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Balloon pulmonary angioplasty attenuates sleep apnea in patients with chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) improves pulmonary hemodynamics in chronic thromboembolic pulmonary hypertension (CTEPH) patients. However, whether it affects the severity of sleep apnea (SA) remains unknown. We investigated the effect of BPA on the severity of SA in CTEPH patients.
Methods: We studied 13 patients with CTEPH who had an apnea hypopnea index (AHI) > 10 before BPA and underwent a second polygraph test 6 months after the last BPA session.
Results: BPA decreased pulmonary vascular resistance, mean pulmonary artery pressure (PAP), and plasma B-type natriuretic peptide levels, and increased the 6-minute walking distance. BPA decreased the AHI (from 20.9 [13.9–35.7] to 16.3 [7.7–21.8] times/hour, $P = 0.023$) and hypopnea index (from 13.2 [8.4–22.5] to 6.4 [3.8–10.9] times/hour, $P = 0.013$), but not the obstructive, central, or mixed apnea index. The change in AHI correlated with that in mean PAP, but not with the change in body mass index or other parameters of hemodynamics.
Conclusions: BPA-induced improvement in hemodynamics was associated with the attenuation of SA in patients with CTEPH and SA. Therefore, close attention should be paid to SA in CTEPH patients, and SA should be re-evaluated after BPA to avoid overestimating its severity.

Introduction

There is accumulating evidence that sleep apnea (SA) is highly prevalent in patients with pulmonary hypertension (PH) including chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension.[1–4] SA is known to be associated with the hemodynamic status in patients with PH.[2,3] For instance, a nocturnal oximetry study in 43 PH patients revealed that nocturnal hypoxemia was associated with advanced PH and right ventricular dysfunction.[2] Orr et al. demonstrated that cardiac index (CI) strongly predicted the presence and severity of SA in CTEPH patients.[3]

Although the mechanism of high prevalence of SA in PH patients still remains to be elucidated, it is plausible that it could be explained by hemodynamics-related mechanisms (e.g. nocturnal rostral fluid shift in congestive status or instability of ventilatory control in low cardiac output states).[5,6] If this is true, hemodynamic improvement could attenuate the severity of SA in PH, as in heart failure.[7–9] Balloon pulmonary angioplasty (BPA) improves the hemodynamics, functional capacity, and right ventricular remodeling in CTEPH patients.[10] Thus, patients treated with BPA are suitable candidates for testing the hypothesis that the severity of SA could decrease in parallel with improvement of hemodynamic parameters. In this study, we investigated the effect of BPA on SA in patients with CTEPH (i.e. comparison of SA severity before and after BPA), and attempted to distinguish those hemodynamic parameters that, when changed, resulted in the most significant change of SA parameters after BPA.

Methods

This was an observational study in a single university-based hospital center in Japan. We examined 53 consecutive CTEPH patients who were candidates for BPA and underwent a polygraph test before BPA from July 2013 to April 2015. The diagnosis of CTEPH was based on the visualization of confirmed pulmonary thromboembolism on contrast-enhanced lung computed tomography, perfusion lung scintigraphy, and pulmonary angiography after ruling out collagen vascular disease, parenchymal lung disease, left heart abnormality, and other systemic diseases by blood tests, pulmonary function tests, and echocardiography.[11] Mean pulmonary artery pressure (PAP) ≥25 mm Hg was confirmed on initial assessment during right heart catheterization (RHC). We excluded 17 patients who underwent polygraph test with oxygen flow, 16 patients with AHI ≤ 10 before BPA, and 7

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patients with incomplete polygraph test data. Finally, we studied 13 patients with CTEPH who had an AHI > 10 before BPA, and these patients underwent a second polygraph test 6 months after the last BPA session.

The polygraph test was performed using an unattended system (Morpheus®; Teijin, Tokyo, Japan) that monitored the electrocardiogram, chest, and abdominal respiratory effort, nasal airflow, and arterial oxyhemoglobin saturation. The accuracy of this type of portable monitor in diagnosing SA and measuring its severity with high reproducibility compared with polysomnography (PSG) has been previously validated.[12–14] A single-night sleep log was used to minimize the potential for overestimating total sleep time. Episodes of apnea and hypopnea were scored according to the American Academy of Sleep Medicine manual.[15] Apnea was defined as a > 90% reduction in the amplitude of nasal pressure and hypopnea was defined as >50% reduction in the amplitude of nasal pressure associated with a ≥ 3% reduction in oxygen saturation for at least 10 s. The total number of apnea and hypopnea episodes was divided by the total sleep time to calculate the AHI. The major polygraphic parameters investigated were the AHI, the central apnea index, the obstructive apnea index, mixed apnea, hypopnea, and% total sleep time with < 90% SpO_2 (T90%).

All patients underwent RHC for the measurement of right atrial pressure (RAP) and PAP prior to and 6 months after BPA. The cardiac index (CI) was determined by the Fick technique. The pulmonary vascular resistance (PVR) was calculated by subtracting the pulmonary capillary wedge pressure (PCWP) from the mean PAP, and dividing it by the cardiac output, as reported previously.[16,17] Their laboratory data were evaluated and the functional capacity was determined (World health organization [WHO] functional class and 6-minute walking distance [6MWD]) within 1 day of the polygraph test. All patients provided informed consent, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

Values are expressed as median (25th to 75th percentile) for continuous variables, and as number and percentage for categorical variables. Changes in RHC parameters, polygraph test data, laboratory data, body mass index (BMI), and functional capacity between before and 6 months after BPA were compared using Wilcoxon matched-pairs signed rank test. Kendall's rank correlation coefficients were used to evaluate the correlation between the change in AHI and other parameters. *P* values less than 0.05 were considered statistically significant. Data were analyzed using the SPSS statistical software (SPSS Inc., Chicago, IL, USA).

Results

A total of 13 patients with SA who underwent BPA were enrolled (age 57 [53–65] years; 6 male [46%]; 13 [11–15] target vessels per patient; 6 [4–8] sessions per patient). Twelve patients (92%) were receiving home oxygen therapy before BPA. No patient was previously treated with pulmonary endarterectomy. Warfarin, loop diuretics, phosphodiesterase type-5 inhibitors, endothelin receptor antagonists, prostacyclin analogues, and soluble guanylate cyclase stimulators had been prescribed for all patients (100%), 4 patients (31%), 7 patients (54%), 2 patients (15%), 1 patient (8%), and 1 patient (8%), respectively.

Table 1 shows the changes in RHC parameters, polygraph test data, laboratory data, BMI, and functional capacity between before and 6 months after BPA. BPA decreased PVR, mean RAP, mean PAP, and plasma B-type natriuretic peptide (BNP) level, and increased blood gas oxygen saturation (SaO_2) level at rest, and 6MWD. The WHO functional class of the patients improved and their BMI increased after BPA. A significant decrease in AHI (Table 1 and Fig. 1A), hypopnea index, and T90% was observed 6 months after BPA.

Table 1
Changes in RHC parameters, polygraph test data, laboratory data, BMI, WHO functional class, and 6MWD

	Before BPA	6 months after BPA	*P*-value
RHC parameters			
mean RAP, mmHg	6 (4–10)	2 (1–5)	0.002
mean PAP, mmHg	39 (32 –49)	18 (16–23)	0.001
CI, L/min	2.2 (1.9 –2.5)	2.1 (2.0 –3.1)	0.263
PCWP, mmHg	10 (6 –12)	6 (5 –9)	0.050
PVR, dynes·sec·cm^{-5}	523 (478 –1020)	239 (149 –323)	0.001
Polygraph test data			
AHI, times/hour	20.9 (13.9 –35.7)	16.3 (7.7 –21.8)	0.023
Obstructive apnea index, times/hour	1.6 (0.8 –12.8)	7.1 (1.9–12.2)	0.152
Central apnea index, times/hour	0.7 (0.0 –1.9)	0.1 (0.0 –1.0)	0.173
Mixed apnea index, times/hour	0.0 (0.0–0.7)	0.1 (0.0 –0.3)	0.213
Hypopnea index, times/hour	13.2 (8.4 –22.5)	6.4 (3.8 –10.9)	0.013
% Total sleep time <90% SpO_2, %	74.8 (31.9–85.6)	11.9 (2.7–22.8)	0.005
BMI, kg/m^2	22.6 (20.5–26.3)	23.5 (21.9–28.0)	0.039
Laboratory data			
BNP, pg/mL	22.1 (16.0–208.1)	11.8 (8.0–47.4)	0.028
eGFR, mL/min/1.73 m^2	69.0 (53.5 –73.0)	74.0 (57.5 –82.0)	0.126
SaO_2, %	89.8 (88.2–91.2)	95.5 (94.6 –96.2)	0.001
WHO functional class, n (%)			0.002
I	0 (0)	7 (54)	
II	2 (15)	6 (46)	
III	11 (85)	0 (0)	
IV	0 (0)	0 (0)	
6MWD, m	358 (249 –398)	500 (445 –558)	0.001

Values are expressed as median (25th–75th percentile) for continuous variables, and as number and percentage for categorical variables.
RHC, right-sided heart catheterization; BMI, body mass index; WHO, world health organization; 6MWD, 6-min walking distance; BPA; balloon pulmonary angioplasty; RAP, right atrial pressure; PAP, pulmonary artery pressure; CI; cardiac index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; AHI, apnea hypopnea index; SpO_2, oxygen saturation; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

Before BPA, 10 patients (77%) had obstructive-type SA (OSA) and 3 patients (23%) had central-type SA (CSA). Six months after BPA, 2 patients had unrecognized SA and no patient had CSA, while the other 11 patients (85%) had OSA. The change in AHI significantly correlated with the change in mean PAP (Fig. 1B), but not with the change in CI ($r = -0.256$, $P = 0.222$), T90% ($r = -0.026$, $P = 0.903$), BMI ($r = 0.282$, $P = 0.180$), 6MWD ($r = 0.256$, $P = 0.222$), plasma BNP level ($r = 0.359$, $P = 0.088$), blood gas SaO_2 level ($r = -0.260$, $P = 0.221$) or other hemodynamic parameters (mean RAP; $r = 0.325$, $P = 0.135$, PVR; $r = 0.308$, $P = 0.143$).

Discussion

To our knowledge, this is the first study revealing that BPA attenuated the severity of SA in patients with CTEPH. SA, particularly OSA, is mainly caused by the presence of excessive soft tissue in the neck, and obesity is one of the main risk factors.[18] In the present study, very few patients were overweight or obese. Further, AHI decreased although BMI increased after BPA, strongly suggesting that SA in patients with CTEPH might be caused by other mechanisms. In patients with left heart failure, the use of carvedilol,[7] cardiac resynchronization therapy,[8] and left ventricular assist device[9] reduces the severity of SA. The previous studies suggest that SA was associated with hemodynamic changes in heart failure; increase in cardiac output as well as decrease in PCWP was associated with a decrease in SA severity, mainly through the attenuation of CSA.[9,19] However, little

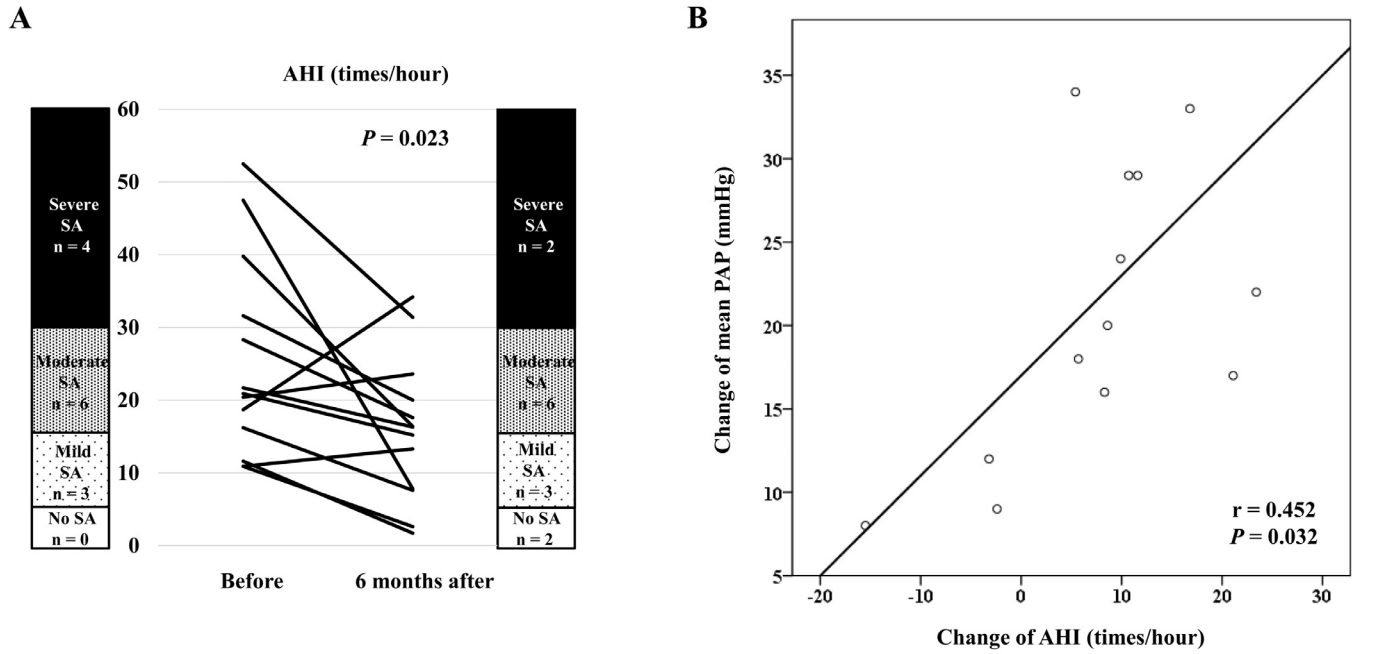

Fig. 1. Severity of SA before and 6 months after BPA for CTEPH (A) and correlation between the changes in AHI and mean PAP 6 months after BPA (B)
SA, sleep apnea; BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; AHI, apnea hypopnea index; PAP, pulmonary artery pressure.

had been known about whether changes in hemodynamics could affect the severity of SA in patients with PH. We demonstrated that a change in mean PAP was associated with a change in AHI, suggesting that SA could be associated with the hemodynamic status of the PH patient.

Although the elucidation of the mechanisms of improvement in SA after BPA is beyond the scope of our current study, there are several plausible mechanisms. First, the high prevalence of OSA in non-obese patients led us to hypothesize that fluid retention, and more specifically, nocturnal shift of dependent fluid rostrally while recumbent during sleep, is involved in the pathogenesis of SA.[5] Thus, the hemodynamic improvement by BPA might attenuate the fluid retention in the legs and its rostral shift, leading to the observed improvement in SA. Second, low CI contributes to unstable breathing,[6] which may be relevant in SA, although our data do not support this view because there was no significant association between change of AHI and that of CI after BPA. Third, patients with CTEPH are known to have low baseline oxygen saturation, which probably contributes to the high prevalence of SA. Due to significant ventilation/perfusion mismatch in CTEPH, the oxygen saturation of hemoglobin is on the steeper part of the dissociation curve, whereby relatively small perturbation can result in significant desaturation, as discussed in the other paper.[3] After BPA, improvement in ventilation/perfusion mismatching may have resulted in decreased AHI. Since our data are a preliminary result, the interpretation of these results needs to be made with caution. The attenuation of SA after BPA could be multifactorial, and the comprehensive assessment of rostral fluid shift, cardiac output and breathing stability during sleep, and gas exchange efficiency in a large multicenter study will likely be required to elucidate the detailed mechanism of SA attenuation after BPA in future. From the clinical point of view, close attention should be paid to SA in patients with CTEPH, and mean PAP could be an indicator of SA severity.

Although hemodynamic status could affect SA severity according to our data, apnea-induced hypoxemia and sustained periods of nocturnal oxygen desaturation are also known to induce pulmonary arterial vasoconstriction, which may contribute to exacerbation of PH.[18,20] These findings suggest that there might be a bidirectional relationship between SA and PH. In addition to treatment for SA itself, management of hemodynamics could be an important clinical strategy for the treatment of SA in patients with CTEPH. Whether treatment of residual SA as part of the management of PH could affect PH severity and long-term clinical outcome needs to be evaluated in a future study. This kind of research may justify initiatives to identify the presence of SA in patients with CTEPH by routine screening and to identify those needing treatment using continuous positive airway pressure.

The results of our study suggest that SA needs to be re-evaluated after BPA to avoid overestimating its severity. Thus, in addition to the screening for SA in PH patients, which was described in the recently reported expert opinion statement,[21] repeated assessments for SA might be required during the treatment for PH. For future research, the pathological effect of SA and the impact of its treatment need to be elucidated, as discussed above. Larger multi-center studies are required to define the role of SA in the pathogenesis or progression of CTEPH and the clinical impact of its treatment (e.g. continuous positive airway pressure, adaptive servo ventilation, or nocturnal supplemental oxygen).

The present study has several limitations that should be considered when interpreting the results. First, because our findings were based on observations at a single institution and the number of patients was small, the statistical power might be inadequate to detect any negative outcomes, especially their association with hemodynamics and SA parameters. Second, PSG evaluation will be needed to evaluate the precise severity and type of SA, exact total sleep duration, and sleep stages. Third, our study population included only patients who underwent BPA. Thus, there is no control condition (e.g. CTEPH patients treated with medication intended to treat PH) in this study and it cannot be determined whether reduction in the severity of SA can be attributed to BPA or whether medical therapy would have a similar benefit. Despite these limitations, this study has highlighted dynamic changes of SA status in CTEPH patients treated with BPA.

In conclusion, BPA attenuates SA in patients with CTEPH, suggesting that the severity of SA in patients with CTEPH could be modulated by a change in hemodynamic parameters. Therefore, close attention

should be paid to SA in patients with CTEPH; in addition, SA should be re-evaluated after BPA to avoid overestimating the severity of SA.

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Conflict of interest

The authors declare that there are no conflicts of interest including related consultancies, shareholdings, and funding grants.

Statements of ethics

This study was approved by the Keio University School of Medicine Ethics Committee. Informed consent was obtained from patients.

References

1. Ulrich S, Fischler M, Speich R, Bloch KE. Sleep-related breathing disorders in patients with pulmonary hypertension. *Chest*. 2008;133:1375–1380.
2. Minai OA, Pandya CM, Golish JA, et al. Predictors of nocturnal oxygen desaturation in pulmonary arterial hypertension. *Chest*. 2007;131:109–117.
3. Orr JE, Auger WR, DeYoung PN, Kim NH, Malhotra A, Owens RL. Usefulness of low cardiac index to predict sleep-disordered breathing in chronic thromboembolic pulmonary hypertension. *Am J Cardiol*. 2016;117:1001–1005.
4. Kohno T, Kataoka M, Kawakami T, et al. Moderate-to-severe obstructive sleep apnea is associated with subclinical myocardial injury and impaired hemodynamics in pulmonary hypertension patients. *Sleep Med*. 2017;30:121–127.
5. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. *Circulation*. 2012;126:1495–1510.
6. Yumino D, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. *Proc Am Thoracic Soc*. 2008;5:226–236.
7. Tamura A, Kawano Y, Kadota J. Carvedilol reduces the severity of central sleep apnea in chronic heart failure. *Circ J*. 2009;73:295–298.
8. Stanchina ML, Ellison K, Malhotra A, et al. The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. *Chest*. 2007;132:433–439.
9. Agostoni P, Contini M, Vignati C, et al. Acute increase of cardiac output reduces central sleep apneas in heart failure patients. *J Am Coll Cardiol*. 2015;66:2571–2572.
10. Tsugu T, Murata M, Kawakami T, et al. Significance of echocardiographic assessment for right ventricular function after balloon pulmonary angioplasty in patients with chronic thromboembolic induced pulmonary hypertension. *Am J Cardiol*. 2015;115:256–261.
11. Galie N, Humbert M, Vachiery JL, 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*. 2016;37:67–119.
12. Santos-Silva R, Sartori DE, Truksinas V, et al. Validation of a portable monitoring system for the diagnosis of obstructive sleep apnea syndrome. *Sleep*. 2009;32:629–636.
13. Redline S, Tosteson T, Boucher MA, Millman RP. Measurement of sleep-related breathing disturbances in epidemiologic studies. Assessment of the validity and reproducibility of a portable monitoring device. *Chest*. 1991;100:1281–1286.
14. Takama N, Kurabayashi M. Effectiveness of a portable device and the need for treatment of mild-to-moderate obstructive sleep-disordered breathing in patients with cardiovascular disease. *J Cardiol*. 2010;56:73–78.
15. Chesson Jr. AL, Berry RB, Pack A. American academy of sleep M, American Thoracic S, American College of Chest P. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. *Sleep*. 2003;26:907–913.
16. Kataoka M, Inami T, Hayashida K, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Intervent*. 2012;5:756–762.
17. Kimura M, Kohno T, Kawakami T, et al. Midterm effect of balloon pulmonary angioplasty on hemodynamics and subclinical myocardial damage in chronic thromboembolic pulmonary hypertension. *Can J Cardiol*. 2017;33:463–470.
18. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*. 2008;118:1080–1111.
19. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. *Circulation*. 1999;99:1574–1579.
20. Sajkov D, Wang T, Saunders NA, Bune AJ, McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *American journal of respiratory and critical care medicine*. 2002;165:152–158.
21. Randerath W, Verbraecken J, Andreas S, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J*. 2017;49.