

# Chapter 6

## Pulmonary Hypertension in Obstructive Sleep Apnea



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### Introduction

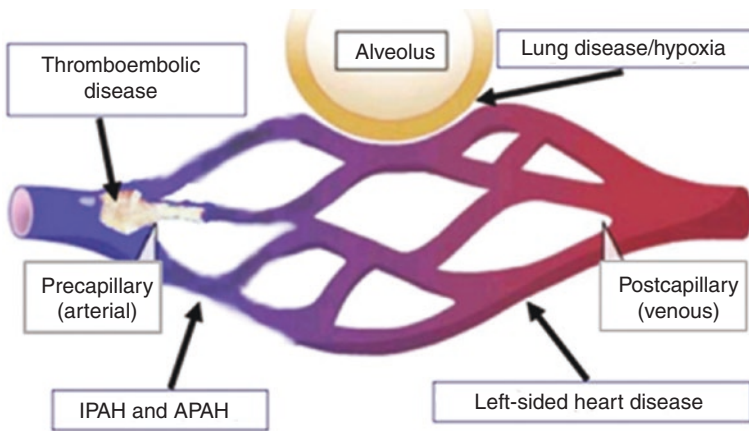
Pulmonary hypertension (PH) is a hemodynamic and pathophysiological state that is classified according to the hemodynamic profile of the pulmonary circulation — pre-capillary, post-capillary, or both (Fig. 6.1). Common causes of pre-capillary PH are related to chronic thromboembolic PH and pulmonary arterial hypertension that can be found in three main forms: idiopathic pulmonary arterial hypertension, familial form, and PH associated with other risk factors and medical conditions, such as collagen vascular diseases. Pre- and post-capillary PH is caused by heart disease and lung disease. All types of PH share common pathological changes in the form of proliferative vasculopathy, characterized by vasoconstriction and cell proliferation. Left heart disease (WHO Group 2) is the most common cause of PH in Western countries. The second most common cause of PH is WHO Group 3 that is comprised of lung disease associated with hypoxia and sleep-disordered breathing. Owing to their high prevalence, sleep-disordered breathing and chronic obstructive pulmonary disease (COPD) are by far the most common causes of PH in Group 3. Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, affecting up to 50% of men and 25% of women in the middle-aged population [1, 2]. In general, 27–30% of patients with OSA without left ventricular dysfunction or hypoxemic lung disease have PH, which tends to be mild to moderate in severity. However, severe PH can occur in the setting of OSA [3–5]. Nocturnal hypoxemia can be an important indicator of the presence of PH in this population. Patients with OSA and PH have a worse prognosis with a lower quality of life and higher mortality than those without PH. Treatment of OSA is associated with decreased pulmonary artery pressure (Ppa).

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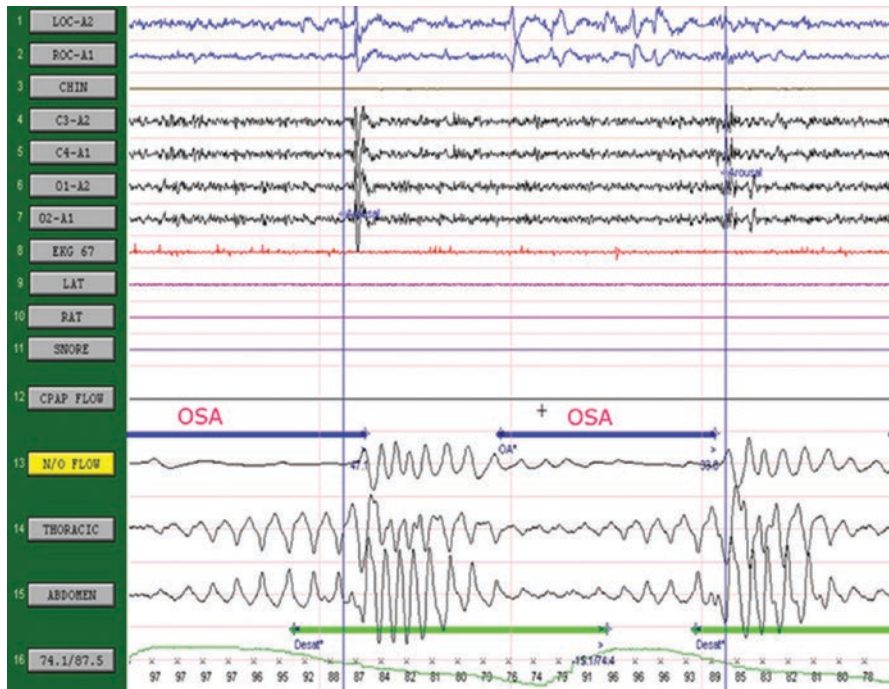


**Fig. 6.1** Major causes of pre-capillary PH are related to pulmonary arterial hypertension and chronic thromboembolic PH. Common causes of post-capillary pulmonary hypertension are left-sided heart disease, lung disease, and hypoxia

## Case Report

A 40-year-old man was seen in the pulmonary clinic because of increasing dyspnea and excessive daytime sleepiness. The patient gave a history of habitual snoring and unrefreshing sleep with daytime fatigue for approximately 3 years before the clinic visit. Shortness of breath on exertion developed about a year ago. The patient reported gasping awake occasionally, heartburn, and one- to two-time nocturia.

On examination, the patient appeared comfortable. The blood pressure was 158/92 mm Hg, the pulse 88 beats per minute, and the oxygen saturation 96% while he was breathing ambient air. The height was 171.5 cm, the weight was 91.6 kg, and the body mass index was 31 kg/m<sup>2</sup>. The upper airway examination showed narrowed oropharyngeal inlet due to increased soft tissue mass. Neck circumference was 40 cm. The jugular veins were not visible due to a short neck. Heart sounds were distant, without a murmur, rub, or gallop, and lungs were clear. There was leg edema to the knees; the remainder of the examination was normal. The complete blood count and serologic testing for collagen vascular disease were essentially normal. An electrocardiogram (ECG) showed sinus rhythm at a rate of 92 beats per minute and right axis deviation. Echocardiogram showed normal left ventricular cavity size, hyperdynamic left ventricular systolic function, and moderate concentric left ventricular hypertrophy. Left ventricular ejection fraction was >70%. Left ventricular ejection fraction was >70% with mildly decreased right ventricular systolic function; the right ventricular systolic pressure (RVSP) was estimated to be 65 mm Hg. Right and left atria were mildly dilated. The chest radiograph showed enlargement of the right, left, and main pulmonary arteries. The lungs were clear, with no evidence of interstitial lung disease or emphysema. A CT scan of the chest and a subsequent pulmonary CT angiogram confirmed the enlargement of the main



**Fig. 6.2** A polysomnograph of 60 s in duration shows two obstructive apneas during REM sleep with oxygen desaturations to a nadir of 74%

pulmonary artery and no evidence of pulmonary emboli. The right ventricle was enlarged; the wall of the right ventricle was thick (5 mm), with flattening of the inter-ventricular septum. Polysomnography was performed. A 60-s epoch of the polysomnography shows two obstructive apneas during REM sleep with oxygen desaturations to a nadir of 74% (Fig. 6.2). Apnea-hypopnea index (AHI) was 29 events per hour with mean asleep arterial oxygen saturation of 94%, and time with oxygen saturation below 90% was 36 min.

## Discussion

### *Mechanism of PH in OSA*

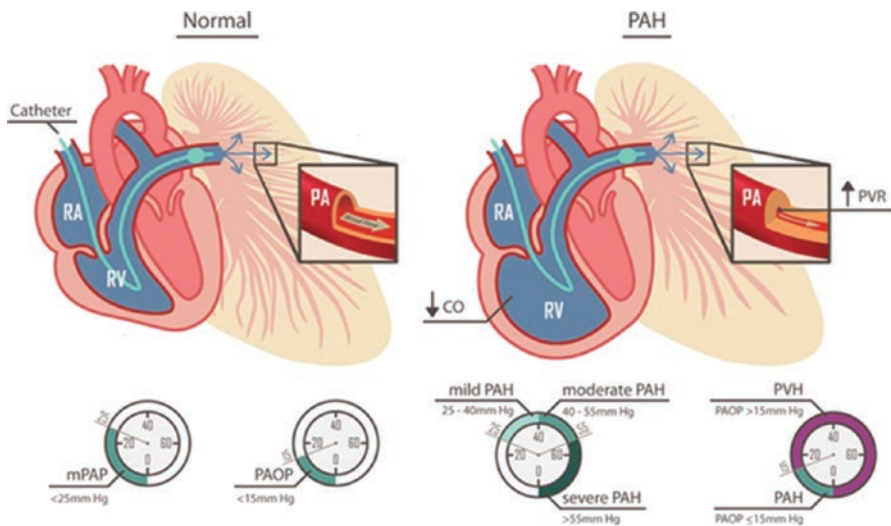
Many patients with OSA experience cyclical oxygen desaturations during sleep. The cumulative effect of intermittent hypoxia can lead to PH [6, 7]. Most patients with OSA have normal oxygen saturation while awake, apart from those patients who also have an obesity-hypoventilation syndrome or underlying lung disease.

Left ventricular dysfunction accounts for a large proportion of PH in patients with OSA [8–12]. However, PH and right heart failure can develop in patients with OSA with preserved left ventricular ejection fraction [13]. The prevalence of PH in heart failure with preserved left ventricular ejection fraction (HFpEF) was reported in the range of 52% (defined as mean Ppa >25 mmHg by right heart catheterization) [14]. This prevalence was comparable to 62% in a cohort of 379 patients with heart failure with reduced ejection fraction (HFrEF), who had a mean Ppa >20 mmHg by right heart catheterization [15]. Mathematical models demonstrate that there is an initial passive increase in pulmonary blood volume secondary to the hydrostatic forces resulting from heart failure with either reduced or preserved systolic function [13]. The result of this initial insult is a passive post-capillary PH with a normal transpulmonary pressure gradient and, consequently, relatively normal pulmonary vascular resistance. Over time, long-standing venous PH results in pulmonary arterial endothelial dysfunction, leading to elevated levels of endothelin-1, decreased nitric oxide levels, and a decrease in brain natriuretic peptide-mediated vasodilatation [16]. These biochemical changes result in active pulmonary arterial vasospasm, leading to a further increase in pulmonary arterial pressures. In addition to this pressure-dependent mechanism, hypoxia-sensitive inflammatory and proliferative pathways may be involved in the development of PH in OSA [17]. Animal models have demonstrated that brief, repetitive exposure to hypoxemia over just a few weeks, a situation akin to intermittent hypoxia in OSA, is sufficient to cause pulmonary arteriolar remodeling and right ventricular hypertrophy [18, 19]. A meta-analysis of 16 studies demonstrated right ventricular hypertrophy and enlargement and decreased right ventricular ejection fraction in patients with OSA [20]. Continuous monitoring of Ppa in OSA patients showed a gradual rise in mean Ppa throughout nighttime sleep compared with snorers-only subjects [21].

### *Diagnostic Considerations*

The evaluation process for a patient with suspected PH requires a series of investigations intended to confirm the diagnosis, which is best done in a multidisciplinary pulmonary vascular center. Patients with PH may be asymptomatic or present with symptoms of dyspnea, lightheadedness on exertion, fatigue, chest pain, syncope, palpitations, and/or lower extremity edema. However, patients with suspected OSA and PH may not have these symptoms. Transthoracic echocardiography provides several variables that correlate with right heart hemodynamics, including estimated systolic Ppa, and should always be performed in the case of suspected PH as a screening modality. A systematic review and meta-analysis of 29 studies with a total patient population of 1998 demonstrated an overall correlation coefficient of 0.70 (95% confidence interval [CI], 0.67–0.73) for estimated systolic Ppa between color Doppler echocardiography (tricuspid regurgitant jet method) and right heart catheterization, with a sensitivity and specificity of 83% (95% CI, 73–90%) and 72% (95% CI, 53–85%), respectively [22]. Of note, the agreement between Doppler

echocardiography and right heart catheterization data was similar at both mild and moderately elevated systolic Ppa values. Right heart catheterization is confirmatory, yields more precise pressure measurements, and allows assessment of the vasodilatory capacity of pulmonary vasculature that can help guide therapy (Fig. 6.3). PH is defined hemodynamically by right heart catheterization by a mean Ppa greater than or equal to 25 mm Hg at rest [23]. However, in the recent World Symposium on Pulmonary Hypertension 2018 in Nice, the definition of PH was revised: “Based on data from normal subjects, the normal mean pulmonary arterial pressure (mPAP) at rest is approximately  $14.0 \pm 3.3$  mm Hg [24]. Two standard deviations above this mean value would indicate that an mPAP  $>20$  mmHg is the threshold for abnormal pulmonary arterial pressure (above the 97.5th percentile). However, this level of mPAP is not sufficient to define pulmonary vascular disease since it could be due to increases in cardiac output or pulmonary artery wedge pressure (PAWP). The task force has, therefore, proposed including a pulmonary vascular resistance (PVR)  $\geq 3$  WU into the definition of pre-capillary PH associated with mPAP  $>20$  mmHg, irrespective of etiology” [25]. Pulmonary artery occlusion pressure (PAOP or PAWP) of greater than 15 mm Hg denotes elevated left ventricular pressure, in either HFrEF or HFpEF. Pulmonary artery diastolic pressure gradient (DPG = diastolic Ppa – PAOP) distinguishes pre-capillary ( $\geq 7$  mm Hg) and post-capillary ( $<7$  mm Hg) PH in setting of normal or reduced left ventricular ejection fraction. The combination of Ppa  $\geq 25$  mm Hg, PAOP  $> 15$  mm Hg, and DPG  $\geq 7$  mm Hg indicates combined pre- and post-capillary (pulmonary venous) PH (Fig. 6.3) [26].



**Fig. 6.3** Right heart catheterization hemodynamics in normal and in pulmonary arterial hypertension (PAH). PVH, pulmonary venous hypertension; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance. The 2018 proposed definition of PH is mPAP  $>20$  mm Hg and PVR  $\geq 3.0$  WU [25]

There are no formal guidelines for routine sleep study in patients with PH; however, given the high prevalence of nocturnal hypoxemia and OSA in patients with PH [27], patients with PH should be screened for sleep-disordered breathing by a sleep study. Other diagnostic tests may include serologic testing for collagen vascular diseases, pulmonary function tests, chest imaging, ventilation-perfusion scanning, and arterial blood gases for underlying pulmonary diseases.

### ***Effect of Treatment of OSA on PH***

The studies on the effect of treatment of OSA on pulmonary hemodynamics and PH are limited. Treatment with continuous positive airway pressure (CPAP) for 6 months in six patients with OSA and PH diagnosed on echocardiography and confirmed by right heart catheterization with normal PAOP values reduced mean Ppa values from  $25.6 \pm 4.0$  mm Hg to  $19.5 \pm 1.6$  mm Hg ( $P < 0.001$ ) [3]. In a prospective study involving 22 patients with OSA (mean AHI,  $48.6 \pm 5.2$  events/h), five of whom had mean Ppa 20 mm Hg, 4 months of CPAP treatment decreased mean Ppa from  $17.0 \pm 1.2$  mm Hg to  $14.5 \pm 0.8$  mm Hg in the entire group ( $P < 0.05$ ). The most significant treatment effects occurred in the five patients who had PH at baseline. The reduction in mean Ppa was attributed to decreased pulmonary vascular resistance and decreased vasoconstrictive response to a hypoxic stimulus [28]. In a randomized, sham-controlled cross-over study involving ten patients with OSA and PH (RVSP  $> 30$  mm Hg estimated by Doppler echocardiography) and no known cardiac or lung diseases, 12 weeks of CPAP therapy decreased RVSP from  $28.8 \pm 7.9$  mm Hg to  $24.0 \pm 5.8$  mm Hg ( $P < 0.0001$ ) [29]. Higher reduction in RVSP after effective CPAP therapy was observed in patients with OSA with either left ventricular diastolic dysfunction (change,  $7.3 \pm 3.3$  mm Hg vs.  $1.6 \pm 1.8$  mm Hg in those without left ventricular diastolic dysfunction;  $P < 0.001$ ) or presence of PH at baseline (change,  $8.5 \pm 2.8$  mm Hg vs.  $2.6 \pm 2.8$  mm Hg in those without PH at baseline;  $P < 0.001$ ) [29]. In a meta-analysis of 7 studies with 222 patients (mean age of 52.5 years) with OSA and AHI of greater than 10 events/h (mean AHI of 58 events/h) and PH, defined as Ppa  $> 25$  mm Hg (mean Ppa of  $39.3 \pm 6.3$  mm Hg), CPAP treatment for 3 to 70 months was associated with a decrease in Ppa of 13.3 mm Hg (95% CI 12.7–14.0) [30]. CPAP therapy for 6–24 months improved right ventricular ejection fraction estimated by nuclear ventriculography, which increased from  $30\% \pm 3\%$  to  $39\% \pm 3\%$  ( $P < 0.01$ ) [31]. Based on currently available data, we recommend the treatment of mild-to-moderate PH with OSA-specific therapy for 6 months with follow-up echocardiography and consideration for the addition of pharmacotherapy in those with severe PH.

The index patient was treated with CPAP, and follow-up echocardiography after 6 months showed RVSP had decreased from 65 mm Hg to 50 mm Hg with the patient reporting some improvement in shortness of breath during exertion. Because of evidence for the persistence of PH and residual symptoms, right heart catheterization was performed for consideration of PH-specific treatment.



### Clinical Pearls and Pitfalls

- OSA is a highly prevalent sleep-disordered breathing that is associated with an increased risk of cardio-cerebrovascular complications and increased mortality.
- PH is a common comorbid disorder in a patient with OSA and, in large part, related to nocturnal hypoxemia and left ventricular dysfunction.
- Patients with OSA, especially those with daytime hypoxemia and hypercapnia or significant nocturnal oxygen desaturations, should be screened for PH by echocardiography.
- Treatment of OSA with CPAP therapy improves PH.

### References

1. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *J Thorac Dis.* 2015;7(8):1311–22.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* 2015;3(4):310–8.
3. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB. Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. *Respiration.* 2001;68(6):566–72.
4. Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. *Thorax.* 2000;55(11):934–9.
5. Sajkov D, McEvoy RD. Obstructive sleep apnea and pulmonary hypertension. *Prog Cardiovasc Dis.* 2009;51(5):363–70.
6. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. *Pulm Circ.* 2015;5(2):220–7.
7. Mohsenin V. The emerging role of microRNAs in hypoxia-induced pulmonary hypertension. *Sleep Breath.* 2016;20(3):1059–67.
8. Hetzel M, Kochs M, Marx N, Woehrle H, Mobarak I, Hombach V, et al. Pulmonary hemodynamics in obstructive sleep apnea: frequency and causes of pulmonary hypertension. *Lung.* 2003;181(3):157–66.
9. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. *Clin Chest Med.* 2007;28(1):233–41, x.
10. Minai OA, Ricaurte B, Kaw R, Hammel J, Mansour M, McCarthy K, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am J Cardiol.* 2009;104(9):1300–6.
11. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart.* 2012;98(24):1805–11.
12. Hansdotir S, Groskreutz DJ, Gehlbach BK. WHO's in second?: a practical review of World Health Organization group 2 pulmonary hypertension. *Chest.* 2013;144(2):638–50.
13. Segers VF, Brutsaert DL, De Keulenaer GW. Pulmonary hypertension and right heart failure in heart failure with preserved left ventricular ejection fraction: pathophysiology and natural history. *Curr Opin Cardiol.* 2012;27(3):273–80.

14. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53(13):1119–26.
15. Ghio S, Gavazzi A, Campana C, Inerra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37(1):183–8.
16. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. *Circulation*. 2000;102(14):1718–23.
17. Voelkel NF, Mizuno S, Bogaard HJ. The role of hypoxia in pulmonary vascular diseases: a perspective. *Am J Physiol Lung Cell Mol Physiol*. 2013;304(7):L457–65.
18. McGuire M, Bradford A. Chronic intermittent hypercapnic hypoxia increases pulmonary arterial pressure and haematocrit in rats. *Eur Respir J*. 2001;18(2):279–85.
19. Campen MJ, Shimoda LA, O'Donnell CP. Acute and chronic cardiovascular effects of intermittent hypoxia in C57BL/6J mice. *J Appl Physiol* (1985). 2005;99(5):2028–35.
20. Maripov A, Mamazhakypov A, Sartmyrzaeva M, Akunov A, Muratali Uulu K, Duishobaev M, et al. Right ventricular remodeling and dysfunction in obstructive sleep apnea: a systematic review of the literature and meta-analysis. *Can Respir J*. 2017;2017:1587865.
21. Sforza E, Laks L, Grunstein RR, Krieger J, Sullivan CE. Time course of pulmonary artery pressure during sleep in sleep apnoea syndrome: role of recurrent apnoeas. *Eur Respir J*. 1998;11(2):440–6.
22. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart*. 2011;97(8):612–22.
23. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol (Engl Ed)*. 2016;69(2):177.
24. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888–94.
25. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th world symposium on pulmonary hypertension. *Eur Respir J*. 2019;53(1):1802148. <https://doi.org/10.1183/13993003.02148-2018>.
26. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in “out-of-proportion” pulmonary hypertension. *Chest*. 2013;143(3):758–66.
27. Jilwan FN, Escourrou P, Garcia G, Jais X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. *Chest*. 2013;143(1):47–55.
28. Sajkov D, Wang T, Saunders NA, Bune AJ, McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;165(2):152–8.
29. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. *Eur Heart J*. 2006;27(9):1106–13.
30. Imran TF, Ghazipura M, Liu S, Hossain T, Ashtyani H, Kim B, et al. Effect of continuous positive airway pressure treatment on pulmonary artery pressure in patients with isolated obstructive sleep apnea: a meta-analysis. *Heart Fail Rev*. 2016;21(5):591–8.
31. Nahmias J, Lao R, Karetzky M. Right ventricular dysfunction in obstructive sleep apnoea: reversal with nasal continuous positive airway pressure. *Eur Respir J*. 1996;9(5):945–51.