors might be involved in desaturation. We also demonstrated that, lower %VC, higher mean PAP, and higher VE/VCO_2 slope after BPA were independently correlated with larger exertional desaturation. Additionally, higher VE/VCO_2 slope after BPA was associated with larger nocturnal desaturation. Residual PH reflects abnormal pulmonary vascular reserve. Apart from residual obstructive lesions, previous reports have suggested that the existence of microvasculopathy, including diffuse distal thrombi, was strongly related to residual PH after adequate BPA [13,36]. Therefore, microvasculopathy, including diffuse distal thrombi, may be one of the causes of desaturation.

Elevated VE/VCO_2 is the marker of ventilatory inefficiency and reflects ventilation perfusion mismatch [37]. Even though all possible accessible lesions had been treated after adequate BPA, our study indicated residual ventilation perfusion mismatch at not only the segmental level but also the local microvascular level, which causes exertional or nocturnal desaturation. Moreover, Godinas et al. reported that compared with PAH, ventilatory efficiency was more impaired in distal CTEPH, and this was associated with increased physiologic dead space at rest and at peak exercise. Increased dead-space ventilation also might be involved in remaining desaturation [21].

In this study, medical treatment with PAH-specific drugs was not associated with improved exertional or nocturnal desaturation. BPA, which could achieve nearly normal hemodynamics, is a promising treatment strategy for inoperable CTEPH; however, some limitations remain to be resolved. Exertional desaturation is one of the causes of exertional dyspnea or residual symptoms, which could impair patients' quality of life. Moreover, hypoxia can induce pulmonary vasoconstriction via its effects on pulmonary vascular smooth muscle and endothelial cells, resulting in elevated PVR. Daytime SpO_2 measurements at rest could underestimate the existence of exertional or nocturnal hypoxia after BPA [35] which may impair not only patients' quality of life but also their clinical condition. Domiciliary oxygen therapy can improve exercise capacity, quality of life, and functional class in CTEPH patients with exercise-induced hypoxemia in a randomized trial [38].

Table 3
Correlations between desaturation in 6-min walk test and each clinical parameter post BPA.

Variable	Univariate					Multivariate			
	r^2	Estimate	SE	*t* value	*p* value	Estimate	SE	*t* value	*p* value
Patient characteristics (post BPA)									
Age (years)	0.015	−0.002	0.001	−1.45	0.13				
Gender (male)	−0.01	0.16	1.5	0.1	0.91				
Medication	−0.01	0.78	1.3	0.6	0.56				
Respiratory parameters (post BPA)									
VC (%)	0.03	0.09	0.04	2.2	0.03	0.12	0.042	2.72	0.01
DLCO (%)	0.1	0.15	0.05	3.2	<0.01				
A-aDO2 (mmHg)	0.01	0.14	0.11	1.3	0.19				
Intrapulmonary shunt ratio	0.03	−4.96	2.9	−1.7	0.10				
AHI	0.08	−0.19	0.11	−1.6	0.11				
Exercise capacity (post BPA)									
Peak VO_2 in CPET (ml/min/kg)	0.04	0.21	0.11	1.9	0.06				
VE/VCO2 in CPET	0.18	−0.21	0.06	−3.7	<0.01	−0.23	0.073	−3.19	<0.01
Hemodynamics (post BPA)									
RAP (mmHg)	−0.01	−0.02	0.21	−0.10	0.91				
Mean PAP (mmHg)	0.08	−0.33	0.12	−2.8	<0.01	−0.30	0.12	−2.52	0.02
Cardiac index ($L/min/m^2$)	−0.01	−0.55	0.98	−0.56	0.58				
PVR ($dyne/s/cm^{-5}$)	0.08	−0.01	0.004	−2.8	<0.01				

List of abbreviations: BPA: balloon pulmonary angioplasty; VC: vital capacity; DLCO: diffusing capacity for lung carbon monoxide; A-aDO_2: alveolar-arterial oxygen difference; AHI: apnea hypopnea index; VO2: oxygen uptake; CPET: cardiopulmonary exercise testing; VE: ventilation; VCO_2: carbon dioxide production; RAP: right atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance.

A nocturnal oximetry test, or 6-MWT should be considered as part of the routine evaluation after BPA, and domiciliary oxygen therapy or nocturnal oxygen therapy should be continued, if necessary. Further studies are required to document the implications of hypoxia and clarify the use of oxygen therapy in CTEPH patients.

4.1. Limitation

The main limitation of this study is its retrospective observational nature. Therefore, the occurrence of some missing values was unavoidable and might have influenced the results in the multivariate regression model. Moreover, the number of patients was relatively small, and the data were collected in a single center. A multicenter, prospective study is needed for further evaluation of oxygenation after BPA. Furthermore, it is undeniable that less experience with the procedure in the initial stages of our program might have affected BPA outcomes.

4.2. Conclusion

Although hemodynamics nearly normalized after BPA, oxygenation did not. Moreover, exertional or nocturnal desaturation remained unchanged. Sustained desaturation was strongly associated with exertional dyspnea or residual symptoms despite nearly normalized hemodynamics. Various factors are involved in remaining desaturation. In our experience, medical therapy was not effective to combat remaining exertional or nocturnal desaturation. To improve clinical outcomes including residual symptoms, domiciliary or nocturnal oxygen therapy should be continued, if necessary. More work is required to develop further treatment for CTEPH patients.

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Author statement

Dr. Matsuoka, Dr. Taniguchi were responsible for study conceptualization, methodology, formal analysis, and prepared the manuscript. Dr. Matsuoka, Dr. Miwa, Dr. Sumimoto, Dr. Onishi, Dr. Yanaka, and Dr. Tsuboi participated to data curation. Dr. Taniguchi, Dr. Emoto, Dr. Hirata were responsible for manuscript review and editing.

Declaration of Competing Interest

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