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Nocturnal desaturation in patients with non-operable chronic thromboembolic pulmonary hypertension

Yu Taniguchi[1*], Miki Sakamoto[1], Hiroyuki Fujii[1], Keisuke Miwa[1], Yasunori Tsuboi[1], Kenichi Yanaka[1], Noriaki Emoto[1,2] and Hiromasa Otake[1]

Abstract

Background Nocturnal desaturation is occasionally observed in patients with chronic thromboembolic pulmonary hypertension (CTEPH) despite the absence of parenchymal lung disease; however, the underlying mechanism remains unclear. This study aimed to clarify the clinical features of nocturnal desaturation in patients with CTEPH.

Methods Data of 163 patients with CTEPH who underwent balloon pulmonary angioplasty (BPA) between March 2011 and December 2022 were retrospectively analyzed. We evaluated their hemodynamics using right heart catheterization, arterial blood gas examination, respiratory function tests, nocturnal oximetry, and cardiopulmonary exercise testing, which were routinely performed at baseline and after BPA.

Results A higher ratio of dead space to tidal volume (VD/VT) ($p < 0.001$) and higher alveolar-arterial oxygen difference (A-aDO2) ($p = 0.026$) at baseline were associated with greater nocturnal desaturation in the multivariable linear analysis. After BPA, nearly normal hemodynamics was achieved (mean pulmonary arterial pressure: 37.5 ± 10.0 to 20.2 ± 4.9 mmHg, $p < 0.01$). Nocturnal desaturation also improved from $-13.3 \pm 5.8\%$ at baseline to $-10.3 \pm 5.4\%$ after BPA ($p < 0.01$). Improvement in VD/VT correlated well with improvement in nocturnal desaturation after BPA ($p < 0.001$, R^2 linear = 0.18).

Conclusions Nocturnal desaturation often coexists with CTEPH. VD/VT, a marker of physiologic dead-space fraction, A-aDO2, a marker of ventilation-perfusion mismatch, and lung diffusing capacity were strongly associated. Nocturnal desaturation improved slightly after BPA, which was associated with a decrease in the physiological dead-space fraction. Our study emphasizes the importance of including nocturnal oximetry in routine evaluations and continuation of nocturnal oxygen therapy, if necessary, in patients with CTEPH.

Summary at a glance

Nocturnal desaturation often coexisted with chronic thromboembolic pulmonary hypertension despite the absence of parenchymal lung disease. The ratio of dead space to tidal volume (a marker of the physiologic dead-space) and alveolar-arterial oxygen difference (a marker of ventilation-perfusion mismatch and lung diffusing

*Correspondence:
Yu Taniguchi
yutani@med.kobe-u.ac.jp

Full list of author information is available at the end of the article

capacity) were strongly associated with nocturnal desaturation. Nocturnal desaturation improved slightly after balloon pulmonary angioplasty, which was associated with a decrease in the physiological dead-space fraction.

Keywords Chronic thromboembolic pulmonary hypertension, Oxygenation, Nocturnal desaturation, Balloon pulmonary angioplasty

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and obstruction of the pulmonary arteries caused by non-resolving, organized thromboemboli, leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), and right heart failure [1–3]. CTEPH is categorized under group 4 in the clinical classification of the PH guideline of the European Society of Cardiology and European Respiratory Society, 2022 [4]. In the last 10 years, the management of non-operable CTEPH has evolved with the availability of balloon pulmonary angioplasty (BPA) and the concurrent use of approved pulmonary vasodilators. These interventional treatments dramatically improved hemodynamics to nearly normal, which translates into excellent survival in non-operable CTEPH in the modern management era [4–6]. However, the oxygenation problems remain unresolved. Several reports have shown that oxygenation is not normalized in most cases despite normalized hemodynamics at rest, even after successful BPA [7–9]. Although there had been no clear criteria for oxygen supplementation, and misuse of oxygen therapy for CTEPH might be common, data of BPA cohorts from France and Japan showed that approximately half of the patients required continued ambulatory oxygen therapy after BPA [8, 9]. Our BPA team previously reported that exertional desaturation remained unchanged despite nearly normalized hemodynamics after BPA, which was strongly associated with exertional dyspnea or residual symptoms. Moreover, we previously demonstrated that large nocturnal desaturation persisted after BPA treatment despite the absence of parenchymal lung disease [9]. However, studies on nocturnal desaturation in patients with CTEPH are limited. The mechanisms underlying nocturnal desaturation, the effects of BPA on it, and factors associated with its improvement remain unclear. Therefore, in this study, we aimed to clarify the clinical features of nocturnal desaturation in patients with CTEPH.

Methods

This retrospective study was conducted in compliance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Kobe University Hospital (approval number: B240066). All enrolled patients were provided with the option to opt out if they did not wish to participate in the study. The requirement for written informed consent was waived because the data was retrospectively collected.

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Patients / study design

This retrospective observational study included consecutive patients who underwent BPA at Kobe University Hospital (Kobe, Japan) between March 2011 (the commencement of our BPA program) and December 2022. In all patients diagnosed with CTEPH, treatment strategies were assessed by a multidisciplinary team of experts, including experienced BPA interventionists and pulmonary endarterectomy (PEA) surgeons, as recommended by the clinical guidelines of the European Society of Cardiology and European Respiratory Society, during the observational period [10–12]. Routine clinical assessments, including hemodynamic characteristics and mixed venous oxygen saturation in the pulmonary artery assessed using right heart catheterization (RHC), respiratory function tests, arterial blood gas analysis, nocturnal oximetry tests, functional status based on the New York Heart Association functional class (NYHA-FC), and exercise capacity using the 6-min walk test (6-MWT), cardiopulmonary exercise test (CPET) were performed at baseline (i.e., at the time of CTEPH diagnosis) and re-evaluated at 3 months after the last BPA session. To assess the exact oxygenation and original hemodynamics, RHC and arterial blood gas analysis were performed without administering oxygen (room air condition; for patients receiving domiciliary oxygen therapy, the tests were performed 10 min after discontinuing oxygen). Patients without baseline respiratory function data, nocturnal oximetry tests, arterial blood gas analysis, and those who did not undergo re-evaluation (3 months after the last BPA) using RHC were excluded.

BPA procedure

We approached right or left main pulmonary artery through the right femoral vein using a 6-Fr long guiding sheath (Parent Plus; Medikit Terumo, Tokyo, Japan). A 6-Fr guiding catheter (Profit®, Multipurpose right, or Judkins left 4.0; Goodman, Nagoya, Aichi, Japan) was inserted through the 6-Fr long guiding sheath into the target segmental vessels. A 0.014-inch guide wire (Athlete Bpahm®; Japan Lifeline, Tokyo) was passed across the target lesions. Subsequently, 2.0–9.0-mm balloon

catheters were chosen to dilate the lesions, depending on the vessel diameter based on selective pulmonary angiography. For patients with severe hemodynamics, smaller sized balloon catheters were chosen in the first or second session to avoid lung vessel injury. These lesions were dilated with appropriate sized balloon after hemodynamics improved. We repeated the procedures until all accessible lesions were treated, regardless of normalized mean pulmonary arterial pressure (PAP).

Cardiac function, respiratory function, and nocturnal oximetry tests

Hemodynamic characteristics of systolic and diastolic blood pressure, mean PAP, mean right atrial pressure, pulmonary artery wedge pressure, cardiac index, and PVR were evaluated using RHC. The cardiac ejection fraction was assessed using echocardiography within 2 days following RHC. The respiratory function of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), percent vital capacity (%VC), and diffusing capacity of lung carbon monoxide (DLCO) were assessed using a spirometer (Autospirometer S21; Minato Medical Co., Osaka, Japan) within approximately 2 days following RHC. 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, apnea-hypopnea index (AHI), and 3% and 90% oxygen desaturation indices. Nocturnal desaturation was defined as the difference between baseline percutaneous arterial oxygen saturation (SpO_2) and minimum SpO_2 during oximetry test.

CPET and arterial blood gas analysis

CPET was conducted using an incremental symptom-limited cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan) and performed using a method similar to that used in our previous report, in accordance with the American Thoracic Society guidelines, within 2 days following RHC [13]. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), and the partial pressure of mixed-expired carbon dioxide ($PECO_2$) 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 VE versus VCO_2 over the linear component of the plot [14]. Arterial blood gases for oxygen saturation and arterial partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) at rest under room air conditions were measured by radial artery puncture. The alveolar-arterial gradient of oxygen ($A\text{-}aDO_2$) was calculated using the following equation:

$$A\text{-}aDO_2 = PAO_2 - PaO_2.$$
$$= FiO_2 \times (Patm - PH_2O) - PaCO_2/RQ - PaO_2$$
$$\approx 0.21^* \times (760^{**} - 47^{***}) - PaCO_2/0.8 - PaO_2.$$

PAO_2: partial pressure of alveolar oxygen, FiO_2: fraction of inspiratory oxygen (*room air), Patm: atmospheric pressure (**0 m above sea level), PH_2O: vapor pressure of water (***37°C), RQ: respiratory quotient.

The ratio of dead space to tidal volume (VD/VT) was calculated according to the Enghoff modification of the Bohr dead space equation as below [15].

$VD/VT = (PaCO_2 - PECO_2)/PaCO_2$.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 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-minute walking distance, hemodynamic data, and respiratory function or oxygenation parameters before and after BPA 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 of the NYHA-FC are expressed as numbers and percentages and compared using the χ^2 test for independence. Univariate and multivariable analyses based on the linear regression model were constructed to assess the adjusted relationships between nocturnal desaturation and clinical parameters, including age, hemodynamic data, and respiratory function or oxygenation parameters, in patients with CTEPH at baseline. In a multivariable regression model, respiratory-related variables considered to be clinically associated with nocturnal desaturation (baseline %VC, FEV1/FVC, %DLCO, and PaO_2), as well as variables with p-values < 0.20 in univariate analyses served as candidate predictors in the model building procedure. Forward-backward stepwise variable selection (criteria: probability-of-F-to-enter ≤ 0.05, probability-of-F-to-remove ≥ 0.10) was used to identify predictors for the final multivariable model. The level of statistical significance was set at $p < 0.05$.

Results

Patient population

A total of 243 patients were diagnosed with CTEPH between March 2011 and December 2022. Of these, 51 patients were judged as operable and underwent PEA, 175 non-operable patients underwent BPA, and 17 did not undergo any interventional treatment, mainly because of their refusal or severe comorbidities. Of the 51 patients who underwent PEA, 27 underwent additional

BPA for residual PH or symptoms. Of the 202 patients who underwent BPA, 39 were excluded (12 patients had not completed re-evaluation with RHC or lung function test after the last BPA session; 27 patients had no data of nocturnal oximetry test, lung function test, and arterial blood gas test at baseline). In total, 163 patients were enrolled in this study. The patient selection is shown in Fig. 1. The baseline characteristics of the enrolled patients are summarized in Table 1. In nocturnal oximetry test, minimum SpO_2 during sleep was 78.2 ± 6.9%, average of maximum desaturation during sleep was − 13.1 ± 5.7%, and median AHI was 16.1 (IQR: 8.6; 26.5) at baseline. Almost half of patients received domiciliary oxygen therapy.

Predictors of nocturnal desaturation

Table 2 summarizes the results of linear regression analysis of the association between nocturnal desaturation and clinical parameters in patients with CTEPH at baseline. In the univariate analysis, higher AHI, lower PaO_2, higher VD/VT, and higher A-aDO_2 at baseline were significantly associated with nocturnal desaturation. In addition to the four respiratory-related variables based on clinical considerations (baseline %VC, FEV1/FVC, %DLCO, and PaO_2), AHI, VD/VT, and A-aDO_2 which gave a p-value < 0.20 in univariate analyses served as candidate predictors in multivariate modeling. After stepwise variable selection, VD/VT (adjusted $p < 0.001$) and A-aDO_2 (adjusted $p = 0.026$) were retained in the final model (variance inflation factor: 1.009). Although VD/VT and A-aDO_2 might act as confounding factors, A-aDO_2 was retained in the additional analysis excluding VD/VT ($p = 0.043$), and VD/VT was retained in the additional analysis excluding A-aDO_2 ($p < 0.001$). Higher VD/VT and A-aDO_2 at baseline were associated with greater nocturnal desaturation (adjusted R-square = 0.282). However, the severity of sleep apnea index such as AHI, was not associated in the multivariable analysis.

Efficacy of BPA

Table 3 shows the efficacy of BPA on hemodynamic parameters, respiratory function, oxygenation, exercise capacity, and nocturnal oximetry test results. BPA could improve hemodynamics and exercise capacities significantly (mean PAP: $p < 0.001$, PVR: $p < 0.001$, and 6-minute walking distance: $p < 0.001$). Oxygenation and respiratory parameters also improved after BPA (PaO2: 60.4 ± 13.0 mmHg to 68.4 ± 16.1 mmHg; $p < 0.001$ and %VC: 89.8 ± 16.5% to 93.6 ± 31.4%; $p = 0.047$); however, the FEV1/FVC did not. Parameters which were associated with nocturnal desaturation improved after BPA (VD/VT: 0.322 ± 0.09 to 0.276 ± 0.08; $p < 0.001$ and A-aDO_2: 49.9 ± 39.2 mmHg to 34.8 ± 15.2 mmHg; $p < 0.001$). Each parameter in the nocturnal oximetry test also improved (baseline SpO_2:91.3 ± 3.4% to 92.8 ± 3.7%; $p < 0.001$, minimum SpO_2:78.2 ± 6.9% to 82.7 ± 6.5%; $p < 0.001$, and

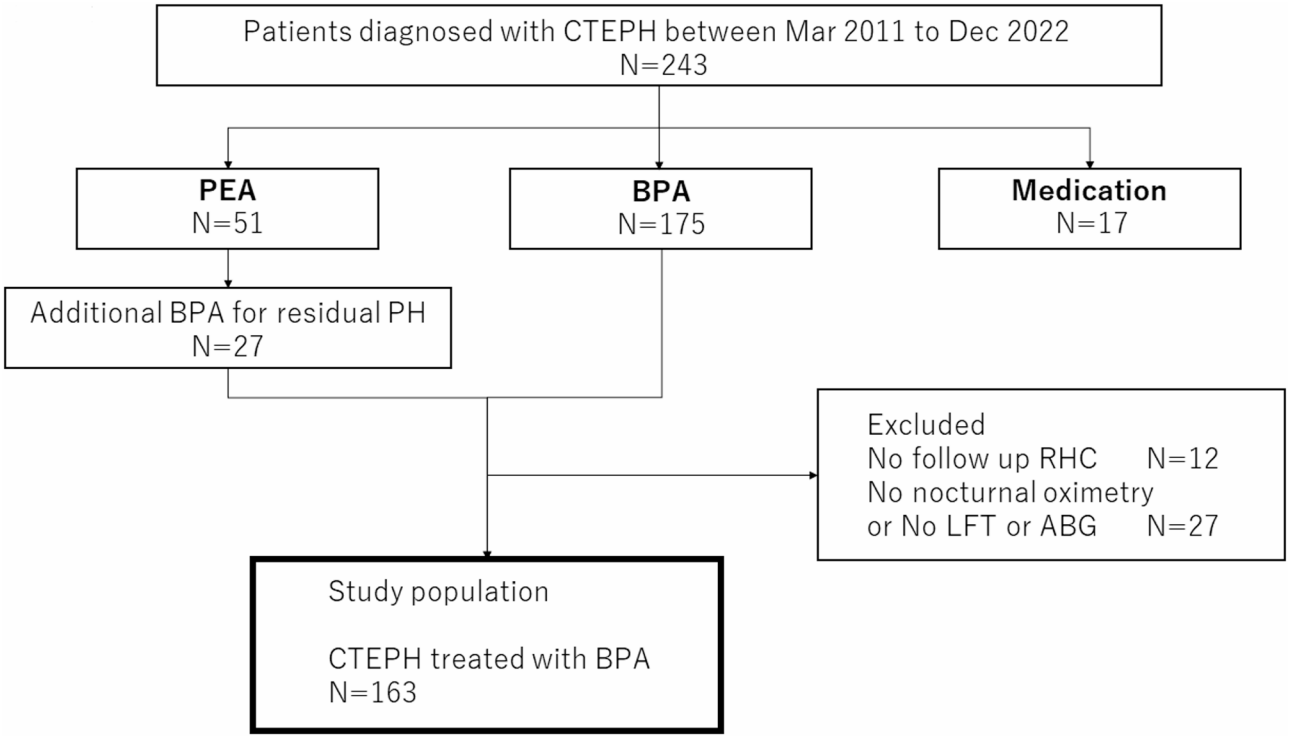

Fig. 1 Flow chart showing the patient cohort selection. CTEPH: chronic thromboembolic pulmonary hypertension; BPA: balloon pulmonary angioplasty; PEA: pulmonary endarterectomy; RHC: right heart catheterization; LFT: lung function test; ABG: arterial blood gas test

Table 1 Clinical characteristics and hemodynamic data at baseline

Variable	*N* = 163
Baseline characteristics	
Age (years)	68.0 ± 11.4
Male (n, %)	37 (22.7)
NYHA Fc I/II/III/IV (%)	1 / 26 / 65 / 8
BNP (pg/ml)	70 [177]
BMI (kg/m^2)	23.2 ± 3.5
Ejection fraction (%)	56.7 ± 7.7
PaO_2 (mmHg)	60.4 ± 13.0
$PaCO_2$ (mmHg)	37.4 ± 4.9
Lung function test	
VC (%)	89.8 ± 16.5
FEV1/FVC (%)	73.3 ± 9.4
Nocturnal oximetry test	
Minimum SpO_2 in sleep (%)	78.2 ± 6.9
Desaturation in sleep (%)	-13.1 ± 5.7
AHI	16.1 [17.9]
PAH specific drugs at any time	
sGC Stimulator (n, %)	98 (60.1)
ERA (n, %)	22 (13.5)
PDE5-I (n, %)	12 (7.4)
Prostacyclin analog (n, %)	23 (14.1)
Anticoagulation drug	
Warfarin (n, %)	126 (77.3)
DOAC (n, %)	37 (22.7)
Domiciliary oxygen therapy at any time (n, %)	81 (49.7)

List of abbreviations: NYHA FC: New York Heart Association functional class; BNP: brain natriuretic peptide; BMI: body mass index; PaO_2: partial pressure of arterial oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; VC: vital capacity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; SpO_2: saturation of percutaneous oxygen; AHI: apnea hypopnea index; sGC: soluble guanylate cyclase; ERA: endothelin-receptor antagonists; PDE5-i: phosphodiesterase type-5 inhibitors; DOAC: direct oral anticoagulant

Data are given as mean ± standard deviation or median [interquartile range]

desaturation during sleep: -13.1 ± 5.7% to -10.3 ± 5.4%; $p < 0.001$); however, nocturnal hypoxia persisted after BPA.

Figure 2 shows the correlation between changes in nocturnal desaturation and VD/VT after BPA. Improvement in VD/VT correlated well with improvement in nocturnal desaturation after BPA ($p < 0.001$, R^2 linear = 0.18). No significant correlation was found between the changes in nocturnal desaturation and changes in A-aDO_2 after BPA.

Discussion

In this study, nocturnal desaturation often coexisted with CTEPH despite the absence of parenchymal lung disease. Various factors were involved in nocturnal desaturation; however, VD/VT, a marker of the physiologic dead-space fraction, and A-aDO2, a marker of ventilation-perfusion mismatch and lung diffusing capacity, were strongly associated. Nocturnal desaturation improved slightly after BPA, which was associated with a decrease in the physiological dead-space fraction.

Oxygenation in CTEPH

Several studies have reported impaired oxygenation in patients with CTEPH. Godinas et al. reported that gas exchange was more impaired in distal CTEPH than in pulmonary arterial hypertension (PAH), which could be explained by a more pronounced blood flow redistribution in CTEPH due to nonuniform vascular obstruction [16]. Hypoxia persisted even after a successful BPA, and oxygenation slightly improved after interventional treatment with BPA or PEA; however, it did not normalize despite nearly normalized hemodynamics in studies of a multicenter registry [7, 8]. Moreover, it has also been reported that exertional desaturation remains unchanged and sustained exertional desaturation could be one of the causes of exertional dyspnea or residual symptoms after successful BPA [9]. Nocturnal hypoxia in patients with PH is occasionally reported in clinical settings [17–19]. Murta et al. reported that three-quarters of patients had sleep-disordered breathing, and almost half of the patients had nocturnal hypoxia defined by an average SpO2 < 90% in a study of 36 patients with PAH or CTEPH. The most common sleep-disordered breathing condition is obstructive sleep apnea (OSA). In this study, only mean PAP was associated with nocturnal desaturation; however, other hemodynamic parameters and the respiratory disturbance index were not [20]. Hildenbrand et al. reported that the mean nocturnal SpO2 was 89% whereas the resting SpO2 was 95% during the daytime in a study of 44 patients with PAH and 19 patients with CTEPH. In this study, more than half of the patients spent > 50% of their time in bed with SpO2 < 90% (sustained desaturation), and nocturnal SpO2 was negatively correlated with the tricuspid pressure gradient [19]. Another study by Minai et al. demonstrated that almost 70% of patients spent > 10% of their time in bed with SpO2 < 90%, and severe hemodynamics, including lower cardiac index, higher mean PAP, and higher PVR, were predictors of nocturnal desaturation in a study of 43 patients with PAH [17]. Nocturnal hypoxia could be common in patients with PAH or CTEPH despite often normal SpO2 in the daytime and severer hemodynamics were associated with nocturnal hypoxia in those studies. Moreover, patients with PAH or CTEPH are at risk of developing sleep-related breathing disorders [21]. However, the precise mechanisms underlying nocturnal hypoxia in patients with PH remain unclear.

Sleep apnea and nocturnal hypoxia

Sleep apnea is a serious sleep disorder in which pauses in breathing or periods of shallow breathing occur during sleep more often than normal, causing nocturnal

Table 2 Associations between nocturnal desaturation and clinical parameters at baseline in CTEPH

Variable	Univariate				Multivariable			
	Unstandardized B	S.E. of B	95% CI for B	*P* value	Unstandardized B	S.E. of B	95% CI for B	*P* value
Patient characteristics								
Age (years)	0.009	0.040	-0.070–0.088	0.818				
Respiratory parameters								
AHI	0.074	0.034	0.006–0.142	0.032				
%VC (%)	0.002	0.028	-0.053–0.058	0.939				
FEV1/FVC (%)	0.023	0.050	-0.077–0.122	0.652				
%DLCO (%)	-0.040	0.026	-0.092–0.013	0.136				
PaO_2 (mmHg)	-0.090	0.035	-0.158– -0.022	0.010				
VD/VT	22.96	4.356	14.35–31.58	< 0.001	22.19	4.42	13.37–30.87	< 0.001
A-aDO_2 (mmHg)	0.054	0.023	0.008–0.099	0.021	0.048	0.021	0.006–0.089	0.026
Exercise capacity								
6MWT distance (m)	0.002	0.005	-0.008–0.011	0.701				
Peak VO_2 in CPET (ml/min/kg)	-0.040	0.128	-0.294–0.213	0.753				
VE/VCO_2 slope in CPET	0.032	0.043	-0.054–0.117	0.466				
Hemodynamics								
Mean PAP (mmHg)	0.044	0.042	-0.039–0.128	0.298				
Cardiac index (L/min/m^2)	0.652	0.637	-0.606–1.909	0.308				
PVR (dyne/sec/cm^{-5})	0.001	0.001	-0.002–0.003	0.545				

List of abbreviations: AHI: apnea hypopnea index; %VC: percent predicted vital capacity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; %DLCO: percent predicted diffusing capacity for lung carbon monoxide; PaO_2: partial pressure of arterial oxygen; VD/VT: ratio of dead-space to tidal volume; A-aDO_2: alveolar-arterial difference for oxygen; 6MWT: 6-minute walk test; VO2: oxygen uptake; CPET: cardiopulmonary exercise testing; VE: ventilation; VCO_2: carbon dioxide production; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance

hypoxia [22]. OSA is the most common condition in which breathing is interrupted by a blockage of airflow through the lingual root or soft palate when the throat muscles relax during sleep. Central sleep apnea occurs when the respiratory control centers of the brain are imbalanced and do not send proper signals to the muscles that control breathing during sleep [23]. In clinical practice, OSA sometimes coexists with CTEPH. Yu et al. reported that 32 of 57 patients with CTEPH (56%) had OSA diagnosed with overnight polysomnography monitoring; their average AHI was 16.7 ± 12.2. Worse hemodynamics are associated with OSA [24]. Another study by Jilwan et al. reported that nocturnal hypoxia was common in patients with idiopathic PAH and CTEPH (observed in > 80% cases; mean AHI, 24.9 ± 22.1) without parenchymal lung disease and obesity [25]. Kohno et al. reported that BPA reduced AHI from a median 20.9 to 16.3 ($p = 0.023$) in a study of 13 patients with CTEPH [26]. In the present study, the baseline median AHI was 16.1, which tended to decrease to 14.4 after BPA. Mild-to-moderate sleep apnea may be a medical condition associated with CTEPH. Sleep apnea may be a factor in nocturnal desaturation; however, sleep apnea syndrome alone cannot explain nocturnal hypoxia. Studies on sleep-related breathing disorders in patients with PAH or CTEPH by Hildenbrand et al. and Dumitrascu et al. also demonstrated that nocturnal desaturation was not associated with a higher AHI [19, 27]. In the aforementioned study by Jilwan et al., the major mechanism of nocturnal hypoxia was ventilation-perfusion mismatch or associated obstructive apneic events [25]. In the present study, AHI (severity of sleep apnea syndrome) was associated with nocturnal desaturation in the univariate analysis but not in the multivariable analysis. VD/VT, a marker of physiologic dead-space fraction, A-aDO2, a marker of ventilation-perfusion mismatch, and lung diffusing capacity were strongly associated. This was partially consistent with a previous study by Jilwan et al. that reported that ventilation-perfusion mismatch caused nocturnal hypoxia; however, we also focused on the role of the physiologic dead-space fraction in patients with CTEPH. We also demonstrated that the improvement in dead space correlated well with an improvement in nocturnal desaturation after BPA.

However, the change in VD/VT must be interpreted with caution because it may also reflect factors other than the physiological dead space. In patients with CTEPH, ventilation of non-perfused area contributes to an increased dead space resulting in elevated VD/VT [16, 28]. The physiological VD is also associated with intrapulmonary shunt and heterogeneity of the alveolar ventilation/perfusion ratio [28, 29]. VD/VT is highly sensitive to hyperventilation that increases the alveolar ventilation/perfusion ratio [28]. BPA improves distal pulmonary blood flow, thereby increasing the area involved in gas exchange, resulting in the improvement of dead space and ventilation-perfusion mismatch. Moreover, a decrease in intrapulmonary shunt [30], an improvement

Table 3 Hemodynamic and oxygenation parameters change before and after BPA ($n = 163$)

Variable	Baseline	After the last BPA	*p* value*
Baseline characteristics			
NYHA FC (I /II / III /IV) (%)	1 / 26 / 65 / 8	31 /57 /12 /0	< 0.001
Respiratory parameters			
VC (%)	89.8 ± 16.5	93.6 ± 31.4	0.047
FEV1/FVC (%)	73.4 ± 9.4	73.9 ± 8.6	0.850
DLCO (%)	65.1 ± 17.8	62.6 ± 15.6	0.010
SaO_2 (%)	90.3 ± 5.0	93.3 ± 4.4	< 0.001
PaO_2 (mmHg)	60.4 ± 13.0	68.4 ± 16.1	< 0.001
PaCO2 (mmHg)	37.4 ± 4.9	38.6 ± 4.4	0.001
SvO_2 (%)	63.2 ± 9.6	67.0 ± 6.6	< 0.001
A-aDO_2 (mmHg)	49.9 ± 39.2	34.8 ± 15.2	< 0.001
VD/VT	0.322 ± 0.09	0.276 ± 0.08	< 0.001
Nocturnal oximetry test			
Baseline SpO_2 in sleep	91.3 ± 3.4	92.8 ± 3.7	< 0.001
Minimum SpO_2 in sleep (%)	78.2 ± 6.9	82.7 ± 6.5	< 0.001
Desaturation in sleep (%)	-13.1 ± 5.7	-10.3 ± 5.4	< 0.001
AHI	16.1 [17.9]	14.4 [15.9]	0.296
3%ODI	22.4 ± 17.6	17.4 ± 12.2	< 0.001
90%ODI	36.6 [57.2]	7.3 [40.7]	< 0.001
Exercise capacity			
6MWT distance (m)	326 ± 101	376 ± 106	< 0.001
Peak VO_2 in CPET (ml/min/kg)	12.8 ± 3.9	15.9 ± 4.7	< 0.001
VE/VCO_2 slope in CPET	40.7 ± 11.5	30.8 ± 8.8	< 0.001
Baseline hemodynamics			
Mean RAP (mmHg)	4.8 ± 3.3	4.0 ± 2.8	0.003
Systolic PAP (mmHg)	65.5 ± 18.9	34.1 ± 10.2	< 0.001
Diastolic PAP (mmHg)	21.3 ± 7.5	11.5 ± 4.6	< 0.001
Mean PAP (mmHg)	37.3 ± 10.7	20.1 ± 5.5	< 0.001
PAWP (mmHg)	8.1 ± 3.4	8.3 ± 3.6	0.630
Cardiac index (L/min/m^2)	2.26 ± 0.73	2.55 ± 0.66	< 0.001
PVR (dyne/sec/cm^{-5})	775 ± 472	265 ± 139	< 0.001

List of abbreviations: NYHA FC: New York Heart Association functional class; VC: vital capacity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusing capacity for lung carbon monoxide; SaO_2: arterial oxygen saturation; PaO_2: partial pressure of arterial oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; SvO_2: mixed venous oxygen saturation; A-aDO_2: alveolar-arterial oxygen difference; VD/VT: ratio of dead-space to tidal volume; SpO_2: percutaneous oxygen saturation; AHI: apnea hypopnea index; ODI: oxygen desaturation index; 6MWT: 6-minute 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]

in heterogeneity of the alveolar ventilation/perfusion ratio, and a decrease of ventilation after BPA may contribute to the improvement in VD/VT, and these factors do not necessarily indicate a decrease in the true physiological dead space [28].

Physiological dead-space fraction in CTEPH

Physiological dead space, which consists of anatomic and alveolar dead spaces, represents the volume of ventilated air that does not participate in gas exchange [31]. A higher physiological dead space is involved in ventilatory inefficiency, which contributes to exercise intolerance and disability in patients with PAH or CTEPH [32]. Godinas et al. reported that compared with PAH, increased dead-space ventilation that resulted in worse ventilatory efficiency and survival was observed in distal CTEPH from the results of CPET in 49 patients with CTEPH and 45 patients with PAH [16]. Increased dead-space ventilation is also associated with hypoxia or dyspnea in CTEPH, and a decrease in dead-space ventilation by PEA or BPA may contribute to improved oxygenation. In a study involving 23 patients, Minatsuki et al. reported that the dead-space ratio could be a marker of improved arterial oxygen saturation after BPA [30]. Similarly, van der Plas et al. reported that the relief of dead-space ventilation by the removal of chronic thromboembolism with PEA could contribute to the postoperative recovery of symptomatic dyspnea [33]. In the present study, we demonstrated that VD/VT, a marker of physiological dead-space fraction, and A-aDO2, a

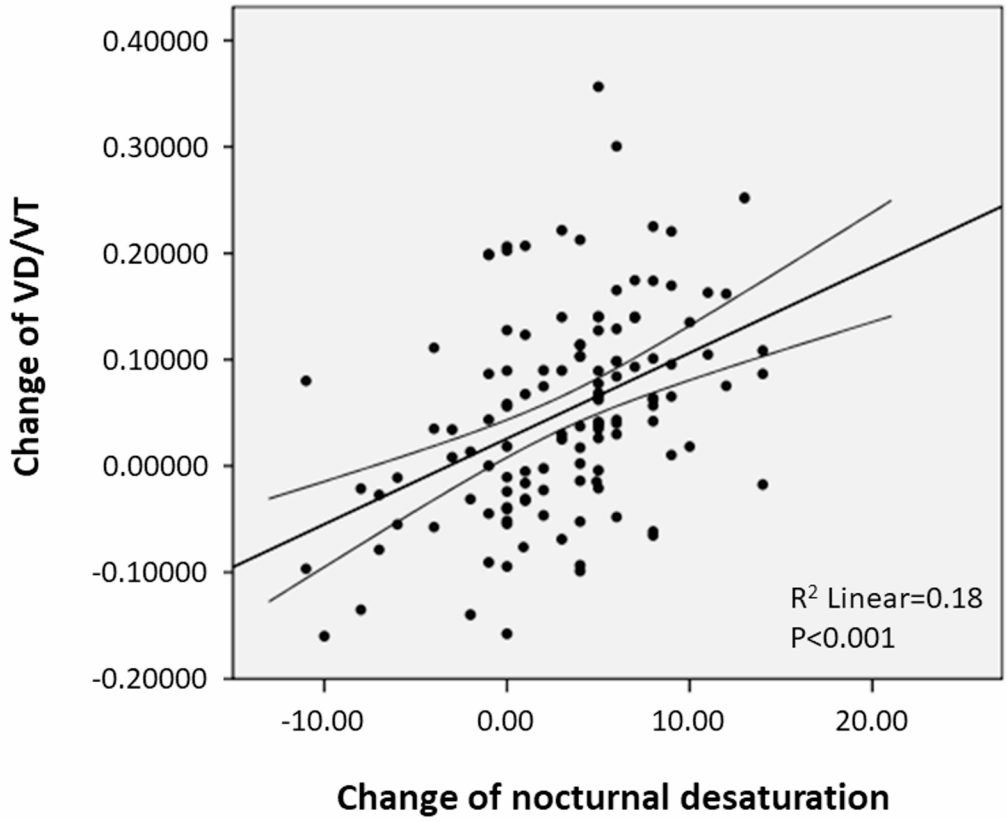

Fig. 2 Correlations between changes in nocturnal desaturation and VD/VT after BPA. ($p < 0.001$, R^2 linear = 0.18). BPA: balloon pulmonary angioplasty; VD/VT: the ratio of dead space to tidal volume

marker of ventilation-perfusion mismatch and lung diffusing capacity, were strongly associated with nocturnal desaturation in patients with CTEPH. However, the precise physiological mechanism of nocturnal desaturation remains ambiguous. In addition to the aforementioned factors, comorbid sleep apnea with slightly elevated AHI and fluid displacement due to decubitus position might be compositely involved. Further investigation using full-scale polysomnography is needed for better understanding of nocturnal desaturation.

The decrease in the physiological dead-space fraction may contribute to the improvement of nocturnal desaturation. However, these improvements are limited compared to those in hemodynamics. Even though all possible accessible lesions had been treated after adequate BPA, residual ventilation-perfusion mismatch or impaired physiological dead space at the segmental and local microvascular levels, might cause nocturnal desaturation [9]. Nocturnal desaturation is highly prevalent; however, it is underestimated in daytime assessments of patients with PAH or CTEPH [19]. Nocturnal oximetry tests should be included as a routine evaluation for these patients and nocturnal oxygen therapy should be continued, if necessary.

Limitations

This study has several limitations, the main of which is its single-center, retrospective, observational nature. Therefore, missing values were unavoidable and may have influenced the results of the multivariable regression model. Moreover, although variance inflation factor in the multivariable regression model was low, there might be a potential bias that VD/VT and A-aDO2 were confounding variables. Furthermore, the nocturnal oximetry test using oximetry monitor is a simplified test, not a full-scale test for sleep apnea. Another limitation is that the sample size was relatively small. It cannot be denied that less experience with the procedure in the initial stages of our BPA program could have affected the BPA outcomes, including oxygenation.

Conclusion

Nocturnal desaturation often coexists with CTEPH, despite the absence of parenchymal lung disease. The causes of nocturnal desaturation might be multifactorial. In our experience, larger physiological dead-space fraction, larger ventilation-perfusion mismatch, and lower lung diffusing capacity were strongly associated with nocturnal desaturation. BPA could improve distal pulmonary

blood flow, thereby increasing the area involved in gas exchange, resulting in the improvement of physiological dead space and ventilation-perfusion mismatch. Nocturnal desaturation improved slightly after BPA. Our study emphasizes the importance of including nocturnal oximetry in routine evaluations and continuation of nocturnal oxygen therapy, if necessary.

Abbreviations

A-aDO_2	Alveolar-arterial difference for oxygen
AHI	Apnea-hypopnea index
BPA	Balloon pulmonary angioplasty
CPET	Cardiopulmonary exercise test
CTEPH	Chronic thromboembolic pulmonary hypertension
DLCO	Diffusing capacity for lung carbon monoxide
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
NYHA-FC	New York heart association functional class
OSA	Obstructive sleep apnea
PAP	Pulmonary arterial pressure
PaCO2	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PAH	Pulmonary arterial hypertension
PEA	Pulmonary endarterectomy
$PECO_2$	Partial pressure of mixed-expired carbon dioxide
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
SpO_2	Percutaneous arterial oxygen saturation
RHC	Right heart catheterization
VC	Vital capacity
VD/VT	Ratio of dead space to tidal volume
VE/VCO_2	Minute ventilation/carbon dioxide production
VO_2	Oxygen uptake
6-MWT	6-minute walk test

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Author contributions
Y.T. and M.S. designed the study. H.F., K.M., Y.T. and K.Y. collected the data. Y.T., N.E., and H.O. analyzed the data. All authors participated in this work and approved the final manuscript.

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Data availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Kobe University Hospital (approval number: B240066). All enrolled patients were provided with the option to opt out if they did not wish to participate in the study. The requirement for written informed consent was waived because the data was retrospectively collected.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 6500017, Japan
[2]Laboratory of Clinical Pharmaceutical Science, Kobe Pharmaceutical University, Kobe, Japan

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