Sleep-related breathing disorders and pulmonary hypertension

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In some clinical situations, important to identify, sleep-related breathing disorders can be responsible for severe pulmonary haemodynamic consequences. In these situations, it is important to treat apnoeas, hypopnoeas and nocturnal oxygen desaturations. https://bit.ly/30akkoM

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

Patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) are at risk of developing SBDs. Obstructive and central apnoea, as well as a worsening of ventilation–perfusion mismatch, can be observed during sleep. There should be a strong suspicion of SBDs in such a patient population; however, the precise indications for sleep studies and the type of recording remain to be specified. The diagnosis of OSAS in patients with PAH or CTEPH should encourage treatment with continuous positive airway pressure (CPAP). The presence of isolated nocturnal hypoxaemia should also prompt the initiation of long-term oxygen therapy. These treatments are likely to avoid worsening of PH; however, it is prudent not to treat central apnoea and Cheyne–Stokes respiration (CSR) 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 SBDs on pulmonary haemodynamics in patients with and without chronic respiratory disease (group 3 of the clinical classification of PH) and the effect of treatments of respiratory events during sleep on PH. The prevalence and consequences of SBDs in PAH and CTEPH (groups 1 and 4 of the clinical classification of PH, respectively), as well as therapeutic options, will also be discussed.

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Introduction

Pulmonary hypertension (PH), defined by right-heart catheterisation (RHC) as mean pulmonary arterial pressure (PAP) >20 mmHg, is a haemodynamic state categorised as either as pre-capillary PH, post-capillary PH, or combined pre-capillary and post-capillary PH. The current definition of pulmonary arterial hypertension (PAH) is mean PAP >20 mmHg, pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg and pulmonary vascular resistance (PVR) ⩾3 Wood units [1]. 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 disorder (SBD) classification system of the American Academy of Sleep Medicine describes obstructive sleep apnoea (OSA), central sleep apnoea (CSA) with or without a Cheyne–Stokes breathing pattern and sleep-related hypoventilation [2]. An apnoea is defined by a cessation of airflow for at least 10 s. The obstructive nature of apnoea is evidenced by increased inspiratory effort (figure 1). The definition of hypopnoea can be summarised as a decrease in airflow for at least 10 s, associated with oxygen desaturation and/or an electro-encephalographic arousal, and it requires a continuous measurement of thoracoabdominal respiratory movements or a surrogate of intrathoracic pressure [3]. Obstructive sleep apnoea syndrome (OSAS) is an extremely common condition in the general adult population [4]. It requires the presence of symptoms and an apnoea–hypopnoea index (AHI) of >5 events·hour^{-1} (mainly consisting of obstructive respiratory events). CSA is defined by a cession of airflow due to lack of inspiratory effort for at least 10 s. In contrast to obstructive apnoea, there is no significant variation in intrathoracic pressure during central apnoea. Such apnoeas are infrequent in the general population [5] but are commonly seen in patients with congestive heart failure (CHF) and are possibly associated with Cheyne–Stokes respiration (CSR). Sleep-related hypoventilation is characterised by a significant increase in nocturnal arterial carbon dioxide tension (P_{aCO_2}) to ⩾45 mmHg or by abnormally increased in P_{aCO_2} values compared to those of the waking state [6]. Sleep disordered breathing (SDB) can lead to group 3 PH [7].

The purpose of this review is to discuss current knowledge around the consequences of SBDs on pulmonary haemodynamics in patients with and without chronic respiratory disease, as well as the effects of treatment of respiratory events during sleep on PH and conversely to review the prevalence, consequences and therapeutic options for SBDs in PAH (group 1 PH) and chronic thromboembolic pulmonary hypertension (CTEPH) (group 4 PH).

TABLE 1 The five groups of pulmonary hypertension (PH) from the updated clinical classification, of which only groups 1 and 3 are detailed. Adapted from reference [1] with permission

1 PAH
- 1.1 IPAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 CTD
  - 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/capillary involvement (PVOD/PCH)
- 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 CTEPH

5 PH with unclear and/or multifactorial mechanisms

PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; CTD: connective tissue disease; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; CTEPH: chronic thromboembolic pulmonary hypertension.

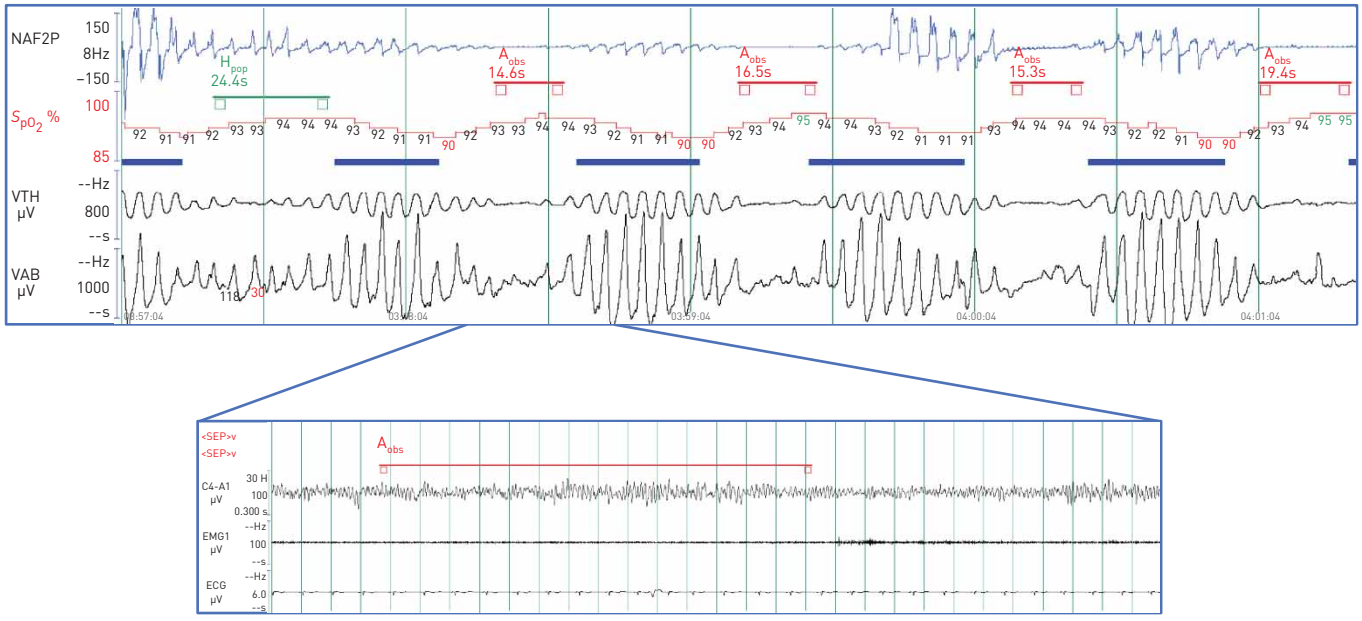

FIGURE 1 A hypopnoea and four obstructive apnoeas (H_{pop} and A_{obs}, respectively) are displayed on a polysomnography extract. The desaturations in oxygen after hypopnoea and apnoea, as well as the continuity of respiratory efforts during the stop in breathing, are worth noting. The enlargement shows the period during an apnoea where one can see an extrasystole (ECG trace) and then, during ventilatory recovery, an increase in muscle tone (EMG1 trace) and an increase in the frequency of the EEG waveform (C4-A1 trace). These immediate consequences of obstructive apnoea lead to an increase in pulmonary arterial pressure (PAP), due to alveolar hypoxia when the oxyhaemoglobin desaturation is deep, as well as activation of the sympathetic system. NAF2P: nasal airflow; S_{pO_2}: oxygen saturation measured by pulse oximetry; VTH: thoracic effort channel; VAB: abdominal effort channel; C4-A1: C4-A1 electroencephalographic electrode; EMG1: submental electromyogram channel; ECG: electrocardiogram.

The links between sleep apnoea and PH due to left-heart disease will not be discussed here, as they have been the subject of recently published reviews [8, 9].

Immediate consequences of SBDs on pulmonary haemodynamics

Immediate consequences of OSA on pulmonary haemodynamics

In contrast to subjects without respiratory or cardiovascular disease, where mean PAP is similar during wakefulness compared to sleep periods [10], mean PAP increases during OSA. OSA leads to a series of inspiratory efforts against a complete obstruction of the upper airways. It lasts from 10 s to 2 min with increasingly negative pleural pressure up to −60 mmH_2O just before the resumption of ventilation. These sleep-related respiratory events generate hypoxaemia, hypercapnia, swings in intrathoracic pressure and post-apnoeic arousals associated with sympathetic surges. All these phenomena can potentially modify PAP due to change of vascular tone and cardiac output (CO) [11].

In contrast to systemic circulation, the right ventricle and the pulmonary vessels are subjected to the same external pressure (intrathoracic pressure) and, as such, only transmural PAP can accurately characterise right-ventricular afterload and distending vascular pressure. This is consistent with the general recommendation to record PAP in an awake subject at end-expiration when intrathoracic pressure is close to atmospheric pressure [12]. It is also confirmed by the different trend of intravascular PAP compared to transmural PAP during obstructive apnoea (figures 2a and 2b). Such a measurement can be performed taking oesophageal pressure as the zero reference instead of atmospheric pressure, allowing the description of three 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, 15].

The recording of oxygen saturation measured by pulse oximetry (S_{pO_2}) shows regular, relatively small oscillations during a succession of obstructive respiratory events, which are associated with rapid, small peaks in PH (figure 2c). These rapid changes in 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 15–20 mmHg and does not return to the previous value after the respiratory event ends. Thus, two patterns of change in transmural PAP are observed: fast changes (figure 2c) and fast plus slow changes (figure 2d) [14]. Fast changes correspond to exaggerated inspiratory swings in intrathoracic pressure due to airway occlusion, which cause a significant increase in

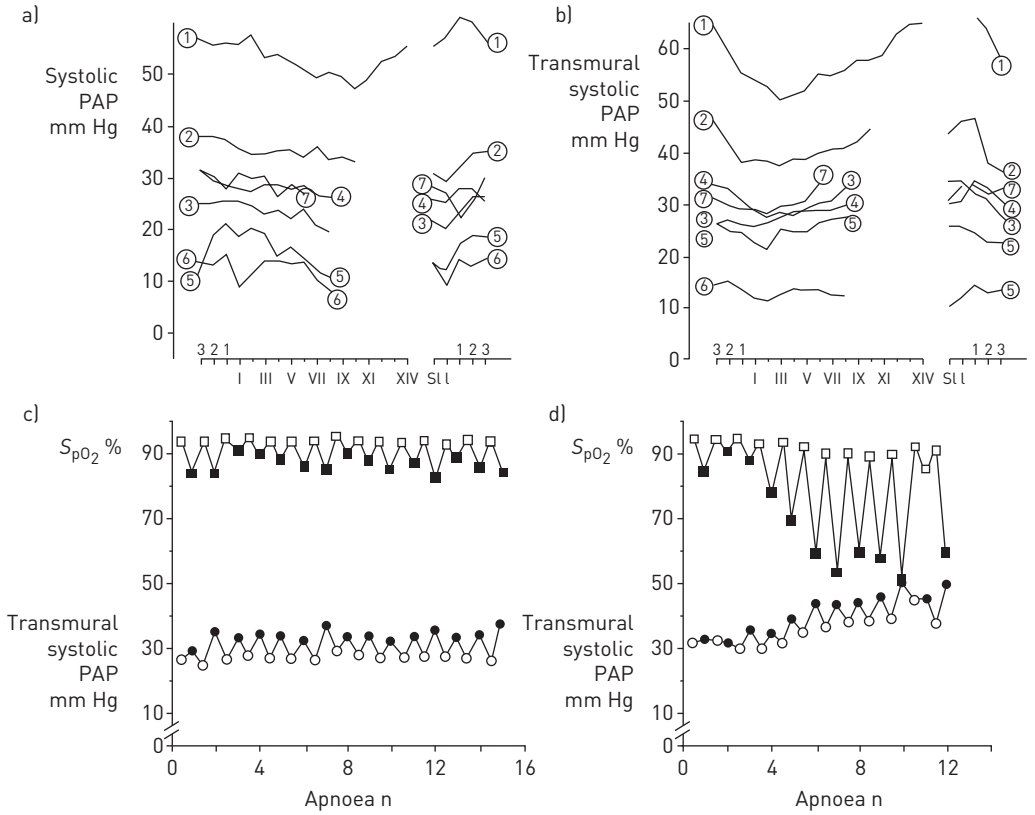

FIGURE 2 a) Intravascular systolic pulmonary artery pressure (PAP) and b) transmural systolic PAP of seven patients during an apnoea cycle. Transmural pressure corresponds to the intravascular pressure from which the oesophageal pressure is subtracted, the latter being an estimate of the pleural pressure. It was recorded as three pre-apnoeic breaths, six to 14 occluded breaths and three breaths after the resumption of ventilation. In all patients, except patient number 6, transmural systolic PAP increased slightly and regularly at the end of the apnoeic period, while the intravascular pressure showed oscillations (due to the rapid changes) and a gradual decrease (due to the significant decrease in pleural pressure) during the apnoeic period. Oxygen saturation measured by pulse oximetry (S_{pO_2}) during an obstructive apnoea sequence and the concomitant measurement of transmural systolic PAP are also shown. The two patterns of change in transmural PAP, c) fast changes and d) fast plus slow changes, were observed. Open symbols indicate the beginning of apnoea and closed symbols indicate the end. Unlike a) and b), where only one apnoeic cycle is shown per patient, c) and d) show sequences of apnoeic cycles. The slow changes in PAP were well correlated with changes in S_{pO_2} and are therefore compatible with the mechanism of hypoxic pulmonary vasoconstriction. Adapted from references [13] and [14] with permission.

systemic venous return and a significant increase in left-ventricular afterload. Slow changes in transmural PAP are characterised by a gradual increase in transmural PAP after each apnoeic cycle (figure 2d). They occur when S_{pO_2} is not brought back to the baseline value, causing more and more hypoxaemia after each preceding apnoea. These slow changes in PAP are well correlated with changes in S_{pO_2} and this fits with the observation of highest PAP during the night-time periods when apnoea and hypopnoea are the most severe, with the worst S_{pO_2} values. As such, these later increases in PAP are compatible, at least in part, with acute hypoxic pulmonary vasoconstriction [16]. 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 S_{pO_2} [13] and the variable effect of oxygen administration on the decrease of PAP during obstructing apnoea [17].

CO decreases during the obstruction phase due to a decrease in stroke volume (SV) and a decrease in heart rate (HR) [18, 19]. During ventilatory resumption both SV and cardiac frequency increase sharply, contributing to the increase in PAP [20]. It should be noted that systemic arterial pressure concomitantly undergoes significant increase as it is subjected to activation by the sympathetic nervous system, the effect of which on pulmonary circulation is limited [21, 22]. Older studies have suggested that PAWP contributes to the increase in PAP during sleep-related obstructive respiratory events. In fact, its contribution is negligible [23].

Hypercapnia and acidosis can occur during the apnoeic cycle in patients with OSA that is responsible for severe and prolonged oxyhaemoglobin desaturation. Acidosis is able to potentiate hypoxic pulmonary

vasoconstriction but probably does not play a major role [23]. Furthermore, repeated arousals that cause sharp increases in systemic blood pressure have not demonstrated any significant effect on PAP [21, 22].

In summary, obstructive apnoea and hypopnoea lead to complex pathophysiological interactions resulting in a transient increase in PAP. The more S_{pO_2} decreases during these nocturnal respiratory events, the more PAP increases (figure 3). However, other factors than the decrease in S_{pO_2} seem to intervene, such as variations in CO and hypercapnia.

Immediate consequences of CSA 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 on PAP similar to that of OSA. Indeed, the main stimulus leading to an increase in PAP during an obstructive respiratory event is oxygen desaturation However, it should be noted that, in contrast to OSA, when CSA is present as CSR then oxygen saturation between apnoea returns to baseline. As such, there is no deeper and deeper oxyhaemoglobin desaturation under these 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 of sleep-related hypoventilation on pulmonary haemodynamics are scarce and have been performed exclusively in chronic obstructive pulmonary disease (COPD) [26–28]. During falls in S_{pO_2}, increases in mean PAP are sometimes observed with an amplitude >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 PH. We do not know whether milder sleep-related hypoventilation leads to an acute increase in PAP. The age and scarcity of the clinical studies in this field are due to the technical problems caused by the study of gas exchange during sleep, and the technical and ethical problems of measuring PAP invasively during sleep.

Patients with interstitial lung disease (ILD) also experience nonapnoeic drops in S_{pO_2} during sleep [29, 30]. However, there is no pulmonary hemodynamic study during sleep in these patients. By analogy with our knowledge of COPD, it can be assumed that PAP increases during the deepest and most prolonged drops in S_{pO_2}.

Nocturnal hypoxaemia can be very severe in obesity hypoventilation syndrome (OHS), with a minimum nocturnal saturation value of 60% and a time spent under 90% saturation of more than 50% of total sleep time [31]. In OHS, most of the falls in S_{pO_2} during sleep are due to obstructive apnoea and hypopnea; however, sleep-related hypoventilation also plays an important role [32]. Although there is no study of OHS with a direct measurement of PAP during sleep-related hypoventilation, it is very likely that PAP increases significantly during these episodes of alveolar hypoventilation.

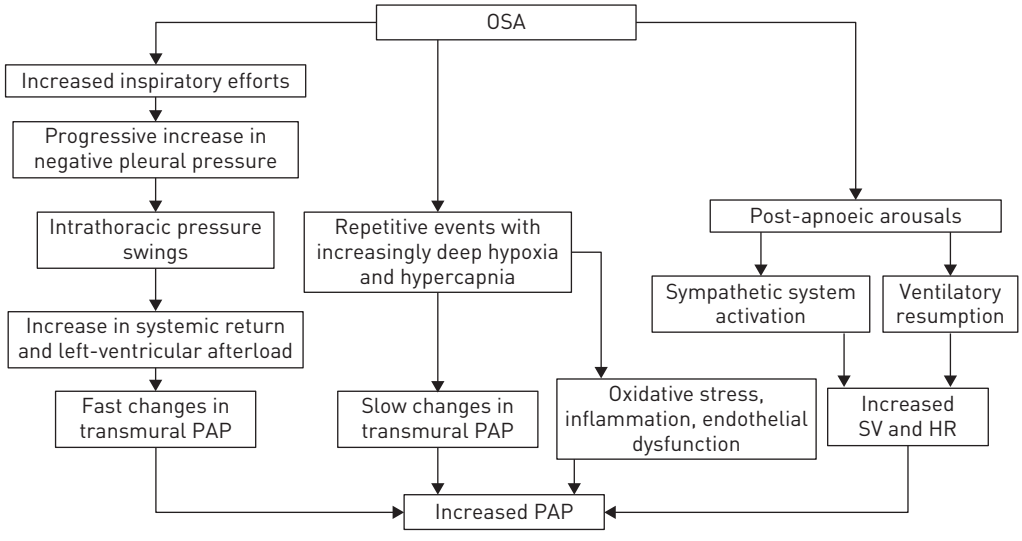

FIGURE 3 Pathophysiology of increased pulmonary arterial pressure (PAP) due to obstructive sleep apnoea (OSA). SV: stroke volume; HR: heart rate.

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

Permanent PH and SBDs

Role of sleep apnoea and hypopnoea in the development of permanent PH

The downstream consequences of sleep apnoea have been extensively studied [9]. Sleep apnoea induces increased sympathetic nerve activity, metabolic dysregulation, inflammation, oxidative stress, endothelium dysfunction and intermittent hypoxia. These promote development of hypertension, atrial fibrillation and heart disease. All these factors are potentially involved in PH [16]; however, their role as a cause of PH 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 are retrospective and not all of them use RHC, the gold standard for PH diagnosis [38]. Prevalence also depends on the chosen PAP definition threshold, which has recently changed from 25 mmHg to 20 mmHg [1]. Furthermore, patients with comorbidities that may affect PAP, such as heart failure or chronic lung disease, are included in some studies. Early case studies, which include patients with OSA and comorbidities, report a large variability and severity of PH [39, 40]. Sajkov *et al.* [41] investigated 27 patients with OSA (respiratory disturbance index (RDI) >10 events·h^{-1}) by echocardiography for the presence of PH. Patients with clinically significant lung or cardiac diseases were excluded. Eleven OSA patients (41%) were found to have PH that was relatively mild. There were no differences between PH and non-PH patients in terms of 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 pulmonary haemodynamics when awake by echocardiography, pulmonary gas exchange and lung function tests, including small airways function, in 32 patients with OSA who had normal lung volumes [42]. PH was associated with smaller airways' closure during tidal breathing and heightened pulmonary pressor responses, firstly due to hypoxia and secondly to increased pulmonary blood flow. These findings suggest that patients with OSA and PH might have an excessive hypoxic pulmonary vasoconstriction response, as well as vascular remodelling, which promote the development of PH.

Laks *et al.* [43] investigated 100 consecutive OSA patients using RHC. All patients had to have an AHI of ⩾20 events·hour^{-1}. Left-heart failure was excluded and 42% of the cohort had PH defined as mean PAP >20 mmHg. Those with PH were older and had higher P_{aCO_2}, lower arterial oxygen tension (P_{aO_2}) and lower forced expiratory volume in 1 s (FEV_1) values. The presence of daytime hypoxaemia was not found to be a prerequisite in the development of PH. The high prevalence of PH in the study by Laks *et al.* is probably explained by a population with a significantly higher BMI than other studies.

Two studies have shown a similar prevalence of PH (20%) in patients with sleep apnoea [44, 45]. In these studies, patients with COPD were excluded and the determinants of PH were daytime and nocturnal hypoxaemia (in both studies), PAWP (in the first study) [44] and BMI (in the second study) [45].

Minai *et al.* [37] investigated pulmonary haemodynamics in 83 patients with OSA. In this study, 58 patients (70%) had PH and eight of the 28 patients with precapillary PH had severe PH with a mean PAP ⩾40 mmHg. It is likely that patients in the study reflect characteristics close to those of patients with an indication for performing RHC (according to current recommendations [46]) and are not representative of patients seen in a sleep laboratory for suspected OSAS.

One of the largest studies to date using RHC has investigated pulmonary haemodynamics by RHC in 220 patients [36]. OSA was defined by an AHI >20 events·hour^{-1} and PH by resting mean PAP ⩾20 mmHg. PH was observed in 37 out of 220 patients (17%) and was strongly linked to the presence of an obstructive (rather than a restrictive) ventilatory pattern on lung function test, as well as hypoxaemia and hypercapnia, and was generally accounted for by an associated COPD. Interestingly, the severity of OSA played only a minor role in the increase of PAP. The role of airflow limitation in the development of PH in OSA patients is consistent with an older study of 24 patients with both OSA and COPD [47]. Patients with fibrosing ILDs (including idiopathic pulmonary fibrosis (IPF)) frequently have OSA [48–50]; however, the role of OSA as a factor in PH in such a population has not been well demonstrated [51].

In summary, the impact of obstructive apnoea and hypopnoea 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 (18–25 mmHg) [11, 36]. Conversely, when there is an

associated chronic respiratory disease, such as COPD [52] and OHS [53], obstructive apnoea and hypopnoea are an aggravating factor for PH. CSA in nonhypercapnic patients does not lead to permanent PH, as patients with idiopathic CSA do not have PH [54].

Permanent PH and sleep-related hypoventilation

Early studies on this subject [26–28] suggest that hypoxaemia during sleep, due mainly to sleep-related hypoventilation in COPD patients without significant daytime hypoxaemia or OSA, could lead to permanent PH [55, 56]. A more recent study with a larger number of patients showed that daytime mean PAP was identical in COPD patients with and without nocturnal oxyhaemoglobin desaturation [57]. In fibrosing ILDs and particularly in IPF, sleep desaturation is very common [49, 58]. Indeed, one study [58] showed that a quantification of sleep oxyhaemoglobin desaturation, but not AHI, is associated with survival in IPF. This study suggests that lung fibrosis may lead to nocturnal desaturation and PH, leading to a worse prognosis.

The role of sleep-related hypoventilation in OHS as a cause of PH is also difficult to assess. PH is the result of several factors including hypoxaemia, hypercapnia, OSA and, in some patients, left-heart dysfunction [53, 59, 60]. The important point, suggesting that alveolar hypoventilation during sleep is responsible for the severity of PH, is the significant improvement after a few weeks of treatment with noninvasive ventilation (NIV) applied during sleep (in patients with very severe nocturnal hypoventilation in a group where only 10% had OSA) [59].

SBDs in patients with PAH and CTEPH

Age at diagnosis is increasing for PAH 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 [61]. The French PAH registry reported an average age of 50 years at diagnosis [62], while the COMPERA registry reported a mean age of 71 years [63]. 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 the 2599 PAH patients included had OSA, of whom 75% were female [61].

Most studies [64–73] dedicated to SBD in pulmonary vascular disease are compared in table 2. Small studies evaluated the prevalence of SBDs in PAH patients and found that they were common (including OSA, CSA, periodic breathing and oxygen desaturation related to sleep). Schulz *et al.* [65] found periodic breathing in six out of 20 patients with PAH, resulting from prolonged circulation time due to low CO, severe hypoxaemia that stimulated peripheral chemoreceptors and changes in chemosensitivity. Minai *et al.* [66] performed a cross-sectional study that included 43 patients with IPAH or connective tissue disease-associated PAH (CTD-PAH). Of these patients, 30 (70%) were nocturnal oxyhaemoglobin desaturators, of whom 87% were moderate to severe nocturnal desaturators (>20% of the night below an S_{pO_2} of 90%). Nocturnal desaturators were older and had more severe pulmonary haemodynamics. Twenty patients underwent full night polysomnography, showing that only three had an AHI >5 events·h^{-1}. Sleep apnoea was not considered to contribute to the pathogenesis of PH in these three patients. Ulrich *et al.* [67] reported increased prevalence of CSR in a cohort of 38 patients with PAH or CTEPH. Of these patients, 68% were nocturnal oxyhaemoglobin desaturators (>10% of the night below an oxygen saturation measured by pulse oximetry (S_{pO_2}) of 90%). Only four patients had OSA and patients with SBDs did not experience excessive sleepiness but had a worse quality of life compared to the remainder. By contrast, Prisco *et al.* [68] observed a higher prevalence of OSA (50%) and the degree of PAP elevation was similar to that of the other studies quoted, although cardiac index was higher. In addition, the percentage of time spent during the night with an S_{pO_2} <90% was also high (31±36%). In the study by Dumitrascu *et al.* [70], 45 out of 169 patients (26.6%) with PAH who were prospectively investigated by sleep study had an AHI >10 events·h^{-1}. Of these, 27 patients (16%) had OSA and 18 patients (10.6%) had CSA. Patients with OSA were characterised by male gender and higher BMI, whereas those with CSA were older, more hypocapnic and had worse pulmonary haemodynamics. Therefore, from this study, it appears that the prevalence of patients with central and obstructive apnoea is higher among subjects with PAH than among 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). Notable in this study was the use of a transcutaneous capnograph during polysomnography that allowed the observation that certain oxyhaemoglobin desaturations were due to ventilation–perfusion mismatch when S_{pO_2} decreased simultaneously with transcutaneous carbon dioxide tension (P_{CO_2}). As such, the two most common mechanisms for nocturnal hypoxaemia in the Jilwan study were ventilation–perfusion mismatch and OSA. Sleep apnoea were considerably more prevalent than in the general population of similar age. In a retrospective cross-sectional study of 52 PAH patients, Minic *et al.* [72] found 56% with OSA and 44%

TABLE 2 Comparison of studies on sleep-related breathing disorders (SBDs) in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

Reference	Population	Mean age years	% NYHA II:III:IV	Mean PAP mmHg	Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	Sleep study	Definition of SBD	AHI events·h^{-1}	Main mechanism of SBD	Findings
[64]	13 IPAH at time of diagnosis	45	–	61	1.88	Polysomnograpy	Desaturator#	4.6±4.9	Nocturnal desaturations independent of OSA or CSA	77% had significant nocturnal desaturation
[65]	20 IPAH during follow-up	45	40:50:10	56	1.96	Polysomnograpy	OSA excluded Significant periodic breathing	37±5	Periodic breathing and CSA	30% had periodic breathing associated with more severe haemodynamics
[66]	38 IPAH and five CTD-PAH during follow-up	48	42:53:5	51	2.5	Nocturnal oximetry	Desaturator#	–	Nocturnal desaturations independent of OSA or CSA	Nocturnal desaturation frequent (70%) and correlated with right-ventricular dysfunction
[67]	23 PAH and 15 CTEPH during follow-up	61	37:42:21	43	2.4	Polysomnograpy or ambulatory polygraphy compared to oximetry	CSA ⩾10 events·h^{-1}	Median 8 (IQR 4–16)	Periodic breathing and CSA	SBD not associated with excessive sleepiness. Ambulatory sleep study or polysomnography required
[68]	9 IPAH and 19 CTD-PAH at time of diagnosis	55	39:39:4	41	2.9	Polysomnograpy	AHI ⩾5 events·h^{-1}	11.4±19.8	OSA was the main cause of nocturnal desaturation	Symptoms and diurnal S_{pO_2} not predictive of SBD
[69]	44 PAH and 19 CTEPH during follow-up	62	38:49:13	41	2.6	Nocturnal oximetry	Desaturator#	–	Nocturnal desaturation was not associated with a higher AHI	High prevalence of nocturnal desaturation
[70]	169 PAH, CTEPH and various causes of PH during follow-up	61	–:82:–	43	2.4	Ambulatory polygraphy	AHI ⩾10 events·h^{-1} with >50% obstructive events (OSA) AHI ⩾10 events·h^{-1} with >50% central events (CSA)	3±1 (no SBD) 21±10 (OSA) 18±8 (CSA)	16% OSA, 11% CSA and nocturnal desaturations independent of OSA or CSA	Higher prevalence of SBD compared to the general population
[71]	29 IPAH and 17 CTEPH during follow-up	53	70:24:–	44	3.2	Polysomnograpy with capnograph	Desaturator¶ AHI >5 events·h^{-1} (OSA) AHI >5 events·h^{-1} with changing amplitude breathing 10 min (periodic breathing)	25±22	76% ventilation–perfusion mismatch alone or associated with another mechanism, 66% OSA and 10% CSA	High prevalence of nocturnal desaturation. A sleep study should be mandatory

Continued

TABLE 2 Continued

Reference	Population	Mean age years	% NYHA II:III:IV	Mean PAP mmHg	Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	Sleep study	Definition of SBD	AHI events·h^{-1}	Main mechanism of SBD	Findings
[72]	52 PAH	53	50:25:–	46	CO 4.3 $L \cdot min^{-1}$	Polysomnograpy	–	16.5±18.8	56% OSA and 44% CSA	High prevalence of SBD. Age and ESS score >10 were predictive of SDB
[73]	78 IPAH and 73 associated PAH	44	–	46	CO 3.8 $L \cdot min^{-1}$	Polysomnograpy	–	6±8 (no SBD) 14±8 (with SBD)	29 patients had OSA and 29 had CSA	No difference in survival with or without SBD. Mean nocturnal S_{pO_2} was an independent predictor of death

All patients in these studies had a mean PAP ⩾25 mmHg except for [67] where three patients had a mean PAP between 20 and 25 mmHg. NYHA: New York Heart Association; PAP: pulmonary arterial pressure; AHI: apnoea–hypopnoea index; IPAH: idiopathic PAH; S_{pO_2}: oxygen saturation measured by pulse oximetry; OSA: obstructive sleep apnoea; CSA: central sleep apnoea; CTD-PAH: connective tissue disease-associated PAH; IQR: interquartile range; ODI: oxygen desaturation index; CO: cardiac output; ESS: Epworth Sleepiness Scale. #: >10% total sleep time with S_{pO_2} <90%; ¶: 60 min S_{pO_2} <90% or ODI ⩾20 per h.

with CSA. Age and subjective sleepiness were predictive of a SBD. Nagaoka *et al.* [73] have shown a relationship between the importance of nocturnal desaturation and survival, where the more patients desaturate during sleep, the shorter the life expectancy.

The factors involved in the development of these various SBDs in patients with PAH or CTEPH are not fully understood. The decrease in minute ventilation in stage three and rapid eye movement (REM) sleep may contribute to the increase in ventilation–perfusion mismatch revealed by the only study [71] that measured nocturnal transcutaneous P_{CO_2}. The magnitude of these desaturations is also linked to the fact that these patients are located on the steep part of the oxyhaemoglobin dissociation curve [74]. 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 decades of life[4], it is not surprising to find it by chance in a population of patients with an average age of 50–55 years [61, 62]. Secondly, the (moderate) decrease in lung volumes [74] seen most often with hypocapnia, leading to upper airway collapsibility and the likely propensity to arouse in patients seen most often with respiratory control instability, may be contributing factors [75, 76]. In addition, it is likely that the upper airway dilator muscles are affected like skeletal muscles in patients with right-heart failure [77]. All of these anomalies are suspected to promote collapse of the upper airways. Finally, another possible explanation for OSA is fluid retention and fluid shift in patients who often have a degree of congestion, especially in older subjects [78].

Concerning CSA, reactive hyperventilation in response to hypoxaemia and increased chemosensitivity [79] may lead to hypocapnia, which presumably provokes central apnoea by shifting P_{aCO_2} levels below the apnoeic threshold during sleep [80] (a phenomenon which is well-known from CHF patients with CSR). Since hypocapnia is a negative prognostic factor in IPAH patients and is associated with a low CO, low P_{aCO_2} on falling asleep associated with prolonged arterial circulation time meets the conditions necessary for the appearance of CSA [65, 70].

In summary, SBDs are 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 desaturation in these patients are multiple (*i.e.* an increase in ventilation–perfusion mismatch as well as obstructive and central respiratory events during sleep). Further studies are needed in the future to better understand the links between SBDs on the one hand and PAH or CTEPH on the other, and upon their long-term consequences.

Effects of treatment of SBDs on PH

Effects of OSA treatments on PAP and right-heart change

Tracheostomy is an older treatment modality that is rarely performed today. Older studies evaluated changes in PAP in a small number of patients with OSA *via* RHC following tracheostomy [81, 82]. In these studies, subjects had PH at baseline and significant reductions in mean PAP were seen after intervention.

Nasal continuous positive airway pressure (CPAP) is considered to be the most effective treatment for OSA and two studies from the same group [83, 84] have failed to demonstrate any change in resting PAP measured by RHC when CPAP is used. The most recent of these studies [84] showed a decrease in mean PAP of 4 mmHg, after 5 years of treatment with CPAP, in the 11 patients who presented a mean PAP at baseline of $\geqslant$20 mmHg. However, on the basis of such a result and on subgroup analysis comparing 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 developed mild PH (estimated by Doppler echocardiography) which was partially or completely reversed after 6-months of effective CPAP treatment. CPAP reduced both PAP and hypoxic pulmonary vascular reactivity [86] and the greatest treatment effects occurred in patients who had PH at baseline. In a randomised cross-over, echocardiography-based trial that included 23 otherwise healthy OSA patients, Arias *et al.* [87] reported that CPAP application reduced systolic PAP levels. In 21 patients in this study with adequate CPAP compliance, systolic PAP decreased from 29±9 mmHg to 24±6 mmHg. It is thus interesting to note that in a randomised trial PAP decreased under CPAP; however, the clinical significance of such a reduction, where most of the patients presented PAP values considered as normal, is uncertain. Two meta-analyses [88, 89] showed that CPAP is associated with a decrease in PAP in patients with OSA, although these meta-analyses have some limitations.

Two studies [90, 91] evaluated the effect of CPAP on right-ventricular function using three-dimensional (3-D) echocardiography. Vitarelli *et al.* [90] studied 37 patients with OSAS without comorbidities and 30 control subjects. Both 3-D right-ventricular ejection fraction (RVEF) and right-ventricular dyssynchrony were abnormal in OSAS patients in the presence of PH. In addition, both 3-D RVEF and the

measurement of right-ventricular dyssynchrony were independently correlated with the AHI. These abnormalities improved after chronic application of CPAP. A larger study [91] that included 56 OSA patients and 50 controls reported that 24 weeks of effective CPAP treatment resulted in a significant reduction in PVR, a reduction in the right-ventricular end-systolic volume index and an increase in RVEF. Another study [92] combined measurement of biomarkers, echocardiography and cardiac magnetic resonance imaging (MRI) in patients with OSA both before and after treatment with CPAP. This study showed that systolic PAP measured by echocardiography and dilation of the right-heart chambers both decreased after several months of CPAP treatment.

Importantly, all studies with positive effects on PAP or the right ventricle did not use RHC and it is unclear whether the improvements in pulmonary haemodynamics and right-ventricular function were secondary to improvements in systemic hypertension and left-ventricular function, or were in fact the results of direct effects on the pulmonary vasculature [93].

In summary, CPAP has the potential to improve pulmonary haemodynamics, especially in patients who present with PH 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 as use for at least 4 h 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 with a SBD (16 with PAH, seven with CTEPH) in a randomised, placebo-controlled, double-blind, cross-over trial. After as soon as 1 week of nocturnal oxygen therapy, 6-min walk distance (6MWD) improved compared with placebo, along with improvements in the SBD and in haemodynamics. The Ulrich study is the only randomised 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, as 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 h·day^{-1}) must necessarily include periods of sleep in these patients and in patients with other causes of chronic respiratory failure. If hypercapnia prevails, the most appropriate treatment is nocturnal NIV. Such treatments have been shown 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 SBDs and PH, a practical algorithm for diagnosis and treatment of SDB is proposed in figure 4.

Assessment of PH in patients with SBDs

Based on the evidence outlined in our review, routine investigation or screening for PH in patients with sleep apnoea not associated with chronic respiratory failure and without unexplained dyspnoea is not recommended [38]. 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 pulmonary circulation. Doppler echocardiography must be performed in cases 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 it is essential that echocardiography, if not already performed, is conducted in order to explore PAP, the size of the heart chambers and left-heart function [93]. If echocardiography results show a significant increase in PAP then 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 PAH [101]. The appropriate treatment consists of correcting alveolar hypoventilation. The use of NIV, which is often limited to the period of sleep, often leads to a marked improvement in alveolar hypoventilation and PH [53]. Finally, the important point to emphasise is that screening for PH is not recommended in patients with OSAS with no comorbidities.

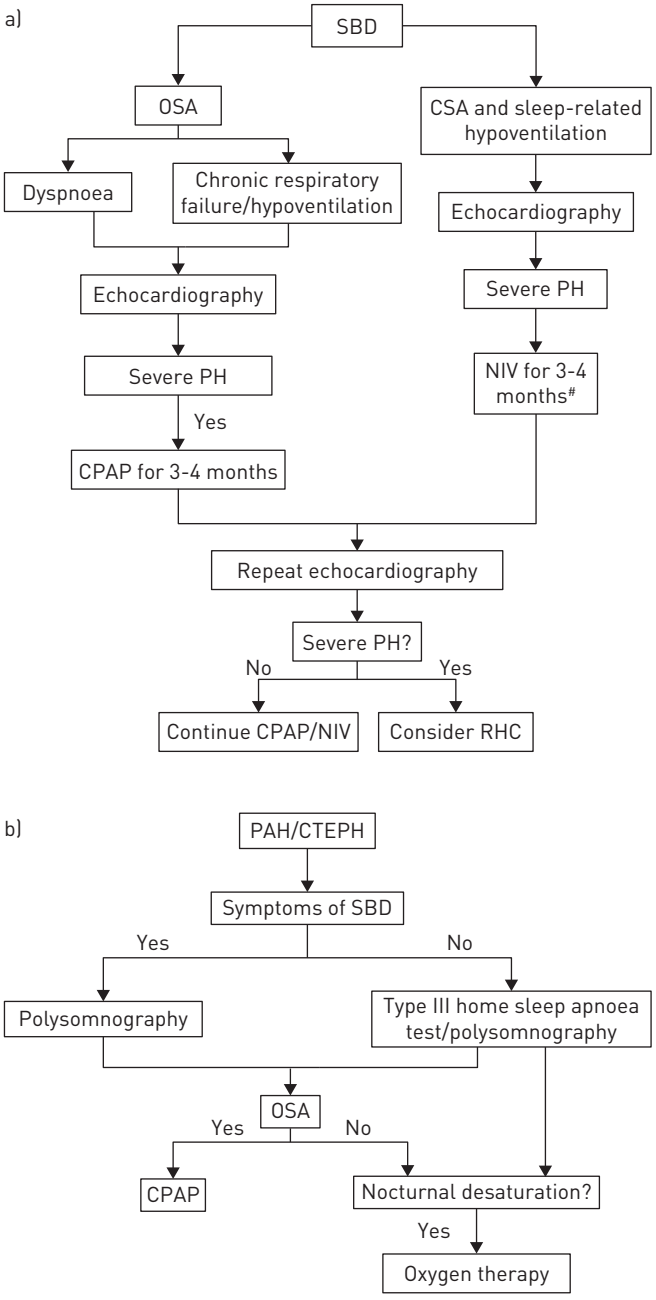

FIGURE 4 Diagnostic and treatment algorithms proposed in clinical situations where an interaction between a sleep-related breathing disorder (SBD) and pulmonary hypertension (PH) is suspected. Panels a) and b) correspond to diagnosis and treatment of PH in patients with a SBD and of SBD in patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH), respectively. OSA: obstructive sleep apnoea; CSA: central sleep apnoea; ECG: echocardiography; CPAP: continuous positive airway pressure; NIV: non-invasive ventilation; RHC: right-heart catheterisation. #: applies to hypercapnic patients.

Assessment and treatment of SBDs in patients with PAH and CTEPH

A sleep study should be performed in all patients with PAH or CTEPH, whether or not there are symptoms suggestive of OSA [102]. 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 nonsevere patients (those corresponding to New York heart Association (NYHA) functional class II) whose haemodynamics do not show a decrease in CO. Although the level of evidence is low, these sleep studies seem justified because SBDs are frequent and lead to hypoxaemia during sleep, variations of intrathoracic pressure (in obstructive events) and stimulation of

TABLE 3 Sleep-related breathing disorder (SBD) and pulmonary hypertension (PH) statements

PH in patients diagnosed with an SBD
It is unclear whether OSA alone, in the absence of daytime hypoxaemia, can cause stable PH
Isolated SBDs have little or no effect on pulmonary haemodynamics, but are an important aggravating factor of PH when associated with a significant chronic respiratory or cardiac disease
In patients with COPD, obesity or severe ILD with chronic hypoxaemia, the association of SBDs 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 hypoxaemia
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 signs suggestive of OSA in patients with PAH or CTEPH, a type III home sleep apnoea test (or 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 CSR in patients with severe PH (with reduced CO) should not be treated with adaptive servo-ventilation. Auto-adjusting positive airway pressure should also be avoided

OSA: obstructive sleep apnoea; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CSA: central sleep apnoea; PAP: pulmonary arterial pressure; OHS: obesity hypoventilation syndrome; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CPAP: continuous positive airway pressure; CSR: Cheyne–Stokes respiration; CO: cardiac output.

the sympathetic system. These consequences of SBDs are likely to alter a haemodynamic state already compromised. As such, 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 desaturation 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 auto-adjusting positive airway pressure devices could potentially induce micro-arousals and change in sleep macrostructure [103]. Regarding OSA, other treatments than CPAP can be beneficial, such as lifestyle measures like 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 arterial oxygen tension (P_{aO_2}) is <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, such that hypoxaemia due to worsening of the ventilation–perfusion mismatch present in these patients during sleep is corrected.

In addition, 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 (⩽45%) left-ventricular ejection fraction (LVEF). In fact, with such a diagnosis of heart failure with low LVEF, adaptive servo-ventilation increased cardiovascular mortality in one study [104].

As a final point, by analogy with heart failure [9, 105], the treatments for PH, right-heart failure or cardiac arrhythmia complicating PH are likely to improve SBDs. It therefore seems important to perform a sleep study and reassess the patient when PH treatments have been optimised.

Conclusions

Several studies have shown that OSA and sleep-related hypoventilation are responsible for an acute increase in PAP. OSA 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 right-ventricular 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 does not otherwise 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 echocardiography is mandatory. Uncertainties regarding the clinical impact of PH and the right-ventricular changes of SBDs require further clinical studies. Currently, there is no clear recommendation about how, when and with which tool to perform a sleep study on diagnosis or during the follow-up of patients with PAH or CTEPH. However, from recent studies showing the high prevalence of SBDs, a type III home sleep study (respiratory polygraphy) and occasionally polysomnography are needed to clarify how to diagnose and treat SBDs in such patients. If OSAS is diagnosed, treatment with CPAP can be proposed with the aim of improving daytime sleepiness and improving sleeping conditions. On the subject of links between SBDs and PH, the authors propose a number of statements based on the references quoted in the present review (table 3).

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