



Early View

Review

Sleep-related breathing disorders and pulmonary hypertension

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Sleep-related breathing disorders and pulmonary hypertension

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Abstract

Sleep-related breathing disorders include obstructive apnoea, central apnoea and sleep-related hypoventilation. These nocturnal events have the potential to increase pulmonary arterial pressure during sleep but also in the waking state. "Pure" obstructive sleep apnoea syndrome is responsible for a small increase in pulmonary arterial pressure whose clinical impact has not been demonstrated. By contrast, in obesity hypoventilation syndrome or overlap syndrome (association of COPD with obstructive sleep apnoea), nocturnal respiratory events contribute to the development of pulmonary hypertension, which is often severe. In the latter circumstances, treatment of sleep-related breathing disorders is essential in order to improve pulmonary haemodynamics.

Patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension are at risk of developing sleep-related breathing disorders. Obstructive and central apnoea can be observed as well as a worsening of the ventilation perfusion mismatch during sleep. There should be a strong suspicion of sleep-related breathing disorders in such a patient population, however the precise indications for sleep studies and the type of recording remain to be specified. The diagnosis of obstructive sleep apnoea syndrome in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension should encourage treatment with continuous positive airway pressure. The presence of isolated nocturnal hypoxemia should also prompt the initiation of long-term oxygen therapy. These treatments are likely to avoid worsening of pulmonary hypertension. However, it is prudent not to treat central apnoea and Cheynes-Stokes respiration with adaptive servo-ventilation in patients with chronic right heart failure because of a potential risk of serious adverse effects from such treatment.

In this review we will consider the current knowledge of the consequences of sleep-related breathing disorders on pulmonary haemodynamics in patients with and without chronic respiratory disease (group 3 of the clinical classification of pulmonary hypertension) and the effect of treatments of respiratory events during sleep on pulmonary hypertension. The prevalence, consequences and therapeutic options of sleep-related breathing disorders in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension will also be discussed (groups 1 and 4 of the clinical classification of pulmonary hypertension, respectively).

Introduction

Pulmonary hypertension (PH), defined by right-heart catheterization (RHC) as mean pulmonary arterial pressure (mPAP) greater than 20 mm Hg, is a haemodynamic state categorized as pre-capillary PH, post-capillary PH, and combined pre- and post-capillary PH. The current definition of pulmonary arterial hypertension (PAH) is mPAP greater than 20 mm Hg, pulmonary arterial wedge pressure (PAWP) less than or equal to 15 mm Hg, and pulmonary vascular resistance greater than or equal to 3 Wood Units¹. The most recent version of the clinical classification of PH appears in Table 1. This classification groups together different conditions with similarities in terms of pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management.

The sleep-related breathing disorders (SBD) classification of the American Academy of Sleep Medicine describes obstructive sleep apnoea (OSA), central sleep apnoea (CSA) with or without Cheyne-Stokes breathing pattern and sleep-related hypoventilation². An apnoea is defined by a cessation of airflow for at least 10 seconds. The obstructive nature of apnoea is evidenced by increased inspiratory effort (Figure 1). The definition of hypopnoea can be summarized by a decrease in airflow for at least 10 seconds associated with an oxygen desaturation and / or an electro-encephalographic arousal and it requires a continuous measurement of thoracoabdominal respiratory movements or a surrogate of intra-thoracic pressure³. Obstructive sleep apnoea syndrome (OSAS) is an extremely common condition in the general adult population⁴; it requires the presence of symptoms and an apnoea-hypopnea index (AHI) greater than five events per hour mainly consisting of obstructive respiratory events. CSA is defined by a cessation of airflow due to lack of inspiratory effort for

at least 10 seconds. In contrast to obstructive apnoea, there is no significant variation in intrathoracic pressure during central apnoea. They are infrequent in the general population⁵ but are commonly seen in patients with congestive heart failure and possibly associated with Cheyne-Stokes respiration. Sleep-related hypoventilation is characterized by a significant increase in nocturnal arterial carbon dioxide tension (PaCO₂) to 45 mmHg or more or by abnormally increased in PaCO₂ values compared to those of the waking state⁶. SDB can lead to group 3 PH⁷.

The purpose of this review is to discuss the current knowledge of the consequences of SDB on pulmonary haemodynamics in patients with and without chronic respiratory disease and the effect of treatments of respiratory events during sleep on PH and conversely to review the prevalence, consequences and therapeutic options of SDB in PAH (group 1 PH) and chronic thromboembolic PH (CTEPH) (group 4 PH).

The links between sleep apnoea and PH due to left heart disease, will not be discussed here as it has been the subject of recently published reviews^{8,9}.

Immediate consequences of sleep-related breathing disorders on pulmonary haemodynamics

Immediate consequences of obstructive sleep apnoea on pulmonary haemodynamics

In contrast to subjects without respiratory or cardiovascular disease, where mPAP is similar during wakefulness compared to sleep periods¹⁰, mPAP increases during OSA. OSA leads to a series of inspiratory efforts against a complete obstruction of the upper airways. It lasts from 10 seconds to 2 minutes with increasingly negative pleural pressure up to -60 mm H₂O just before the resumption of the ventilation. These sleep-related respiratory events

generate hypoxaemia, hypercapnia, swings in intrathoracic pressure and post-apnoeic arousals associated with sympathetic surges; all these phenomenon can potentially modify the PAP due to change of vascular tone and cardiac output ¹¹.

In contrast to the systemic circulation, the right ventricle (RV) and the pulmonary vessels are subjected at the same external pressure (intra thoracic pressure), thus only transmural PAP can accurately characterize the RV afterload and the distending vascular pressure. This is consistent with the general recommendation to record in an awake subject PAP at end-expiration when intra thoracic pressure is close to the atmospheric pressure ¹² and confirmed by the different trend of intravascular PAP compared to transmural PAP during obstructive apnoea (Figure 2A and 2B). Such a measurement can be performed taking oesophageal pressure as zero reference instead of atmospheric pressure. This allows to describe 3 phases during apnoea: phase one with no airflow, normoxaemia and stable PAP, phase two with no airflow, progressive hypoxaemia and an increase in PAP and phase three with resumption of ventilation, further desaturation during the first part of this phase and the highest PAP ^{13,14}.

The recording of arterial oxyhaemoglobin saturation (SaO_2) showed regular and relatively small oscillations during a succession of obstructive respiratory events associated with rapid and small peaks of PH (Figure 2C). These rapid changes of PAP do not correspond to the time required for acute hypoxic pulmonary artery constriction, which is longer. However, when an apnoea extends and generates a deep hypoxaemia, PAP increases by approximately 15 to 20 mmHg and does not return to the previous value after the end of the respiratory event. Thus, 2 patterns of changes in transmural PAP were observed: fast changes (Figure 2C) and fast plus slow changes (Figure 2D) ¹⁵. Fast changes correspond to exaggerated inspiratory

swings in intrathoracic pressure due to airway occlusion causing a significant increase in systemic venous return and a significant increase in left ventricular afterload. Slow changes in transmural PAP are characterized by a gradual increase in transmural PAP after each apnoeic cycle (Figure 2D). They occurred when SaO₂ was not brought back to the baseline value, causing more and more hypoxaemia after each preceding apnoea. These slow changes in PAP were well correlated with changes in SaO₂. This fits with the highest PAP observations during the night-time periods when apnoea and hypopnoea are the most severe with the worst SaO₂ values. Thus, these later increases in PAP are compatible with, at least in part, acute hypoxic pulmonary vasoconstriction¹⁶. The intensity of hypoxic pulmonary vasoconstriction is variable from one individual to another as evidenced by the variability of the increase in PAP for a comparable decrease in SaO₂¹³ and the variable effect of oxygen on the decrease of PAP during obstructing apnoea¹⁷.

Cardiac output decreases during the obstruction phase due to a decrease in stroke volume and a decrease in heart rate^{18,19}. During ventilatory resumption stroke volume and cardiac frequency increase sharply, contributing to the increase in PAP²⁰. It should be noted that concomitantly the systemic arterial pressure increases significantly because it is subjected to the activation of the sympathetic nervous system, while the effect of the latter on the pulmonary circulation is limited^{21,22}. Old studies suggested that PAWP contributes to the increase of the PAP during sleep-related obstructive respiratory events. In fact, its contribution is negligible²³.

Hypercapnia and acidosis can occur during apnoeic cycle in patients with OSA responsible for severe and prolonged oxyhaemoglobin desaturations. Acidosis is able to potentiate hypoxic pulmonary vasoconstriction but probably do not play a major role²³. Furthermore, repeated

arousals that cause sharp increases in systemic blood pressure have not demonstrated any effect significant on PAP^{21,22}.

In summary, obstructive apnoea and hypopnea lead to complex pathophysiological interactions leading to a transient increase in PAP, the more SaO₂ decreases during these nocturnal respiratory events, the more PAP increases (Figure 3). However, other factors than the decrease in SaO₂ seem to intervene such as variations in cardiac output and hypercapnia.

Immediate consequences of central sleep apnoea on pulmonary haemodynamics

To our knowledge there is no clinical study dedicated to measuring PAP during CSA. However, based on animal studies^{24,25} and knowledge of the pathophysiology of OSA^{21,22}, it is very likely that CSA has an acute effect similar to that of OSA on PAP. Indeed, the main stimulus leading to an increase in PAP during an obstructive respiratory event is oxygen desaturation. It should be noted, however, that contrary to OSA, CSA when present as Cheyne-Stokes respiration, oxygen saturation between apnoea returns to baseline. Thus, there is no deeper and deeper oxyhaemoglobin desaturation in those circumstances, as compared to the sequence of prolonged OSA, which induces the largest increases in PAP.

Immediate consequences of sleep-related hypoventilation on pulmonary haemodynamics

Clinical studies investigating the acute effect on pulmonary haemodynamics of sleep-related hypoventilations are scarce and have been performed exclusively in COPD²⁶⁻²⁸. During the falls of SaO₂, increases in mPAP were observed sometimes of an amplitude of more than 20 mmHg throughout the duration of the desaturation. These pulmonary haemodynamic studies have involved patients with severe COPD, marked diurnal hypoxaemia and, most

often, daytime pulmonary hypertension. We do not know whether milder sleep-related hypoventilations lead to an acute increase in PAP. The oldness and scarcity of the clinical studies in this field are due to the technical problems caused by the study of gas exchanges during sleep and the technical and ethical problems of measuring PAP invasively during sleep.

Patients with interstitial lung disease also experience non apnoeic drops in SaO₂ during sleep^{29,30}. However, there is no pulmonary hemodynamic study during sleep in these patients. By analogy with the knowledge on COPD it can be assumed that during the deepest and prolonged drops in SaO₂, PAP increases.

In obesity hypoventilation syndrome (OHS) the nocturnal hypoxemia can be very severe with a minimum nocturnal saturation value of 60% and a time spent under 90% saturation of more than 50% of the total sleep time³¹. Most of falls in SaO₂ during sleep are due to obstructive apnoea and hypopnea in the OHS, however sleep-related hypoventilation also plays an important role³². Although there is no study with a direct measurement of PAP during sleep-related hypoventilation in OHS, it is very likely that during these episodes of alveolar hypoventilation PAP increases significantly.

In summary, the acute and subacute effects of obstructive, central sleep apnoea and sleep-related hypoventilation on pulmonary haemodynamics most likely results primarily from the degree of nocturnal oxygen desaturation, with a contributory effect from negative intrathoracic pressure swings. Patients frequently have a combination of obstructive, central events and sleep-related hypoventilation which are likely to be synergistic, as has been shown in previous studies on the association of OSAS and COPD^{28,33} (overlap syndrome).

Permanent pulmonary hypertension and sleep-related breathing disorders

Role of sleep apnoea and hypopnea in the development of permanent pulmonary hypertension

The downstream consequences of sleep apnoea has been extensively studied⁹. Sleep apnoea induce increased sympathetic nerve activity, metabolic dysregulation, inflammation, oxidative stress, endothelium dysfunction and intermittent hypoxia. These promote development of hypertension, atrial fibrillation and heart diseases. All these factors are potentially involved in pulmonary hypertension¹⁶, however, their role as a cause of pulmonary hypertension due to sleep apnoea has not, to our knowledge, been studied. Only studies in animal or in vitro models have been published on this topic^{34,35}.

The prevalence of PH in patients with OSA is poorly defined with a range of 17%³⁶ to 70%³⁷. Most of the studies were retrospective, not all of them used RHC, the gold standard for PH diagnosis³⁸. It also depends on the chosen PAP definition threshold, which has changed recently from 25 to 20 mmHg¹. Furthermore, patients with comorbidities that may affect the PAP, such as heart failure or chronic lung disease were included in some studies. Early case studies which included patients with OSA and comorbidities reported a large variability and severity of PH^{39,40}. Sajkov *et al.* investigated 27 patients with OSA (respiratory disturbance index [RDI] > 10 events/h) by echocardiography for the presence of PH⁴¹. Patients with clinically significant lung or cardiac diseases were excluded. Eleven OSA patients (41%) were found to have pulmonary hypertension that was relatively mild. There were no differences between PH and non-PH patients in body mass index (BMI), smoking history, or lung function. PH patients were more hypoxaemic when awake than non-PH patients. A further study by the same group evaluated awake pulmonary haemodynamics by

echocardiography, pulmonary gas exchange, and lung function tests including small airways function in 32 patients with OSA who had normal lung volumes⁴². PH was associated with smaller airways closure during tidal breathing and heightened pulmonary pressor responses to hypoxia and during increased pulmonary blood flow. These findings suggest that patients with OSA and PH might have an excessive hypoxic pulmonary vasoconstriction response and vascular remodelling that promote the development of PH.

Laks *et al.* investigated 100 consecutive OSA patients using RHC⁴³. All patients had to have an AHI of at least 20 per hour. Left heart failure was excluded. Forty-two percent of the cohort had PH defined as mPAP > 20 mmHg. Those with PH were older with higher PaCO₂, lower arterial oxygen tension (PaO₂) and lower forced expiratory volume in one second (FEV₁) values. The presence of daytime hypoxaemia was not found as a prerequisite in the development of pulmonary hypertension. The high prevalence of PH in the study by Laks *et al.* is probably explained by a population with a significantly higher body mass index than other studies.

Two studies have shown similar prevalence of pulmonary hypertension of 20% in patients with sleep apnoea^{44,45}. In these two studies, patients with COPD were excluded. The determinants of pulmonary hypertension in both studies were daytime and nocturnal hypoxaemia, PAWP in the first study⁴⁴ and BMI in the second study⁴⁵.

Minai *et al.*³⁷ investigated pulmonary haemodynamics in 83 patients with OSA. Fifty-eight patients (70%) had PH, 33% of them had severe PH with a mPAP equal or greater than 40. It is likely that patients in the study Minai *et al.*³⁷ reflect characteristics close to patients with an indication of performing right cardiac catheterization according to current

recommendations⁴⁶ and are not representative of patients seen in a sleep laboratory for suspected OSAS.

One of the largest studies to date using RHC have investigated pulmonary haemodynamics by RHC in 220 patients³⁶. OSA was defined as apnoea plus hypopnea index > 20. PH, and PH by a resting mPAP \geq 20 mmHg. PH was observed in 37 of 220 patients (17%). In this study, PH was strongly linked to the presence of an obstructive (rather than restrictive) ventilatory pattern on lung function test, hypoxaemia, and hypercapnia, and was generally accounted for by an associated chronic obstructive pulmonary disease. Interestingly the severity of OSA played only a minor role in the rise of PAP. The role of an airflow limitation in the development of pulmonary hypertension in OSA patients is consistent with an older study of 24 patients with both OSA and COPD⁴⁷.

Patients with fibrosing interstitial lung diseases including idiopathic pulmonary fibrosis frequently have OSA⁴⁸⁻⁵⁰. The role of obstructive sleep apnoea as a factor of PH in such a population has not been well demonstrated⁵¹.

In summary the impact of obstructive apnoea and hypopnea on PAP is low in patients with no cardiovascular or respiratory comorbidities. The level of pulmonary pressure in these latter patients is estimated to be close to the upper limit of normal i.e. between 18 and 25 mmHg^{11,36}. Conversely, when there is an associated chronic respiratory disease such as COPD⁵² and OHS⁵³ (discussed below), obstructive apnoea and hypopnea are an aggravating factor of pulmonary hypertension. Central sleep apnoea in non-hypercapnic patients does not lead to permanent PH, as patients with idiopathic CSA do not have PH⁵⁴.

Permanent pulmonary hypertension and sleep-related hypoventilation

Early studies on this subject^{26–28} suggest that hypoxaemia during sleep mainly due to sleep-related hypoventilation in COPD patients without significant daytime hypoxaemia and without OSA could lead to permanent PH^{55,56}. A more recent study with a larger number of patients has shown that daytime mPAP was identical in COPD patients with and without nocturnal oxyhaemoglobin desaturation⁵⁷. In fibrosing interstitial lung diseases and particularly in idiopathic pulmonary fibrosis sleep desaturation is very common^{49,58}. One study showed that a quantification of sleep oxyhaemoglobin desaturation but not AHI is associated with survival in idiopathic pulmonary fibrosis⁵⁸. This study suggests that lung fibrosis may lead to nocturnal desaturation and pulmonary hypertension leading to a worse prognosis.

The role of sleep-related hypoventilation in OHS as a cause of pulmonary hypertension is also difficult to assess. Pulmonary hypertension is the result of several factors including, hypoxemia and hypercapnia, OSA, and in some patients a left heart dysfunction^{53,59,60}. The important point suggesting that alveolar hypoventilation during sleep is responsible for the severity of pulmonary hypertension is its significant improvement after few weeks of treatment with non-invasive ventilation applied during sleep in patients with very severe nocturnal hypoventilation in a group of patients where only 10% had OSA⁵⁹.

Sleep-related breathing disorders in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

The age at diagnosis of PAH is increasing and it is not uncommon to see elderly patients diagnosed with idiopathic PAH (IPAH). In the US-based Registry to Evaluate Early And Long-

term PAH disease management (REVEAL), the mean age at diagnosis was 50 years, and 5% of the patients were diagnosed at ≥ 75 years of age⁶¹. The French PAH registry reported an average age of 50 years at diagnosis⁶², while the COMPERA registry reported a mean age of 71 years old⁶³. With increasing age, a higher proportion of patients experienced comorbidities, as compared with younger patients. Of note, OSA was one of the most common comorbidities at enrolment in the REVEAL Registry where 20% of 2599 PAH patients included had OSA, of whom 75% were female⁶¹.

Most studies dedicated to SBD in pulmonary vascular diseases are compared in Table 2. Small studies evaluated the prevalence of SBD in PAH patients and found that SBD, including OSA, CSA, periodic breathing, and oxygen desaturation related to sleep, were common^{64–73}. Schulz *et al.*⁶⁵ found periodic breathing in 6 out of 20 patients with PAH which result from prolonged circulation time due to low cardiac output, severe hypoxaemia that stimulates peripheral chemoreceptors and changes in chemosensitivity. Minai *et al.*⁶⁶ performed a cross-sectional study. Forty-three patients with IPAH or connective tissue disease-associated PAH were included. Thirty (70%) were nocturnal oxyhaemoglobin desaturators of whom 87% were moderate to severe nocturnal desaturators (more than 20% of the night below a SaO₂ of 90%). Nocturnal desaturators were older and had more severe pulmonary haemodynamics. Twenty patients had a full night polysomnography showing that only 3 patients had an apnoea index above 5 per hour. Sleep apnoea was not considered to contribute to the pathogenesis of PH in these 3 patients. Ulrich *et al.*⁶⁷ reported increased prevalence of Cheyne-Stokes respiration in a cohort of 38 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH). Sixty-eight percent of these patients were nocturnal oxyhaemoglobin desaturators (more than 10% of the night below a SpO₂ of

90%). Only 4 patients had OSA. Patients with SBD did not experience excessive sleepiness but had a worse quality of life compared to the remainders. By contrast, Prisco *et al.*⁶⁸ observed a higher prevalence of OSA (50%). The degree of PAP elevation was similar to that of the other studies quoted, but cardiac index was higher. In that study the percentage of time spent during the night with a SaO₂ below 90% was also high (31% ±[standard deviation] 36%). In the study of Dumitrascu *et al.*⁷⁰ 45 (26.6%) patients out of 169 patients with PAH who were prospectively investigated by sleep study had an AHI >10/h. Of these, 27 patients (16%) had OSA and 18 patients (10.6%) had CSA. Patients with OSA were characterized by male gender and higher body mass index whereas those with CSA were older, more hypocapnic and had worse pulmonary haemodynamics. It therefore appears from this study that among subjects with PAH the prevalence of patients with central and obstructive apnoea is higher than in the general population. In another study by Jilwan *et al.*⁷¹ nocturnal hypoxaemia was found to be common in patients with stable IPAH and CTEPH (observed in > 80% of cases). The particularity of this study was the use during polysomnography of a transcutaneous capnograph allowing to show that certain oxyhaemoglobin desaturations were due to ventilation/perfusion mismatch when the SaO₂ decreased simultaneously with a decrease in transcutaneous PCO₂. Thus, the two most common mechanisms of nocturnal hypoxaemia in the study by Jilwan *et al.* were ventilation/perfusion mismatch and OSA. Sleep apnoea were considerably more prevalent than in the general population of similar age. Minic *et al.*⁷² in a retrospective cross-sectional study of 52 PAH patients found 56% with OSA and 44% with CSA. Age and subjective sleepiness were predictive of SBD. Nagaoka *et al.*⁷³ have shown a relationship between the importance of nocturnal desaturation and survival, the more patients desaturate during sleep, the shorter the life expectancy.

The factors involved in the development of these various SBD in patients with PAH or CTEPH are not fully understood. The decrease in minute ventilation in stage 3 and REM sleep may contribute to the increase in ventilation-perfusion mismatch revealed by the only study that measured nocturnal transcutaneous PCO_2 ⁷¹. The magnitude of these desaturations is also linked to the fact that these patients are located on the steep part of the oxyhaemoglobin dissociation curve⁷⁴. Regarding OSA in patients with PAH or CTEPH, several predisposing factors are suspected. First, OSA being a very frequent disorder over the 4th, 5th and 6th decades⁴, it is not surprising to find it by chance in population of patients of average age of 50-55 years^{61,62}. Second, several other factors can be suspected, such as the (moderate) decrease in lung volumes⁷⁴ and the likely propensity to arouse in patients most often with hypocapnia leading to upper airway collapsibility and respiratory control instability, respectively^{75,76}. In addition, it is likely that the upper airway dilator muscles are affected like skeletal muscles in patients with right heart failure⁷⁷. All these anomalies are suspected to promote collapse of the upper airways. Finally, possible other explanation for OSA is fluid retention and shift in patients who often have a degree of congestion, especially in older subjects⁷⁸. Concerning, CSA, reactive hyperventilation in response to hypoxaemia and increased chemosensitivity⁷⁹ may lead to hypocapnia and presumably provokes central apnoea by shifting the PaCO_2 levels below the apnoeic threshold during sleep⁸⁰, a phenomenon which is well-known from patients with Cheyne-Stokes respiration in congestive heart failure. Since, hypocapnia is a negative prognostic factor in IPAH patients and is associated with a low cardiac output, a low PaCO_2 on falling asleep associated with a prolonged arterial circulation time meets the conditions necessary for the appearance of CSA^{65,70}.

In summary, SBD is more common in pulmonary vascular diseases such as PAH and CTEPH than in the general population. However, they are probably a consequence of PH and not a causative factor. The observational studies quoted above show that the mechanisms of desaturations in these patients are multiple i.e. an increase in ventilation-perfusion mismatch, as well as obstructive and central respiratory events during sleep. Future studies are needed to better understand the links between SBD on the one hand and PAH or CTEPH on the other hand, and their long-term consequences.

Effects of treatment of sleep-related breathing disorders on pulmonary hypertension.

Effects of OSA treatments on PAP and right heart changes

Tracheostomy was an earlier treatment modality that is rarely performed today. Old studies evaluated changes in PAP in a small number of patients with OSA via right heart catheterization following tracheostomy^{81,82}. In these studies, subjects had PH at baseline, and significant reductions in mPAP were seen after intervention.

Nasal continuous positive airway pressure (CPAP) is considered to be the most effective treatment of OSA. Two studies from the same group failed to demonstrate any change of resting PAP measured by RHC with the use of CPAP^{83,84}. The most recent of these 2 studies showed a decrease in mean PAP of 4 mmHg after 5 years of treatment with CPAP in the 11 patients who presented at baseline a mean PAP greater than or equal to 20 mmHg⁸⁴.

However, on the basis of such a result on a subgroup analysis with comparison of the measurement of mean PAP before and after treatment, we cannot conclude that CPAP significantly lowers PAP. In a case-control study of 29 patients, Alchanatis *et al.*⁸⁵ reported that a significant proportion of OSA patients without any lung or cardiac disease develop

mild PH (estimated by Doppler echocardiography) which has been partially or completely reversed after effective 6-month CPAP treatment. CPAP reduced PAP and hypoxic pulmonary vascular reactivity⁸⁶. The greatest treatment effects occurred in patients who had PH at baseline. Arias *et al.*⁸⁷ reported in a randomized cross-over, echocardiography-based trial which included 23 OSA, otherwise healthy patients, that CPAP application reduced systolic PAP levels. In 21 patients in this study with adequate compliance with CPAP, systolic PAP decreased from 29 ± 9 mmHg to 24 ± 6 mmHg. It is thus interesting to note that in a randomized trial PAP decreased under CPAP, however the clinical significance of such a reduction, whereas most of the patients presented PAP values considered as normal, is uncertain. Two meta-analyses showed that CPAP is associated with a decrease in PAP in patients with OSA^{88,89}. But these two meta-analyses have some limitation.

Two studies evaluated the effect of CPAP on RV function using 3-D echocardiography^{90,91}. Vitarelli *et al.*⁹⁰ studied thirty-seven patients with OSAS without comorbidities and 30 control subjects. 3-D RV ejection fraction and RV dyssynchrony were abnormal in OSAS patients in the presence of PH. 3-D RV ejection fraction and the measurement of RV dyssynchrony were independently correlated with the AHI. These abnormalities improved after chronic application of CPAP. A larger study which included 56 OSA patients and 50 controls⁹¹ reported that 24-weeks of effective CPAP treatment resulted in a significant reduction in pulmonary vascular resistance, reduction in the RV end-systolic volume index and increase in RV ejection fraction. Another study combined measurement of biomarkers, echocardiography, and cardiac MRI in patients with OSA before and after treatment with CPAP⁹². This study showed that systolic PAP measured on echocardiography and dilation of the right heart chambers decreased after several months of CPAP treatment.

Importantly all studies with positive effects on PAP or RV did not use RHC and it is unclear whether the improvement in pulmonary haemodynamics and RV function were secondary to improvement of systemic hypertension and left ventricular function or where the results of direct effects on the pulmonary vasculature⁹³.

In summary, CPAP has the potential to improve pulmonary haemodynamics especially in patients who present with pulmonary hypertension before the initiation of CPAP. However, it should be kept in mind that the decrease in PAP is of low magnitude and of uncertain long-term clinical relevance.

Effects of supplemental oxygen during sleep on PAP

Since good adherence to CPAP usually defined by use of at least 4 hours per night can be as low as 40%⁹⁴, the role of nocturnal supplemental oxygen can be considered in certain circumstances. Ulrich *et al.*⁹⁵ studied the effect of nocturnal oxygen and acetazolamide on 23 patients (16 with PAH, 7 with CTEPH) with SBD in a randomized, placebo-controlled, double-blind, cross-over trial. After as soon as one week of nocturnal oxygen therapy, the 6-minute walk distance improved compared with placebo along with improvements in SBD and haemodynamics. The study by Ulrich *et al.*⁹⁵ is the only randomized trial evaluating the effect of correction of nocturnal hypoxaemia with nocturnal oxygen therapy in PAH and CTEPH. However, it should be noted that oxygen therapy during sleep is not the treatment of OSA because it does not reduce the frequency of obstructive events.

In patients with COPD and severe daytime hypoxaemia, the peaks of nocturnal PH are corrected by oxygen therapy^{96,97}. Consequently, the use of long-term oxygen therapy (18 hours per day) must necessarily include the periods of sleep in these patients and in patients with other cause of chronic respiratory failure. If hypercapnia prevails the most appropriate

treatment is nocturnal non-invasive ventilation. Such treatments showed to be effective in improving PH^{59,98}. Supplemental oxygen therapy limited to the night has not been shown to be effective in COPD or other chronic respiratory diseases^{99,100}.

Clinical implications

Considering the interplay between SBD and PH, a practical algorithm for diagnosis and treatment of sleep-disordered breathing is proposed in Figure 4.

Assessment of pulmonary hypertension in patients with sleep-related breathing disorders

Based on the evidence outlined in our review, the routine investigation or screening for PH in sleep apnoea patients not associated with chronic respiratory failure and without unexplained dyspnoea is not recommended³⁸. In addition, if there is a very mild increase in PAP due to sleep apnoea, apnoea treatment would correct this effect of the SBD on the pulmonary circulation.

A Doppler echocardiography must be performed in case of respiratory or cardiovascular comorbidities. Concerning CSA and sleep-related hypoventilation the search for PH is mandatory. Although this is not the subject of this review, it should be pointed out that the existence of CSA in a normocapnic or hypocapnic patient must dictate the search for left heart failure. Patients with sleep-related hypoventilation during sleep always have, at least at an early stage, chronic respiratory failure. In this context if not already done an echocardiography to explore PAP, size of heart chambers and left heart function is essential⁹³. If echocardiography results show significant increase in PAP, some patients may require RHC. Diagnosis of even severe PH in patients with sleep-related hypoventilation during sleep should not lead to treatment with drugs approved for PAH¹⁰¹. The appropriate

treatment consists of correcting alveolar hypoventilation. The use of non-invasive ventilation, which is often limited to the period of sleep, often leads to a marked improvement of alveolar hypoventilation and PH⁵³.

Finally, the important point to emphasize is that in patients with OSA syndrome with no comorbidities screening for PH is not recommended.

Assessment and treatment of sleep-related breathing disorders in patients with PAH and CTEPH

In all patients with PAH or CTEPH a sleep study should be performed whether or not there are symptoms suggestive of OSA¹⁰². Depending on the resources available locally, either a polysomnography or a type III home sleep apnoea test can be performed. When there is no sign of OSA, nocturnal oximetry could be a screening tool in non-severe patients corresponding to NYHA functional class II patients whose haemodynamics do not show a decrease in cardiac output. Although the level of evidence is low, these sleep studies seem justified because of SBD are frequent and lead to hypoxaemia during sleep, variations of intrathoracic pressures (in obstructive events) and stimulation of the sympathetic system. These consequences of SBD are likely to alter a haemodynamic state already compromised. A diagnosis of OSA in these patients should lead to initiation of treatment. Patients with PAH or CTEPH associated with OSA have a high risk of oxygen desaturations due to conditions other than OSA. Therefore, treatment with CPAP should be preferred to auto-adjusting positive airway pressure. Indeed, under such conditions, the pressure variations associated with the functioning of the auto-adjusting positive airway pressure devices potentially induce micro-arousals and change in sleep macrostructure¹⁰³. Regarding OSA other treatment than CPAP can be beneficial as lifestyle measures, avoidance of alcohol and

sedatives and lateral sleeping in patients with OSA predominantly in the supine position. It should be kept in mind that, as in heart failure, the treatment of OSA aims to correct sleepiness and improve sleeping conditions but not haemodynamics or right ventricular function ⁹.

Oxygen therapy is one of the recommended treatments for PAH and CTEPH when PaO₂ is less than 60 mmHg (8 kPa) ⁴⁶. It is important to note that nocturnal oxyhaemoglobin desaturation in these patients can be severe ⁷¹. It is therefore important to ensure that oxygen therapy covers the sleep periods with an adequate flow. Thus, hypoxaemia due to worsening of ventilation-perfusion mismatch during sleep present in these patients is corrected.

Besides, as discussed above, CSA with or without periodic breathing may be present in these patients ^{65,67,70}. Even if the index of central apnoea is high, it seems reasonable not to initiate nocturnal ventilation in these patients due firstly to the lack of controlled studies in this area and secondly by analogy with what has been shown in heart failure with reduced left ventricular ejection fraction ($\leq 45\%$). In fact with such a diagnosis of heart failure with low left ventricular ejection fraction, adaptive servo-ventilation increased cardiovascular mortality in one study ¹⁰⁴.

As a final point, by analogy with heart failure ^{9,105}, the treatments of PH, right heart failure or cardiac arrhythmia complicating PH are likely to improve SBD, it therefore seems important to perform a sleep study and reassess the patient when PH treatments have been optimized.

Conclusions

Several studies have shown that OSA and sleep-related hypoventilation are responsible for an acute increase in PAP. Obstructive sleep apnoea has also been shown to be an aggravating factor for PH and responsible for a small increase in PAP over the long term. Several studies also showed that OSA may lead to RV changes. However, no causal link has been demonstrated between an increase in PAP secondary to sleep apnoea and clinical consequences. Therefore, in most clinical conditions it is not useful to look for PH in a patient with OSA who otherwise does not have severe cardiac or respiratory comorbidities. On the other hand, when there is a severe cardiac and/or respiratory comorbidity associated with OSA or when there is severe sleep-related alveolar hypoventilation, performing an echocardiography is mandatory. Uncertainties about the clinical impact of PH and RV changes of SBD require further clinical studies. Currently, there is no clear recommendation about how, when and with which tool to perform a sleep study in the diagnosis strategy or during the follow-up of patients with PAH or CTEPH. However, from recent studies showing the high prevalence of SBD, type III home sleep study (respiratory polygraphy) and occasionally polysomnography are needed to clarify how to diagnose and treat sleep-related breathing disorders in patients with PAH or CTEPH. If an OSA syndrome is diagnosed, treatment with CPAP can be proposed with the aim of improving daytime sleepiness and improving sleeping conditions. The authors propose on this subject concerning the links between SBD and pulmonary hypertension some statements based on the references quoted in the present review (Table 3).

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Legends of the figures

Figure 1

A hypopnoea and 4 obstructive apnoeas are displayed on this polysomnography extract.

It is worth noting the desaturations in oxygen after hypopnoea and apnoea as well as continuity of respiratory efforts during the stop of breathing.

On the enlargement, one can see during the apnoea an extrasystole (ECG), then during the ventilatory recovery an increase in muscle tone (EMG1) and an increase in the frequency of EEG waveform (C4-A1). These immediate consequences of obstructive apnoea lead to an increase in pulmonary arterial pressure due to alveolar hypoxia when the oxyhaemoglobin desaturation is deep and activation of the sympathetic system.

NAF2P, SAO2, VTH, VAB, C4-A1, EMG1 and ECG correspond to nasal airflow, oxygen saturation by pulse oximetry, thoracic effort channel, abdominal effort channel, C4-A1 electroencephalographic electrode, submental electromyogram channel and electrocardiogram, respectively.

Figure 2

Intravascular systolic pulmonary artery pressure (sPAP) (A) and transmural systolic pulmonary artery pressure (tm sPAP) (B) of 7 patients during an apnoea cycle. Transmural pressure corresponds to the intravascular pressure from which the oesophageal pressure is subtracted, the latter being an estimate of the pleural pressure. It was recorded 3 pre-apnoeic breaths, 6 to 14 occluded breaths and 3 breaths after the resumption of ventilation. In all patients except in patient number 6, tm sPAP increased slightly and regularly at the end of the apnoeic period while the intravascular pressure showed oscillations and a gradual decrease during the apnoeic period due to the rapid changes and the significant decrease in pleural pressure, respectively.

Oxyhaemoglobin saturation by pulse oximetry (SaO₂) during an obstructive apnoea sequence and the concomitant measurement of transmural systolic pulmonary arterial pressure (tm sPAP). Open symbols indicate beginning of apnoea and closed symbols indicate end of apnoea.

The two patterns of changes in transmural PAP were observed, fast changes (C) and fast plus slow changes (D). The slow changes in PAP were well correlated with changes in SaO₂ and therefore are compatible with the mechanism of hypoxic pulmonary vasoconstriction.

Adapted from references 13 and 15.

Figure 3

Pathophysiology of increased pulmonary arterial pressures due to obstructive sleep apnoea

HR: heart rate, LV: left ventricle, PAP: pulmonary arterial pressure, SV: stroke volume

Figure 4

Diagnostic and treatment algorithms proposed in clinical situations where an interaction between sleep-related breathing disorder and pulmonary hypertension is suspected.

* This applies to hypercapnic patients

CPAP: continuous positive airway pressure, CSA: central sleep apnoea, CTEPH: chronic thromboembolic pulmonary hypertension, NIV: non-invasive ventilation, OSA: obstructive sleep apnoea, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, RHC: right heart catheterisation, SBD: sleep-related breathing disorder

Table 1

The 5 groups of pulmonary hypertension (PH) from the updated clinical classification of which only groups 1 and 3 are detailed. Adapted from reference 1,

1 Pulmonary Arterial Hypertension (PAH)

1.1 Idiopathic PAH

1.2 Heritable PAH

1.3 Drug- and toxin-induced PAH

1.4 PAH associated with:

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart disease

1.4.5 Schistosomiasis

1.5 PAH long-term responders to calcium channel blockers

1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement

1.7 Persistent PH of the new-born syndrome

2 PH due to left heart disease

3 PH due to lung diseases and/or hypoxia

3.1 Obstructive lung disease

3.2 Restrictive lung disease

3.3 Other lung disease with mixed restrictive/obstructive pattern

3.4 Hypoxia without lung disease

3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions including Chronic thromboembolic PH

5 PH with unclear and/or multifactorial mechanisms

Table 2

Comparison of studies on sleep-related breathing disorders in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

Ref./year	Population	Mean age, y	% NYHA I and II:III:IV	mPAP, mmHg	CI, L/min/m ²	Sleep study	Definition of SBD	AHI events/h	Main mechanism of SBD	Findings
Rafanan <i>et al.</i> ⁶⁴ 2001	13 iPAH at the time of diagnosis	45	-	61	1.88	PSG	Desaturator > 10% TST with SpO ₂ < 90%	4.6±4.9	Nocturnal desaturations independent of OSA or CSA	77% of the patients had significant nocturnal desaturation
Schulz <i>et al.</i> ⁶⁵ 2002	20 iPAH during the follow-up	45	40:50:10	56	1.96	PSG	OSA excluded, significant periodic breathing	37±5	Periodic breathing and central sleep apnoea	30% of patients had periodic breathing associated with more severe haemodynamics
Minai <i>et al.</i> ⁶⁶ 2007	38 iPAH and 5 CTD-PAH during the follow-up	48	42:53:5	51	2.5	Nocturnal oximetry	Desaturator > 10% TST with SpO ₂ < 90%	-	Nocturnal desaturations independent of OSA or CSA	Nocturnal desaturation is frequent (70%) and correlated with right ventricular dysfunction

Ulrich <i>et al.</i> ⁶⁷ 2008	23 PAH and 15 CTEPH during the follow-up	61	37:42:21	43	2.4	PSG, PG compared to oximetry	Central sleep apnoea ≥ 10 events/h	Median 8 IQR: 4-16	Periodic breathing and central sleep apnoea	SBD not associated with excessive sleepiness. Ambulatory sleep study or polysomnography is required
Prisco <i>et al.</i> ⁶⁸ 2011	9 iPAH and 19 CTD-PAH at the time of diagnosis	55	18:39:39:4	41	2.9	PSG	AHI ≥ 5 /h	11.4 \pm 19.8	OSA was the main cause of nocturnal desaturation	Symptoms and diurnal SpO ₂ were not predictive of SDB
Hildenbrand <i>et al.</i> ⁶⁹ 2012	44 PAH and 19 CTEPH during the follow-up	62	38:49:13	41	2.6	Nocturnal oximetry	Desaturator > 10% TST with SpO ₂ < 90%	-	Nocturnal desaturation was not associated with a higher AHI	High prevalence of nocturnal desaturation
Dumitrascu <i>et al.</i> ⁷⁰ 2013	169 PAH, CTEPH and various causes of PH during the follow-up	61	:-82:-	43	2.4	PG	OSA: AHI ≥ 10 /h, > 50% obstructive events CSA: AHI ≥ 10 /h, > 50% central	No SBD: 3 \pm 1 OSA: 21 \pm 10 CSA: 18 \pm 8	16% of OSA, 11% of CSA and nocturnal desaturations independent of OSA or CSA	Higher prevalence of SBD compared to the general population

Jilwan <i>et al.</i> ⁷¹ 2013	29 iPAH and 17 CTEPH during the follow-up	53	11	44	3.2	PSG + capnograph	Desaturator: 60 minutes SpO ₂ < 90% or ODI ≥ 20/h OSA: AHI > 5:h PB : AHI > 5/h changing amplitude breathing 10 minutes	25±22	76% \dot{V}_a/\dot{Q} mismatch alone or associated with another mechanism, 66% of OSA and 10% with CSA	High prevalence of nocturnal desaturation. A sleep study should be mandatory
Minic <i>et al.</i> ⁷² 2014	52 PAH patients	53	50:25:-	46	4.3 L/min (cardiac output)	PSG		16.5 ± 18.8	56% OSA and 44% CSA	High prevalence of SDB. Age and ESS > 10 were predictive of SDB
Nagaoka <i>et al.</i> ⁷³ 2018	78 iPAH and 73 associated PAH	44	-	46	3.8 L/min (cardiac output)	PSG		Without SBD: 6±8 With SBD: 14±8	29 patients had OSA and 29 had CSA	No difference in terms of survival between patients with or without SDB. Mean nocturnal SpO ₂ was an independent predictor of death

All patients in these studies had a mean pulmonary arterial pressure ≥ 25 mmHg except in reference 67 where 3 patients had a mean pulmonary arterial pressure between 20 and 25 mmHg.

AHI: apnoea-hypopnoea index, CI: cardiac index, CSA: central sleep apnoea, CTEPH: chronic thromboembolic pulmonary hypertension, CTD-PAH: pulmonary arterial hypertension associated with connective tissue disease, ESS: Epworth Sleepiness Scale, iPAH: idiopathic pulmonary arterial hypertension, mPAP: mean pulmonary arterial pressure, OSA: obstructive sleep apnoea, PB: periodic breathing, PG: ambulatory polygraphy, PSG: polysomnography, SBD: sleep-related breathing disorders, SpO₂: pulse oxygen saturation, TST: total sleep time, \dot{V}_a/\dot{Q} : ventilation/perfusion.

Table 3

Sleep-related breathing disorders and pulmonary hypertension- statements

Pulmonary hypertension in patients diagnosed with sleep breathing disorders

- It is unclear whether OSA alone, in the absence of daytime hypoxaemia can cause stable PH.
- Isolated SBD has little or no effect on the pulmonary haemodynamic, but it is an important aggravating factor of PH when it is associated with a significant chronic respiratory or cardiac disease.
- In patients with COPD, obesity or severe ILD with chronic hypoxemia, the association of SBD and nocturnal hypoventilation can lead to extremely severe nocturnal hypoxaemia. This combination may lead to the development of precapillary PH that may be complicated by right heart failure.
- In patients with OSA not associated with chronic respiratory failure and without unexplained dyspnoea, screening for PH is not recommended
- In patients with CSA or sleep-related hypoventilation echocardiography to evaluate left and right ventricular function and PAP is mandatory.
- In patients with PH and sleep-related hypoventilation during sleep i.e. OHS or overlap syndrome there is no indication for treatment with drugs approved for PAH. The appropriate treatment consists of correcting alveolar hypoventilation and hypoxemia.

Diagnosis and treatment of SBD in patients with PAH and CTEPH

- SBD is more common in pulmonary vascular diseases such as PAH and CTEPH than in the general population.
 - With increasing age of patients diagnosed with PAH the prevalence of comorbidities including OSA is increasing.
 - If there are any suggestive signs of OSA in patients with PAH or CTEPH a type III home sleep apnoea test (or a polysomnography) is recommended. In all other clinical situations, a sleep test can also be performed.
 - If OSA is diagnosed in patients with PAH or CTEPH treatment with CPAP is indicated.
 - In patients with severe nocturnal desaturation oxygen therapy is needed.
 - CSA or Cheynes-Stokes respiration in patients with severe PH with reduced cardiac output should not be treated with adaptive servo-ventilation. Auto-adjusting positive airway pressure should also be avoided.
-

CPAP: continuous positive airway pressure, CSA: central sleep apnoea, CTEPH: chronic thromboembolic pulmonary hypertension, ILD: interstitial lung disease, OSA: obstructive sleep apnoea, PAH: pulmonary arterial hypertension, PAP: pulmonary artery pressure, PH: pulmonary hypertension, SBD: sleep-related breathing disorders

Figure 1

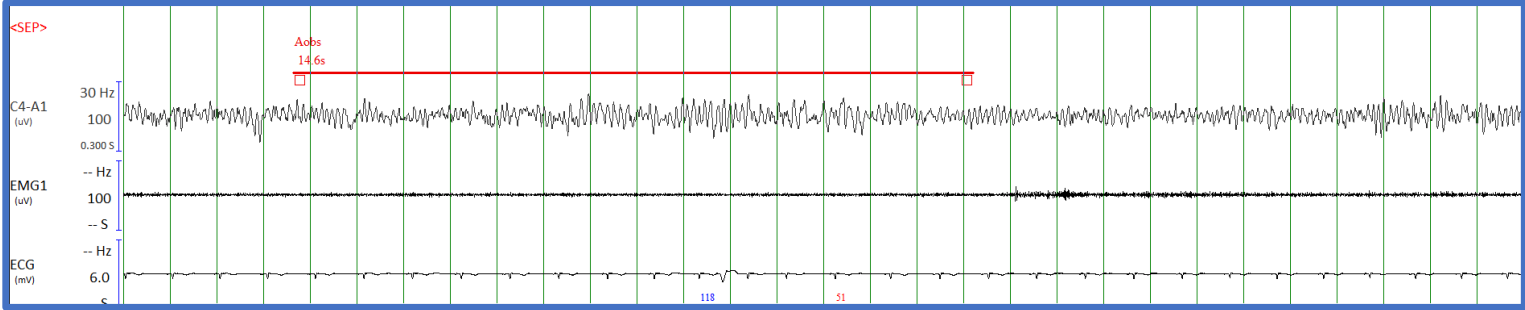
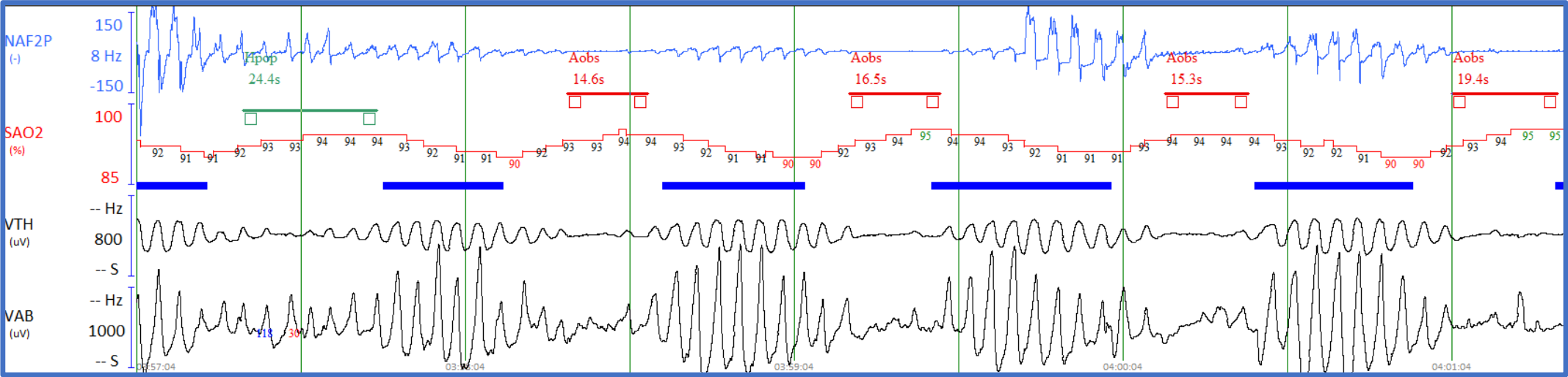


Figure 2

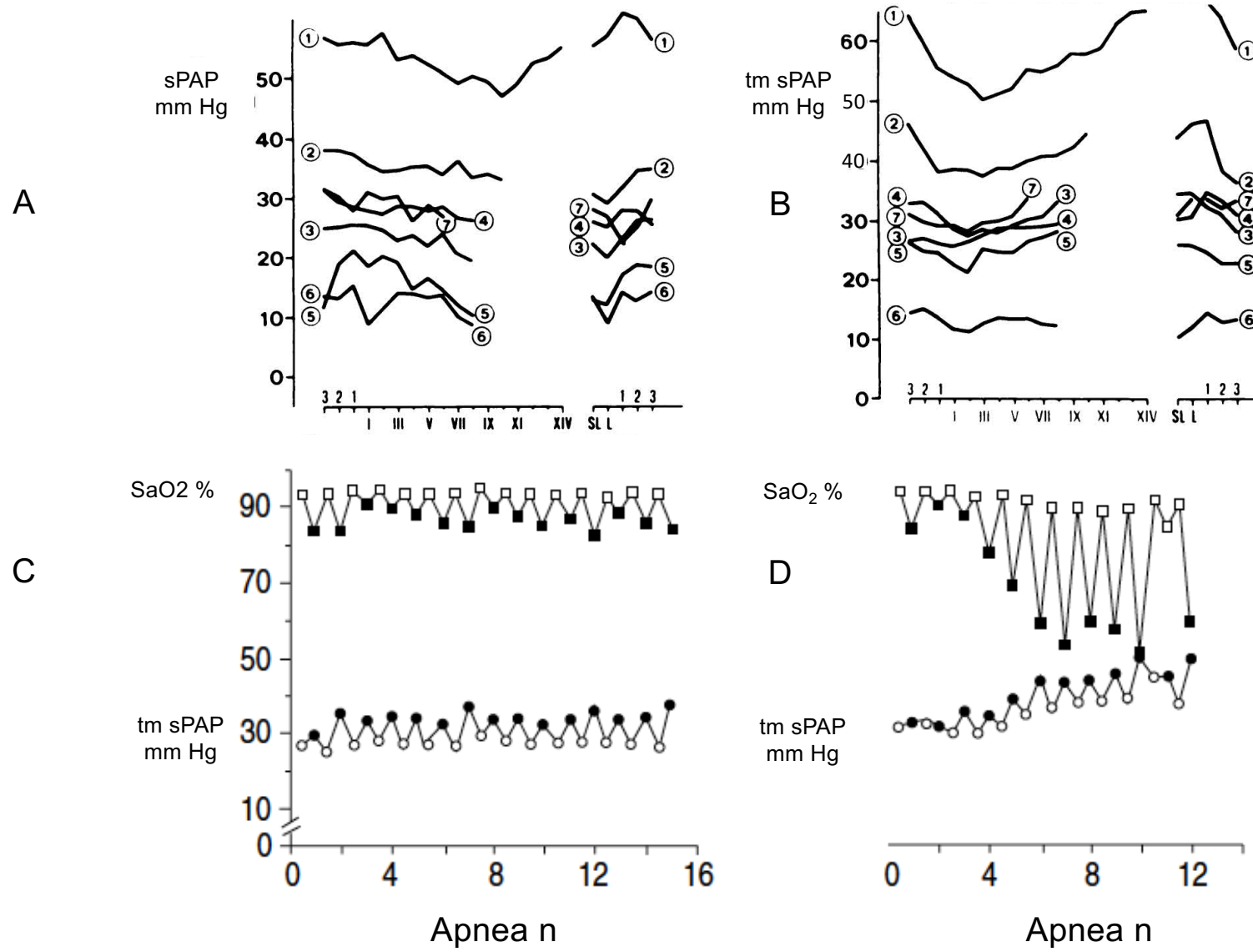


Figure 3

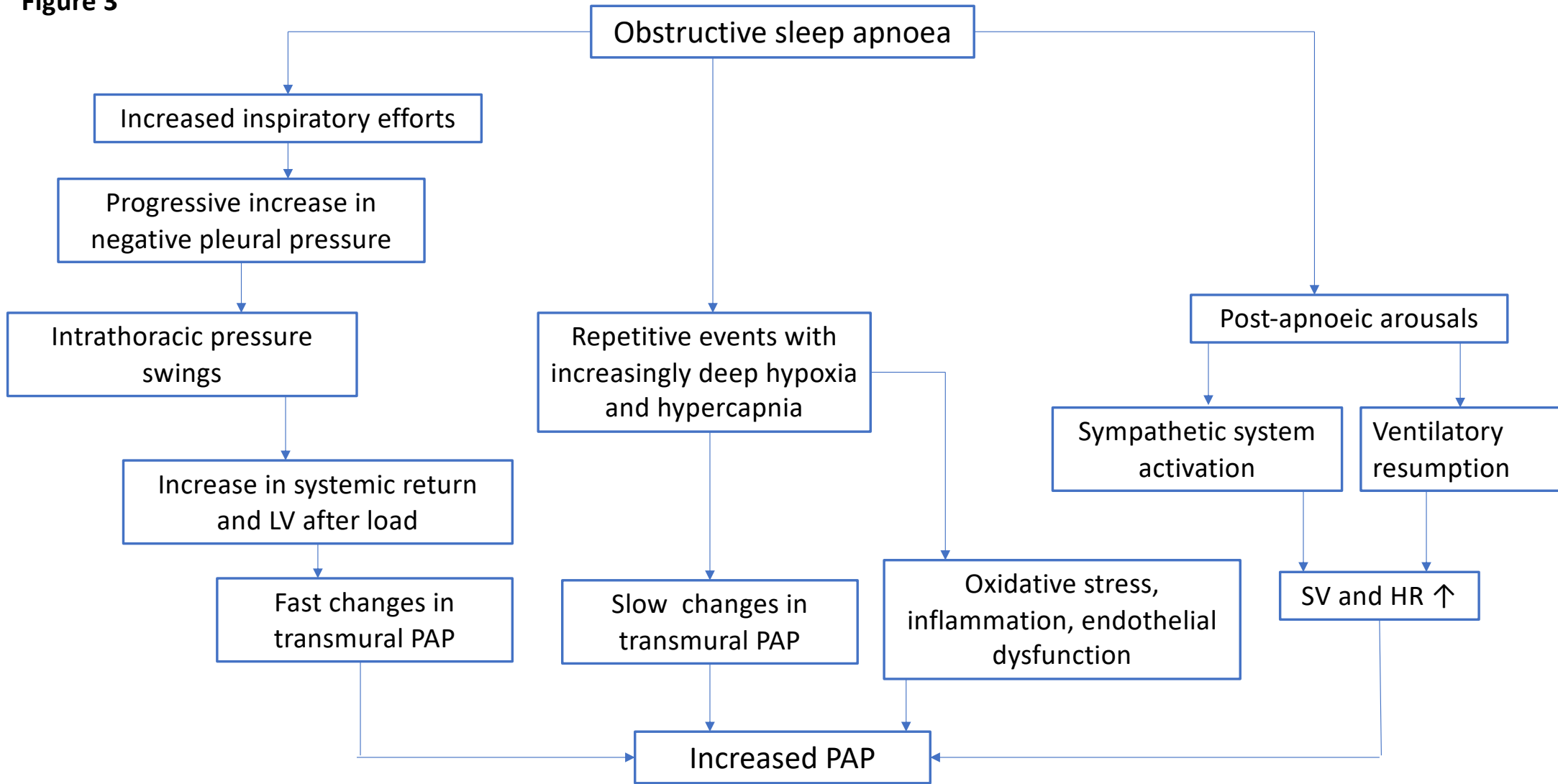


Figure 4

