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## **The association between sleep-related breathing disorders and pre-capillary pulmonary hypertension: a chicken and egg question**

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**Abbreviations :** AHI: Apnea-Hypopnea Index; BMI: body mass index; BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CSA: central sleep apnea; CTEPH: chronic thromboembolic pulmonary hypertension; DLCO: diffusing capacity of carbon monoxide; FEV1: Forced Expiratory Volume in one second; FVC: Forced Vital capacity; HIF: hypoxia inducible factor; mPAP: mean pulmonary arterial pressure; NIV: non-invasive ventilation; OHS: obesity hypoventilation syndrome; OSA: obstructive sleep apnea; PaCO<sub>2</sub>: partial pressure of carbon dioxide; PaO<sub>2</sub>: partial pressure of oxygen; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterization; SBD: sleep-related breathing disorders; SH: sleep hypoxemia; sPAP: systolic pulmonary arterial pressure; TTE: transthoracic echocardiography

## ABSTRACT

The level of knowledge about a direct link between sleep-related breathing disorders and pre-capillary pulmonary hypertension (PH) is low and there is a chicken and egg question to know which disease causes the other. On one hand, sleep-related breathing disorders are considered as a cause of group 3 PH, in the subgroup of patients with hypoxemia without lung disease. Indeed, isolated sleep-related breathing disorders can lead to mild pre-capillary PH on their own, although this is rare for obstructive sleep apnea and difficult to establish for obesity-hypoventilation syndrome, the evolution towards PH being observed especially in the presence of respiratory comorbidities. The hemodynamic improvement under treatment with continuous positive airway pressure or non-invasive ventilation also argues for a causal link between pre-capillary PH and sleep-related breathing disorders. On the other hand, patients followed for pre-capillary PH, particularly pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, develop more sleep-related breathing disorders than the general population, especially sleep hypoxemia, central sleep apnea in patients with severe PH and obstructive sleep apnea in older patients with higher body mass index. The main objective of this article is therefore to answer two main questions, which will then lead us to discuss the bilateral link between these diseases: are sleep-related breathing disorders independent risk factors for pre-capillary PH and does pre-capillary PH induce sleep-related breathing disorders? In other words, who is the chicken and who is the egg?

## 1. Introduction

The 2015 European pulmonary hypertension (PH) guidelines defined pre-capillary PH as a pulmonary vascular disease with mean pulmonary arterial pressure (mPAP) greater than 25mmHg, pulmonary artery wedge pressure (PAWP) less than or equal to 15mmHg and pulmonary vascular resistance (PVR)  $[(mPAP-PAWP)/cardiac\ output]$  greater than or equal to 3WU (mmHg/l/min) [1]. This definition was discussed at the sixth world symposium on PH in order to lower the mPAP threshold to 20 mmHg [2]. PH is classified in 5 groups according to similarities in pathophysiology, clinical management and treatments [2] (Table 1).

Sleep-related breathing disorders (SBD), including obstructive sleep apnea (OSA), central sleep apnea (CSA), obesity hypoventilation syndrome (OHS) and sleep hypoxemia are frequent in the general population and are a public health issue. SBD seem to be central in pre-capillary PH as they could be the cause of PH group 3 and can complicate all other PH groups, especially group 1 (pulmonary arterial hypertension (PAH)) and group 4 (chronic thromboembolic pulmonary hypertension (CTEPH)).

In this review, we will focus on pre-capillary PH as it is already well known that there is a bidirectional relationship between SBD and post-capillary PH (group 2)[3]. Indeed, when a pre-capillary PH associated with SBD is suspected, a post-capillary PH is the main differential diagnosis. First of all, OSA is a cause of arterial hypertension[4] which can induce post-capillary PH by promoting heart failure with preserved ejection fraction. Moreover, despite many confounding factors, including age, sex and obesity, there is accumulating evidence regarding strong associations between OSA and other cardiovascular diseases, i.e. coronary artery disease[5], conduction disorders and arrhythmia[6], cerebrovascular disease[7]. Conversely, heart failure is often complicated by post-capillary PH, which can generate SBD,

with prevalence rates of 50% to 75%[8]. CSA and Cheynes Stokes breathing are then the main disorders observed.

On the contrary, to date, the level of knowledge about a direct link between pre-capillary PH and SBD remains relatively low and there is the chicken and egg problem to know if SBD are a consequence or a cause of PH and if these SBD could lead to a vicious circle and worsen PH. Thus, the main objective of this article is to answer two main questions: are SBD independent risk factors for PH and does PH induce SBD on its own? In other words, who is the chicken and who is the egg? It will then lead us to discuss the pathophysiology of the bilateral link between SBD and PH.

## **2. Are Sleep-related breathing disorders independent risk factors for pre-capillary pulmonary hypertension?**

SBD are considered as a cause of group 3 PH, in the subgroup of patients with hypoxemia without lung disease [2,9] (**Table 1**).

### **2.1. Prevalence of PH in SBD**

#### **2.1.1. PH in OSA**

OSA is a common chronic condition caused by repeated complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. OSA diagnosis is based on a combination of a polysomnographic criteria (Apnea-Hypopnea Index  $\geq 5$  (AHI)) and clinical criteria such as excessive daytime drowsiness and nocturnal snoring. In the 1980s, early studies identified cyclic changes in pulmonary artery pressure (PAP) related to OSA with

elevated PAP values, immediately following the end of the obstructive event [10]. However, whether OSA is responsible for a persistent increase in mPAP independent of associated comorbidities, particularly lung diseases, remains a controversial issue.

The studies measuring the prevalence of PH in OSA are summarized in **Table 2**. Between 1980 and 1990, 4 studies described for the first time the prevalence of chronic PH in OSA [11–14], with measurement of PAP by right heart catheterization (RHC) in 3 of them. The prevalence of PH was around 20%, and PH was generally mild. However, all these study included patients with cardiopulmonary comorbidities and the level of mPAP was correlated with lower diurnal partial pressure of oxygen (PaO<sub>2</sub>), higher diurnal partial pressure of carbon dioxide (PaCO<sub>2</sub>) and lower lung volumes (Forced Expiratory Volume in one second (FEV<sub>1</sub>) and Forced Vital capacity (FVC)) [13,14], suggesting a role of associated lung disease in the development of PH. Thereafter, bigger studies also made evaluations of pulmonary hemodynamics in patients with OSA, without exclusion of patients with lung comorbidities. In 1995, Laks et al [15] found a high percentage of patients with PH (42%) in a cohort of 100 patients with severe OSA (26 with a chronic obstructive airflow limitation). It is important to note that these patients had a more severe obesity than in other studies (mean Body Mass Index (BMI) of 37kg/m<sup>2</sup>). Seventy-three percent of patients with FEV<sub>1</sub>/FVC ratio <70% had PH in this study. In a large prospective study by Chaouat et al[16], RHC was performed in 220 consecutive patients with OSA and a less severe obesity (mean BMI of 32 kg/m<sup>2</sup>). PH was diagnosed in 37 patients (17%). In both studies, PH was mild and the diagnosis of PH was strongly correlated with higher diurnal PaCO<sub>2</sub>, lower diurnal PaO<sub>2</sub>, higher BMI and the presence of an obstructive ventilatory disorder, suggesting the contribution of underlying chronic pulmonary pathology, especially of daytime hypoxemia, hypercapnia and obstructive lung disease to the development of PH. More recently Minai et al included 83 patients with

OSA and found a higher 70% prevalence of PH [17]. However, in this study, undergoing RHC was an inclusion criterion. As RHC is usually done for a clinical suspicion of PH, it could explain the high prevalence of PH. Of note, 40 (48%) patients had a post-capillary PH, suggesting that they included much more patients with left heart diseases than in other studies. Concordant with other studies, 18 (22%) had a pre-capillary PH. Most patients had mild PH but 33% had severe PH, defined by mPAP > 40mmHg. A new finding from this study is that patients with PH had a higher mortality rate compared to those OSA patients without PH. Therefore, all these studies highlight the importance of lung and cardiac comorbidities, as well as obesity and its cardiopulmonary consequences, in the development of PH in OSA. Moreover, in all these studies, there was no direct correlation between AHI, and the level of PAP, suggesting that there was no direct link between OSA severity and pulmonary hemodynamics in these patients.

In the study by Chaouat et al, 30 patients diagnosed as having both chronic obstructive pulmonary disease (COPD) and OSA (also called overlap syndrome), had higher mPAP (20 +/- 6mmHg vs 15 +/- 5 mmHg) as compared to 235 patients with OSA alone, confirming the major contribution of this association on PH development. This led some authors to conclude that PH occurs in OSA only because of associated hypoxemic respiratory diseases or cardiac comorbidities.

Conversely, several studies, have reported PH in OSA patients without evidence of any other pathology. For instance, in the study of Podszus et al, 10/13 patients diagnosed with both OSA and PH had no evidence of respiratory or cardiac disease[11], in the study of Fletcher et al, 2 had normal lung functions and in the study of Laks et al, a subgroup of 6 patients with PH and PaO<sub>2</sub> ≥ 80mmHg at rest had a mean mPAP of 32 mmHg, even with an extreme range

of 52 mmHg[15]. On the contrary, in the study of Chaouat et al, only one patient had PH with PaO<sub>2</sub> > 80mmHg and the authors concluded that PH was unlikely to develop in OSA patients in the absence of daytime hypoxemia[16].

To determine whether OSA-related intermittent nocturnal hypoxemia by itself is sufficient to result in a permanent PH, some studies tried to exclude patients with comorbid lung disease. The prevalence of PH in these studies ranged from 20% to 53%[18–24]. For instance, Sajkov et al included 27 patients with OSA after exclusion of lung and cardiac disease[19]. The diagnosis of PH was made by transthoracic echocardiography (TTE) and they found PH in 11 patients (41%). Patients with PH had no difference in BMI, in lung function, in OSA severity but they were more hypoxemic when awake (77mmHg vs 72mmHg) and there was a correlation between mPAP and diurnal PaO<sub>2</sub>. In another study, the same authors showed that the patients with PH without lung disease had increased ventilation perfusion mismatch, increased small airways closure during tidal breathing and a greater PAP response to hypoxia and to increased pulmonary blood flow (with dobutamine perfusion), compared to patients without PH, suggesting that PH in patients with OSA without lung disease might be explained by an increased sensitivity to hypoxemia and pulmonary blood flow, and a greater pulmonary vascular remodelling [22]. A concern about these studies is that PAP measurements were made by echography without measure of PAWP by RHC, even if there was no difference in the E/A ratio. The repetition of hypoxemia during sleep may therefore be sufficient to result in pre-capillary PH in some OSA patients. Whether mild diurnal hypoxemia is the cause or the consequence of PH, the contribution of obesity, and why these patients might develop pulmonary vascular remodelling remain to be determined. In a more recent study in patients with severe OSA and no associated lung disease, PH was present in 27% of patients and was associated with diurnal and nocturnal hypoxemia, and

also with obesity resulting in lung volume reduction. The authors considered that obesity was the main cause of daytime hypoxaemia in the PH group [23].

### **2.1.2. PH in OHS**

As mentioned above, the contribution of obesity in OSA-associated PH is a major concern. Some studies did not show difference in BMI between OSA patients with or without PH [13,14] while others found higher BMI in patients with PH[15,16,23,24]. As described above, Bady et al attributed the development of PH in OSA to the respiratory consequences of obesity[23]. It is estimated that 15% of patients investigated for suspected OSA have OHS [25]. Conversely, 90% of OHS patients have OSA (IAH  $\geq$  5/h) and 70% have severe OSA (IAH  $\geq$  30/h)[26]. In patients with OHS, prolonged obstructive apneas and decreased tidal volume in deep slow-wave sleep and REM sleep are responsible for hypercapnia and nocturnal hypoxia, which persist throughout the day. OHS is defined by the association of obesity (BMI $>$ 30Kg/m<sup>2</sup>), daytime hypercapnia (PCO<sub>2</sub>  $\geq$  45mmHg on arterial blood gases) and exclusion of other cause of alveolar hypoventilation. Though, some trials have attempted to assess the prevalence of PH among people with OHS. Depending on the studies, it varies from 50 to 80% with again a variability in results due to different study designs and diagnostic techniques employed. Sugerman et al identified PH in 23/26 patients with OHS prior to bariatric surgery [27]. However, only nine patients (35%) had PH without left heart dysfunction. In the study by Kessler et al, RHC was performed in 29/34 patients with OHS, and a mild PH (mPAP 23mmHg, PVR 4WU) was found in 17 (59%) of them [28]. Kauppert et al also evaluated mPAP in 21 patients with OHS and found that 14 (67%) had PH, not related to left heart failure[29]. A larger study by Almeneessier et al included 77 patients with OHS [30]. PH was defined by TTE as a systolic pulmonary arterial pressure (sPAP)  $>$  40 mmHg.

Fifty-three of the 77 patients (69%) had PH. Nevertheless, obese patients had many associated co-morbidities in these studies that could have contributed to PAP increase.

Even if OHS patients are more prone to develop PH compared with patients with isolated OSA, the link between OHS and the severity of PH is not really clear. This relationship remains to be firmly established. Among the previously cited studies, Kessler et al[28] observed higher mean PAP value in patient with OHS (23+/-10mmHg) compared to the patients with OSA plus COPD (20+/-6mmHg). Moreover, Kauppert et al [29]and Sugerman et al[27] described 9 patients with mPAP  $\geq$  25mmHg and 8 patients with mPAP  $\geq$  40mmHg on respective cohorts of 17 and 23 patients followed for OHS with PH. However, it is important to point out that a post-capillary component is found in about half of these patients.

Therefore, pre-capillary PH is frequent in OHS and may be attributed to the persistent hypoxemia and to the consequences of obesity on lung function. Because of the co-morbidities related to obesity, the proof of an independent link between OHS and pre-capillary PH is more difficult to establish and requires larger studies.

## **2.2. Impact of SBD therapy on pulmonary hemodynamics**

Finally, the improvement of PH associated with both OSA and OHS with the treatment of these SBD (continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) respectively) is another argument for a direct link between SBD and PH.

CPAP is the primary treatment for patients with OSA. Limited data are available on the effect of CPAP on PAP in patients with OSA. A meta-analysis on seven studies demonstrated a 13mmHg reduction in mPAP under CPAP treatment in patients with OSA [31]. Two studies

were based on hemodynamic data obtained by RHC [32,33]. Chaouat et al. in 1997 prospectively studied changes in respiratory function, arterial blood gases and pulmonary hemodynamics after 64 +/- 6 months of CPAP therapy in 65 patients followed for OSA [32]. In 11 patients with PH, mPAP was 24 +/- 5mmHg at baseline vs 20 +/- 7mmHg after 5 years of CPAP (p=0.14). Therefore, there was no significant effect of CPAP on pulmonary hemodynamic parameters. In contrast, in two prospective uncontrolled studies, CPAP treatment for 4 [34] and 6 months [33], respectively, was associated with a significant reduction in mPAP levels (mPAP reduced from 16.8 +/- 1.2 to 13.9 +/- 0.6mmHg in the overall study population and from 25.6 +/- 4.0 to 19.5 +/- 1.6mmHg in patients with baseline PH). Arias et al also demonstrated, in a randomized controlled cross-over trial, a reduction in sPAP after 12 weeks of effective vs sham CPAP therapy in patients with OSA [35]. In addition, Sajkov et al reported a decreased pulmonary vascular response to hypoxia after CPAP treatment, which may be related to an improvement in pulmonary endothelial function [34]. They also concluded that the improvement in pulmonary hemodynamics was not due to changes in left ventricular diastolic function. Conversely, in a prospective study of 47 patients, Colish et al found that systolic and diastolic left ventricular function were improved in patients with OSA after 3 months of CPAP treatment [36]. They also reported a progressive improvement in cardiac remodelling after one year of treatment, based on TTE and cardiovascular magnetic resonance imaging criteria.

Regarding OHS, Masa et al showed that oxygen therapy did not improve hemodynamic parameters in patients with PH [37]. On the other hand, CPAP and NIV appeared to improve PH associated with OHS [26,38]. In the study by Held et al, there was a significant decrease in mPAP of 18 mmHg measured by RHC, as well as a decrease in PVR and brain natriuretic peptide level (BNP) after 3 months of NIV [38]. Castro-Añón et al also showed an

improvement in sPAP after 6 months of NIV (from 58±11mmHg to 44 ±12mmHg; p=0.014) in patients with OHS [39]. In a study comparing the effects of CPAP and NIV, the authors reported a significant decrease in sPAP under NIV and it appeared to be more effective than CPAP in reducing left ventricular hypertrophy [40]. In contrast, a recent larger study showed a similar effect of CPAP and NIV on the reduction of sPAP and left ventricular dysfunction [41]. Finally, Kauppert et al established an inverse relationship between the evolution of mPAP and compliance with NIV [42]. All these studies suggest an important role for NIV to treat PH associated with OHS. Despite the persistence of moderate PH, NIV would lead to a significant reduction in PAP values. Finally, we must not neglect hygienic and dietetic measures and the indispensable weight loss in this population. Indeed, in the study by Sugerman et al, there was a prolonged decrease in mPAP in patients who had undergone bariatric surgery responsible for weight loss [43]. The improvement of pre-capillary PH under treatment with NIV or CPAP also argues for a causal link between pre-capillary PH and SBD. However, this reversibility is only partial, and there is likely additional factors and personal susceptibility that play a role in the onset or persistence of PH.

As a conclusion of this first part, isolated SBD can generate pulmonary hemodynamic disorders on their own, although this is rare for OSA and difficult to establish for OHS, the evolution towards PH being observed especially in the presence of respiratory comorbidities. The presence of SBD is an important aggravating factor of PH in patients followed for significant chronic respiratory disease.

### **3. Does pre-capillary pulmonary hypertension induce sleep-related breathing disorders on its own?**

As we have seen that SBD can lead to pre-capillary PH, it is important to determine whether pre-capillary PH is only the egg or if it also could be the chicken and be a cause of SBD. Some authors have studied breathing during sleep in patients with pre-capillary PH and these studies are summarized in **Table 3**.

#### **3.1. Sleep hypoxemia in PAH**

First of all, in 2001, in a small cohort of 13 patients with severe PAH (mPAP 60.8 +/- 15mmHg), Rafanan et al found very few apneas or hypopneas measured during polysomnography but nocturnal hypoxemia in 10/13 patients (characterized by a saturation <90% for at least 10% of the sleep time) [44]. Sleep hypoxemia is the most common SBD in PAH with a prevalence of 21% to 83%, independently of sleep apnea, and it has been recently associated with a poor prognosis in PAH[45]. Minai et al showed that out of 43 patients followed for PAH, 30 had nocturnal hypoxemia [46]. The desaturators had higher haemoglobin, higher BNP, higher mPAP, and lower cardiac index. In a cohort of 63 patients (PAH, CTEPH), Hildenbrand described 63% desaturators (SpO<sub>2</sub><90% for at least 10% of the sleep time) and 52% sustained desaturators (SpO<sub>2</sub><90% for at least 50% of the sleep time) [47]. In a recent study on 15 patients with PAH, only 2 had sleep apnea but 8 had sleep hypoxemia without sleep apnea [48]. In another recent study among 71 patients with PAH or CTEPH, while 69% had sleep apnea, 48% showed nocturnal hypoxemia independent of the presence of sleep apnea and although there was no difference in cardiac evaluation between patients with or without OSA, nocturnal mean SpO<sub>2</sub> was inversely correlated with

right ventricular volumes [49]. However, there was no right heart catheterization data in this study.

### **3.2. Sleep apnea in PAH**

Sleep apnea have also been described in patients with pre-capillary PH. Poms et al reported in the Registry to Evaluate Early and Long-term PAH disease management (REVEAL registry) a prevalence of sleep apnea of 20% among 2959 patients with PAH [50]. However, this prevalence may be underestimated as the diagnosis of sleep apnea was determined based on the medical form. Sleep apnea was not correlated with the functional class and the risk of mortality. Minic et al reported a higher prevalence of 71% of sleep apnea syndrome in 52 patients followed for PAH [51]. Schulz et al showed that 6 out of 20 patients followed for PAH (i.e. 30%) had Cheyne-Stokes respiration during sleep [52]. The presence of periodic breathing was correlated with more severe cardiorespiratory disease with lower PaO<sub>2</sub> and diffusing capacity of carbon monoxide (DLCO), higher mPAP and PVR. In addition, 14 patients had an AHI < 20/h and 6 had an AHI > 20/h, with almost exclusively central events. Finally, in 2008, out of a population of 38 patients including 23 patients with PAH and 15 patients followed for CTEPH, Ulrich et al described a prevalence of CSA/Cheyne-Stokes breathing as high as 45%, and only 11% OSA [53]. These central events were also correlated with poorer quality of life.

Conversely, Prisco et al in 2011[54], Jilwan et al in 2013[55] and Spiesshoefer et al in 2021[49], on respective cohorts of 28, 29 and 71 patients with PAH or CTEPH, reported a clear predominance of OSA. However, this higher prevalence could be explained by a higher proportion of elderly men with a BMI > 25.

### **3.3. Impact of PH therapy on SBD**

Two recent trials have investigated the potential effects of specific CTEPH treatments, namely surgical thromboendarterectomy (the gold standard) and pulmonary angioplasty, on SBD. In 2018, La Rovere et al examined the impact of endarterectomy on SBD associated with CTEPH in a cohort of 50 patients [56]. Prior to surgery, the prevalence of SBD was 64% (slight majority of obstructive apnea). After specific treatment, the prevalence remained the same or even slightly worsened at 68%, with reduction of the central sleep apneas but an increase in the number of obstructive apneas. In contrast, in 2009 Kohno et al described an AHI reduction in patients suffering from CTEPH and SBD after pulmonary angioplasty [57].

In the study of Carvalho et al, among 29 patients with PAH and CTEPH, 13 patients had a follow-up assessment at  $5.2 \pm 2.4$  months following initiation/completion of PH-specific treatment or surgery and sequential polysomnography [58]. Despite a significant improvement in cardiopulmonary haemodynamics in these patients, no differences occurred in the AHI but not all the patients had SBD. There are no large studies evaluating the effect of PH-specific treatment on SBD.

Thus, despite the lack of conclusive data, it appears that SBD are relatively common in patients with pre-capillary PAH and CTEPH and more prevalent than in general population. Therefore, pre-capillary PH seems to be a cause of SBD on its own. CSA and Cheyne-Stokes periodic breathing predominate in young patients with severe PH, while OSA are more common in an older, male population with high BMI.

As a conclusion of this second part, pre-capillary PH is a consequence but can also be a cause of SBD.

#### **4. The bilateral link between sleep-related breathing disorders and pulmonary hypertension**

As clinical data show us that pre-capillary PH could be both a consequence and a cause of SBD, it is necessary to understand the bilateral link underlying this relation (**Figure 1**).

On one hand, SBD could lead to modifications in hemodynamics. First, intermittent hypoxemia occurring during apnea, is responsible for hypoxic pulmonary vasoconstriction which in turn increases the PAP[59]. Second, in OSA, the negative intrathoracic pressure generated by respiratory efforts against the closed upper airway increases venous return, right ventricular preload and blood flow in the pulmonary circulation, which could increase the PAP [60]. Third, SBD lead to the activation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system which could also increase the PAP and have effects on the right ventricle function [61,62]. The increase in PAP is transient. However, when it occurs regularly, it may lead to a chronic pulmonary vascular remodelling. In rodents, studies showed that permanent or intermittent hypoxia during the night without diurnal hypoxia was able to induce a permanent PH associated with a right ventricular hypertrophy and an important pulmonary arterial remodelling with neomuscularization of distal pulmonary circulation [63,64]. Physiological studies in humans with SBD and PH are also in favour of a chronic pulmonary arterial remodelling [22]. Why only some patients will develop this pulmonary arterial remodelling remains not established and it could be due to individual genetic susceptibility to hypoxia or other associated hits. At the functional level, intermittent hypoxia during SBD is responsible of a systemic endothelial dysfunction which has been well described in humans but also certainly of a pulmonary arterial endothelial dysfunction [65]. CPAP therapy has been demonstrated to improve endothelial function, what reinforces the

link between SBD and endothelial dysfunction[66]. At the proteic level, it could be explained by the activation of the transcriptional factor Hypoxia inducible factor (HIF) by nocturnal continuous or intermittent hypoxia. Indeed, HIF is a transcriptional pathway activated by hypoxia, which lead to the transcription of genes involved in cell proliferation and inflammation, and is though involved in pulmonary vascular remodelling. Repeated apneas could also be responsible for oxidative stress[67], inflammation[68] shear stress and a pro-coagulant state with activation of platelets[69,70], participating in pulmonary arterial remodelling.

Concerning hypercapnia observed in OHS, the direct effects on pulmonary vascular tone are controversial but it has been shown to increase hypoxic pulmonary vasoconstriction, which might explain the high frequency of PH in OHS [71].

On the other hand, some pathophysiological features of patients with pre-capillary PH, especially PAH and CTEPH, can promote the development of SBD. Sleep leads to profound physiological respiratory modifications, even in healthy subjects, which include a decrease in respiratory control with alveolar hypoventilation and a decrease in functional residual capacity related to the lying position, a decrease in minute ventilation in stage 3 and REM sleep and in increase in upper airway resistance [72]. These modifications may be well tolerated in healthy individuals but may be responsible for sleep hypoxemia in patients with respiratory disease including pre-capillary PH, especially if they are located close to the steep part of the oxyhaemoglobin dissociation curve. Moreover, there is a well-studied and indisputable link between congestive left heart failure and both OSA and CSA and some of the pathophysiological features observed (decreased cardiac output, increased sympathetic tone) are also found in patients followed for pre-capillary PH with right ventricular failure.

Though, pre-capillary PH complicated by right ventricular failure may promote instability of ventilatory control leading to CSA, as observed in left heart failure [51]. It may also be a cause of hypoventilation, especially because of respiratory muscle dysfunction resulting from muscle wasting and intrinsic contractile dysfunction [73,74]. Fluid accumulation and nocturnal overnight rostral shift from the legs to the upper part of the body in the lying position have also been suspected to be a cause of OSA, CSA and sleep hypoxemia. Indeed, fluid may accumulate in the neck, narrowing upper airway, thereby causing OSA and may accumulate in the lungs, provoking hyperventilation and driving pCO<sub>2</sub> below the apnea threshold, so leading to CSA[75]. In the study from Carvalho et al, there was no difference in the overnight rostral fluid shift between patients with and without sleep apnea among the 29 patients with PAH and CTEPH but there was a significant inverse correlation between the sleep apnea severity and the overnight change in leg fluid[58]. It has also been recently shown that sleep hypoxemia in PAH was associated with higher overnight fluid shift, also suggesting a role of overnight fluid shift, especially to lungs, in the occurrence of sleep hypoxemia, probably by increasing ventilation perfusion mismatch[48].

There is therefore a bilateral link between SBD and PH and each has the potential to promote and maintain the other.

## **5. Conclusion**

This review shows that SBD and pre-capillary PH could be either the chicken or the egg as both has the potential to promote and maintain the other. Therefore, when these two conditions are present together, it may lead to a vicious circle able to deteriorate both

conditions. Clinician must be therefore aware of this bilateral link between SBD and PH and think to look for PH in SBD and for SBD in PH.

Currently, there are no official recommendations of diagnosis and treatment when an interaction between SBD and PH is suspected. Recently, Chaouat et al [76] proposed a practical algorithm in these clinical situations. The routine investigation or screening for PH in patients with OSA but without chronic respiratory failure and without unexplained dyspnoea is not recommended. In case of OSA with respiratory or cardiovascular comorbidities, CSA or sleep-related hypoventilation, a TTE should be carried out. If echocardiography results show signs of severe PH, a specific treatment by CPAP or NIV must be started first. After 3-4 months of adapted treatment, if TTE still shows signs of severe PH, a RHC should be considered. If the PAP decreases, it is proposed to continue the treatment with CPAP or NIV without further investigations for PH. In all patients with PAH or CTEPH a sleep study should be performed whether or not there are symptoms suggestive of OSA (polysomnography or a type III home sleep apnoea test can be performed depending on the resources available locally, or nocturnal oximetry in non-severe patients without signs of OSA). A diagnosis of OSA in these patients should lead to initiation of a treatment by CPAP with a fixed pressure. Indeed, it should be preferred to a treatment by auto-adjusting positive airway pressure, which has the potential to induce deleterious effects for PAH because of micro-arousals and sleep disruption from pressure fluctuations or the return of SBD events when the PAP level is lowered as well as fluctuations of intrathoracic pressures [77].

Further physiological and therapeutic studies are necessary to better understand the bilateral relation between SBD and Pre-capillary PH and the impact of the treatment of each condition on the other.

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**Table 1. Updated clinical classification of pulmonary hypertension (adapted from Simonneau et al [2])**

1. 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 newborn syndrome
2. PH due to left heart disease
  - 2.1. PH due to heart failure with preserved LVEF
  - 2.2. PH due to heart failure with reduced LVEF
  - 2.3. Valvular heart disease
  - 2.4. Congenital/acquired cardiovascular conditions leading to post-capillary PH
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
  - 4.1. Chronic thromboembolic PH
  - 4.2. Other pulmonary artery obstructions
- 5. PH with unclear and/or multifactorial mechanisms
  - 5.1. Haematological disorders
  - 5.2. Systemic and metabolic disorders
  - 5.3. Others
  - 5.4. Complex congenital heart disease

*HIV: human immunodeficiency viruses; LVEF: Left ventricular ejection fraction; PAH: Pulmonary arterial hypertension; PCH: Pulmonary capillary haemangiomatosis; PH: Pulmonary hypertension; PVOD: Pulmonary veno-occlusive disease*

**Table 2: Prevalence of pulmonary hypertension in obstructive sleep apnea syndrome**

<u>Author</u>	<u>Population</u>	<u>Diagnosis of OSA</u>	<u>Diagnosis of PH</u>	<u>Prevalence of PH</u>	<u>Comments</u>
<b>Podszus et al 1986</b> [11]	65 patients with OSA, with or without cardiopulmonary comorbidities	AHI > 5/h	na	Resting PH in 13/65 (20%) and exercising PH in 31/65 (48%)	8 of these patients had cardiopulmonary comorbidity, isolated from 36 other patients
<b>Fletcher et al 1987</b> [12]	24 patients including 19 with underlying pulmonary pathology	na	By RHC mPAP ≥ 25mmHg	RHC possible for 15 patients: PH in 9/15 patients including 7 with pulmonary comorbidity	
<b>Weitzenblum et al 1988</b> [13]	46 patients with OSA, with or without pulmonary co-morbidities	AHI > 5/h	By RHC mPAP ≥ 20mmHg	9/46 (20%)	No correlation with AHI Lower diurnal PaO <sub>2</sub> ; higher diurnal PaCO <sub>2</sub> ; lower FEV <sub>1</sub> and FVC
<b>Krieger et al 1989</b> [14]	114 OSA patients with pulmonary co-morbidities	AHI > 5/h	By RHC mPAP ≥ 20mmHg	19/114 (19 %) 12 % PaCO <sub>2</sub> ≥ 45 mmHg 33 % PaO <sub>2</sub> ≤ 65 mmHg	AHI more severe if mPAP ≥ 20 mmHg. Lower FEV <sub>1</sub> and PaO <sub>2</sub> , higher PaCO <sub>2</sub>
<b>Kurashina et al 1992</b> [18]	24 patients with OSA, free of chronic lung disease	AHI > 20/h	By RHC mPAP > 20mmHg	5/24 patients (21%)	Correlation with BMI, desaturation during exercise and negative correlation with supine PaO <sub>2</sub>

<b>Sajkov et al 1994</b> [19]	27 patients with OSA, free of chronic lung disease	AHI > 10/h	By TTE mPAP > 20mmHg	11/27 (41 %): 20mmHg ≤ mPAP ≤ 26mmHg	Lack of correlation with FEV1, smoking status, BMI
<b>Laks et al 1995</b> [15]	100 patients with OSA, with or without pulmonary comorbidities	AHI > 20/h	By RHC mPAP > 20mmHg	42/100 (42%)	Lower PaO <sub>2</sub> ; Higher PaCO <sub>2</sub> ; Lower FEV1 Correlation with PaO <sub>2</sub> , PaCO <sub>2</sub> and FEV1
<b>Chaouat et al 1996</b> [16]	220 patients with OSA, with and without pulmonary comorbidities	AHI > 20/h	By RHC PAPm ≥ 20mmHg	37/220 (17%)	Correlation with PaO <sub>2</sub> , PaCO <sub>2</sub> , BMI and AHI. Lower PaO <sub>2</sub> , FEV1/FVC, mean nocturnal SaO <sub>2</sub> and higher PaCO <sub>2</sub> and BMI.
<b>Sanner et al 1997</b> [20]	92 patients with OSA, without pulmonary comorbidities	AHI > 10/h	By RHC mPAP > 20mmHg	18/92 (20 %), of which 8 (44%) also had an increase in PAWP	Correlation with PAWP and percentage of time during sleep with SaO <sub>2</sub> < 90%
<b>Nijima et al 1999</b> [21]	19 patients with OSA, with and without pulmonary comorbidities	AHI > 10/h	By RHC mPAP ≥ 20mmHg	10/19 (53%)	Correlation with BMI

<b>Sajkov et al 1999</b> [22]	32 patients with OSA, without pulmonary comorbidities	AHI > 10/h	By TTE mPAP > 20mmHg	11/32 (34%)	No correlation with AHI, lung function, BMI, age. Correlation with airway closure during forced breathing
<b>Bady et al 2000</b> [23]	44 patients with OSA, without pulmonary comorbidities	AHI > 5/h	By RHC mPAP > 20mmHg	12/44 (27%)	No correlation with AHI Correlation with BMI and PaO2
<b>Hetzel et al 2003</b> [24]	49 patients with OSA, without pulmonary comorbidities	AHI > 10/h	mPAP at rest > 20 mmHg mPAP at exercise > 30 mmHg	PH at rest: 6/49 (12%) PH at exercise: 39/49 (80%) No patient has an increased PVR.	mPAP at exercise: 3 independent predictive factors: BMI, age, TLC
<b>Minai et al 2009</b> [17]	83 patients with OSA, with and without pulmonary comorbidities	AHI > 5/h	mPAP at rest > 25 mmHg	58/83 (70%) 18 with PAWP < 15 mmHg. 27 with severe PH (mPAP> 40mmHg)	Correlation with female gender, nocturnal desaturation, FVC and BMI. Decrease in survival in patients with PH. Patients with severe PH had more nocturnal desaturations, worse hemodynamics and greater mortality.

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*AHI: Apnea-hypopnea index; BMI: Body mass index; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; mPAP: Mean pulmonary arterial pressure; na: not available; OSA: Obstructive sleep apnea; PaCO2: Partial pressure of carbon dioxide; PaO2: Partial pressure of oxygen; PAWP: Pulmonary artery wedge pressure; PH: Pulmonary hypertension; PVR: pulmonary vascular resistance; RHC: Right-heart catheterization; SpO2: Oxygen saturation; TLC: Total lung capacity; TTE: Transthoracic echocardiography*

**Table 3: Prevalence of sleep related breathing disorders in pulmonary hypertension**

<b><u>Author</u></b>	<b><u>Population</u></b>	<b><u>mPAP</u></b>	<b><u>PVR</u></b>	<b><u>Parameters measured during sleep</u></b>	<b><u>Prevalence of SBD</u></b>	<b><u>Comments</u></b>
<b><i>Rafanan et al 2001</i></b> [44]	13 patients with PAH	61±15 mmHg	na	Sleep apnea: AHI > 5/h Nocturnal hypoxemia: SpO2 < 90% over 10% of sleep time	OSA: 0/13 Nocturnal hypoxemia: 10/13 (77%)	
<b><i>Schulz et al 2002</i></b> [52]	20 patients with PAH	56±3 mmHg	17.1±1.7 WU	Sleep apnea: AHI > 10/h	CSB: 6/20 (30%) OSA: 0/20	CSB: lower PaO2 and DLCO, Higher mPAP and PVR
<b><i>Minai et al 2007</i></b> [46]	43 patients with PAH	46mmHg	na	Nocturnal hypoxemia: SpO2 < 90% over 10% of sleep time	Nocturnal hypoxemia: 30/43 (70%)	Nocturnal hypoxemia: higher haemoglobin, higher BNP, higher mPAP, lower cardiac index
<b><i>Ulrich et al 2008</i></b> [53]	38 patients with PAH or CTEPH	43 [33-51] mmHg	8.5 [5.4-10.6] WU	Sleep apnea: AHI > 10/h Nocturnal hypoxemia: SpO2 < 90% over 10% of sleep time	OSA : 4/38 (11%) CSB/CSA : 15/38 (39%) Nocturnal hypoxemia: 68%	CSB/CSA: poorer quality of life
<b><i>Prisco et al 2011</i></b> [54]	28 patients with PAH, CTEPH or PH of group 5	41±6 mmHg	6.2±4.7 WU	Sleep apnea: AHI > 5/h	OSA: 14/28 patients (50%) CSA: 0/28 patients	OSA: Higher mPAP

<b>Hildenbrand et al 2012</b> [47]	63 patients with PAH or CTEPH	41 [30-51] mmHg	7.1 [3.3-9.9] WU	Desaturators: SpO2 < 90% over 10% of sleep time  Sustained desaturators: SpO2 < 90% over 50% of sleep time	Desaturators: 49/63 (77%)  Sustained desaturators: 33/63 (52%)	Desaturator: regardless of the diurnal SpO2
<b>Poms et al 2013</b> [50]	2959 patients with PAH	49±14 mmHg	10.2±6.8 WU	Sleep apnea: based on the medical history form	Sleep apnea: 599/2959 (20%)	Sleep apnea: not associated with worse functional class nor with mortality
<b>Dumitrascu et al 2013</b> [78]	169 patients (28 PAH, 51 CTEPH, 59 PH of group 3, 31 others)	43±12 mmHg	8.5±4.8 WU	Sleep apnea: AHI > 10/h	Sleep apnea: 45/169 (27%) OSA: 27/169 (16%) CSA: 18/169 (11%)	OSA: male gender and higher BMI. CSA: older and more hypocapnic
<b>Jilwan et al 2013</b> [55]	29 patients with PAH or CTEPH	44±13 mmHg	8.1±2.8 WU	Sleep apnea AHI > 5/h  Nocturnal hypoxemia: SpO2 < 90% over 60min	OSA: 41/46 (89%) CSA: 4/46 (8%) Nocturnal hypoxemia: 38/46 (83%)	Nocturnal hypoxemia: lower PaO2 and FEV1, higher AHI
<b>Minic et al 2014</b> [51]	52 patients with PAH	46±21 mmHg	9.9±7.3 WU	Sleep apnea AHI ≥ 5/h	Sleep apnea: 37/52 (71%) OSA: 29/52 (56%) CSA: 8/52 (15%)	Sleep apnea: no difference in cardiopulmonary hemodynamics or survival

<b>Nagaoka et al 2018</b> [45]	151 patients with PAH	46±16 mmHg	12±9 WU	Sleep apnea AHI > 5/h Nocturnal hypoxemia: average SpO2 < 90%	Sleep apnea: 58/151 (38%) OSA: 29/151 (19%) CSA: 29/151 (19%) Nocturnal hypoxemia: 31/151 (21%)	Nocturnal hypoxemia associated with mortality but not sleep apnea
<b>Carvalho et al 2019</b> [58]	29 patients with PAH or CTEPH	50±17 mmHg	12±6 WU	Sleep apnea AHI ≥ 5/h	Sleep apnea: 15/29 (52%) OSA: 11/29 (38%) CSA: 4/29 (14%)	Correlation between sleep apnea severity and overnight change in nocturnal fluid shift
<b>Yan et al 2020</b> [79]	50 patients with PAH	na	na	Nocturnal hypoxemia: SpO2 < 90% over 10% of sleep time	Nocturnal hypoxemia: 17/50 (34%)	Nocturnal hypoxemia: shorter six-min walking distance (6MWD), higher mean right atrial pressure, lower daytime PaO2, higher VE/VCO2 and VE/VCO2 slope
<b>Jutant et al 2021</b> [48]	15 patients with PAH	56 [46-68] mmHg	8.8 [6.4-10.1] WU	Sleep apnea AHI > 15/h Nocturnal hypoxemia: SpO2 < 88% over 5min	Sleep apnea 2/15 (13%) Nocturnal hypoxemia 8/15 (53%)	Nocturnal hypoxemia: higher nocturnal fluid shift
<b>Spiesshoefer et al 2021</b> [49]	71 patients with PAH or CTEPH	na	na	Sleep apnea AHI ≥ 5/h Nocturnal hypoxemia: mean SpO2 < 90%	Sleep apnea: 49/71 (69%) OSA: 48/71 (68%) CSA: 4/29 (14%) Nocturnal hypoxemia: 34/71 (48%)	Nocturnal hypoxemia but not OSA correlated with right ventricle volume

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*Data presented as mean±SD or median (25<sup>th</sup>-75<sup>th</sup> percentile). AHI: Apnea-hypopnea index; BNP: Brain natriuretic peptide; CSA: Central sleep apnea; CSB: Cheyne-stokes breathing; CTEPH: Chronic thromboembolic pulmonary hypertension; DLCO: Diffusing capacity of carbon monoxide; FEV1: Forced expiratory volume in one second; mPAP: Mean pulmonary arterial pressure; na: not available; OSA: Obstructive sleep apnea; PAH: Pulmonary arterial hypertension; PaO2: partial pressure of oxygen; PH: Pulmonary hypertension; PVR: pulmonary vascular resistance; SBD: Sleep-related breathing disorders; SpO2: Oxygen saturation; VE/VCO2: carbon dioxide ventilation equivalent WU: Wood units*

**Legend of the figure**

**Figure 1:** Representation of the bilateral link between sleep-related breathing disorders and pre-capillary pulmonary hypertension

RAAS: renin-angiotensin-aldosterone system

