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# Hypoxemia during sleep and overnight rostral fluid shift in pulmonary arterial hypertension: a pilot study

Etienne-Marie Jutant<sup>1,2,3</sup> , David Montani<sup>1,2,3</sup> , Caroline Sattler<sup>1,2,3</sup>, Sven Günther<sup>4,5</sup>, Olivier Sitbon<sup>1,2,3</sup>, Gilles Garcia<sup>1,2,3</sup>, Isabelle Arnulf<sup>6,7</sup>, Marc Humbert<sup>1,2,3</sup>, Thomas Similowski<sup>7,8</sup> and Stefania Redolfi<sup>6,7</sup>

<sup>1</sup>School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France; <sup>2</sup>INSERM UMR\_S 999, Pulmonary Hypertension: Pathophysiology and Novel Therapies, Hôpital Marie Lannelongue, Le Plessis-Robinson, France; <sup>3</sup>Department of Respiratory and Intensive Care Medicine, Assistance Publique-Hôpitaux de Paris (AP-HP), Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France; <sup>4</sup>Innovative Therapies in Haemostasis, INSERM 1140, University of Paris, Paris, France; <sup>5</sup>Department of Respiratory Physiology, AP-HP, Georges Pompidou European Hospital, Paris, France; <sup>6</sup>Service des Pathologies du Sommeil, Département R3S, Groupe Hospitalier Universitaire AHP-Sorbonne Université, site Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>7</sup>UMRSI 158 Neurophysiologie Respiratoire Expérimentale et Clinique, INSERM, Sorbonne Université, Paris, France; <sup>8</sup>Service de Pneumologie, Médecine Intensive et Réanimation, Département R3S, Groupe Hospitalier Universitaire AHP-Sorbonne Université, site Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France

## Abstract

Sleep-related breathing disorders, including sleep apnea and hypoxemia during sleep, are common in pulmonary arterial hypertension, but the underlying mechanisms remain unknown. Overnight fluid shift from the legs to the upper airway and to the lungs promotes obstructive and central sleep apnea, respectively, in fluid-retaining states. The main objective was to evaluate if overnight rostral fluid shift from the legs to the upper part of the body is associated with sleep-related breathing disorders in pulmonary arterial hypertension. In a prospective study, a group of stable patients with idiopathic, heritable, related to drugs, toxins, or treated congenital heart disease pulmonary arterial hypertension underwent a polysomnography and overnight fluid shift measurement by bioelectrical impedance in the month preceding or following a one-day hospitalization according to regular pulmonary arterial hypertension follow-up schedule with a right heart catheterization. Results show that among 15 patients with pulmonary arterial hypertension (women: 87%; median (25–75th percentiles); age: 40 (32–61) years; mean pulmonary arterial pressure 56 (46–68) mmHg; pulmonary vascular resistance 8.8 (6.4–10.1) Wood units), two patients had sleep apnea and eight (53%) had hypoxemia during sleep without apnea. The overnight rostral fluid shift was 168 (118–263) mL per leg. Patients with hypoxemia during sleep had a greater fluid shift (221 (141–361) mL) than those without hypoxemia (118 (44–178) mL,  $p = 0.045$ ). In conclusion, this pilot study suggests that hypoxemia during sleep is associated with overnight rostral fluid shift in pulmonary arterial hypertension.

## Keywords

pulmonary hypertension, rostral fluid shift, sleep hypoxemia, sleep apnea, sleep-related breathing disorders

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## Introduction

Pulmonary arterial hypertension (PAH) is a rare and severe chronic disease caused by a remodeling of small pulmonary arteries leading to right heart failure and death if not treated.<sup>1</sup> Sleep-related breathing disorders, including sleep apnea (obstructive and central) and hypoxemia during sleep, are common in PAH.<sup>2–10</sup> Previous studies included patients with different etiologies, severities of PAH, and

Corresponding author:

Etienne-Marie Jutant, MD Service de Pneumologie et Soins Intensifs Thoraciques Centre de Référence de l'Hypertension Pulmonaire, INSERM U999, Pulmonary hypertension: Pathophysiology and Novel Therapies, Hôpital de Bicêtre, Assistance Publique Hôpitaux de Paris 78, Rue du général Leclerc, 94270 Le Kremlin-Bicêtre, France.  
Email: etienнемarie.jutant@aphp.fr



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clinical characteristics, and did not use a uniform definition for sleep-related breathing disorders. The reported prevalence of sleep apnea in PAH is therefore variable, from 5 to 89%.<sup>4,7</sup> The most frequent sleep-related breathing disorder in PAH is hypoxemia during sleep, with a prevalence ranging from 21 to 83%,<sup>2,5–7,9</sup> that has been recently associated with a poorer patients' prognosis.<sup>10</sup> However, the underlying mechanism of sleep-related breathing disorders in PAH remains to be fully clarified. Overnight rostral fluid shift from the legs to the upper part of the body promotes sleep apnea in several fluid retaining states, like sedentary lifestyle,<sup>11</sup> drug-resistant hypertension,<sup>12</sup> chronic heart failure,<sup>13</sup> end-stage renal failure,<sup>14</sup> and chronic venous insufficiency.<sup>15</sup> Indeed, it has been shown that some of this fluid may accumulate in the neck and predispose to upper airway narrowing, thereby causing obstructive sleep apnea.<sup>16</sup> Fluid may additionally accumulate in the lungs and trigger hypoventilation in patients with heart failure, driving the partial pressure of carbon dioxide below the apnea threshold with subsequent central sleep apnea.<sup>16</sup> Interstitial accumulation of fluid in lungs during the night could also participate in ventilation/perfusion mismatch and contribute to elicit hypoxemia during sleep.<sup>17,18</sup> Since PAH is associated with fluid retention, we postulate that overnight rostral fluid shift to the upper part of the body may participate in the pathogenesis of both sleep apnea and hypoxemia during sleep in PAH. In accordance, overnight rostral fluid shift has been recently described in patients with PAH and chronic thromboembolic pulmonary hypertension, but no difference was found in fluid shift between patients with and without sleep apnea.<sup>19</sup>

The primary aim of this prospective pilot study was to investigate the association of sleep-related breathing disorders with overnight rostral fluid shift measured by bioelectrical impedance in stable patients with PAH.

## Materials and methods

### Participants

We included patients with idiopathic, heritable, related to drugs, toxins, or treated congenital heart disease PAH, accessing the French national reference center of pulmonary hypertension in Bicêtre hospital for a one-day hospitalization according to regular PAH follow-up schedule, when they underwent a right heart catheterization and when they accepted to have a full night video-polysomnography in the Sleep Disorders Unit of the Pitié-Salpêtrière hospital in the month preceding or following the catheterization. We excluded patients with already diagnosed and treated sleep apnea, patients who were dependent on nocturnal oxygen, patients with group 2, 3, 4, or 5 PAH or group 1 PAH associated with connective tissue disease, human immunodeficiency virus infection, portal hypertension,<sup>20</sup> patients with grade 3 obesity (body mass index  $\geq 40$  kg/m<sup>2</sup>), and

patients with signs of right heart failure and/or requiring an hospitalization.

### Measurements

The functional class (New York Heart Association, NYHA), the six-minute walk distance (6MWD), the pulmonary function, including the diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DLCO), brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hemodynamic data at the right heart catheterization were measured. BNP was considered as increased when BNP  $>50$  ng/L or NT-proBNP  $>300$  ng/L. Hemodynamic measurements included mean pulmonary artery pressure (mPAP), right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP), and cardiac output. The cardiac output was determined by the standard thermodilution technique, and the cardiac index (CI) was calculated as the cardiac output divided by body surface area. Pulmonary vascular resistance (PVR) was calculated as (mPAP – PAWP)/cardiac output.

A full night video-polysomnography (Compumedics Ltd, Australia) combined with a transcutaneous pressure of CO<sub>2</sub> (PtcCO<sub>2</sub>) monitoring (TOSCA/CombiM, Radiometer, Basel, Switzerland) was performed in patients breathing room air in the Sleep Disorders Unit of the Pitié-Salpêtrière hospital. Sleep and respiratory events were scored as recommended<sup>21</sup> by an experienced sleep physician blind to all other measures. Based on the international criteria,<sup>22</sup> sleep apnea was defined by an apnea-hypopnea index (AHI)  $>15$ /h, and hypoxemia during sleep as more than five minutes of sleep with pulsed oxygen saturation (SpO<sub>2</sub>) lower than 88% plus an AHI lower than 15/h. Excessive daytime sleepiness was defined by a score  $>10$  on the Epworth sleepiness scale.<sup>23</sup>

The fluid volume of each lower limb was measured in the evening before polysomnography and in the next morning after polysomnography using bioelectrical impedance (Hydra 4200, Xitron Technologies, San Diego, CA, USA) as previously described,<sup>11,14,24</sup> by the same experimenter, blind of the results of the polysomnography. The difference between the mean fluid volume of the two legs before and after polysomnography was calculated and defined as the overnight rostral fluid shift. The neck, thigh, calf, and ankle circumferences were measured using a tape measure on the subject lying down before polysomnography and in the following morning as previously described.<sup>11,12,14,24</sup> For thigh, calf, and ankle circumferences, the results were reported as the mean of the two legs.

### Statistical analysis

The data are presented as median (25–75th percentile) for continuous variables and number and frequency (percentage) for categorical variables. The groups were compared using the non-parametric Mann–Whitney *U* test for

continuous variables and Fisher's exact test for categorical variables. A *P* value lower than 0.05 was set as the significance threshold. The statistical analysis was performed using GraphPad Prism 9 (GraphPad Software Inc., La Jolla California, USA).

### Ethics rules

The institutional review board for human studies approved the study (Comité de Protection des Personnes Ile de France VI, reference number 2015-A01947-42). All participants signed a written informed consent.

## Results

### Characteristics of the patients with PAH

Over a period of 14 months, all the eligible patients meeting the inclusion criteria who accessed the French national reference center of pulmonary hypertension in Bicêtre hospital for a one-day hospitalization with a right heart catheterization were proposed to undergo a polysomnography in the Sleep Disorders Unit of the Pitié-Salpêtrière hospital in the month preceding or following the right heart catheterization, for a systematic screen for sleep-disordered breathing and for a measurement of overnight rostral fluid shift. Seventeen patients accepted to participate in the study. One of them was excluded from the analysis because he could not sleep without oxygen and one because of sudden death during the night of polysomnography (Fig. 1). The 15 analyzed patients with PAH were young, non-obese, and mainly women (Table 1, first column). Most of them had idiopathic PAH. Dyspnea was mild-to-moderate as the patients were largely in NYHA functional class I or II. Exercise capacity, assessed by the 6MWD, was mildly reduced. As usually described in PAH,

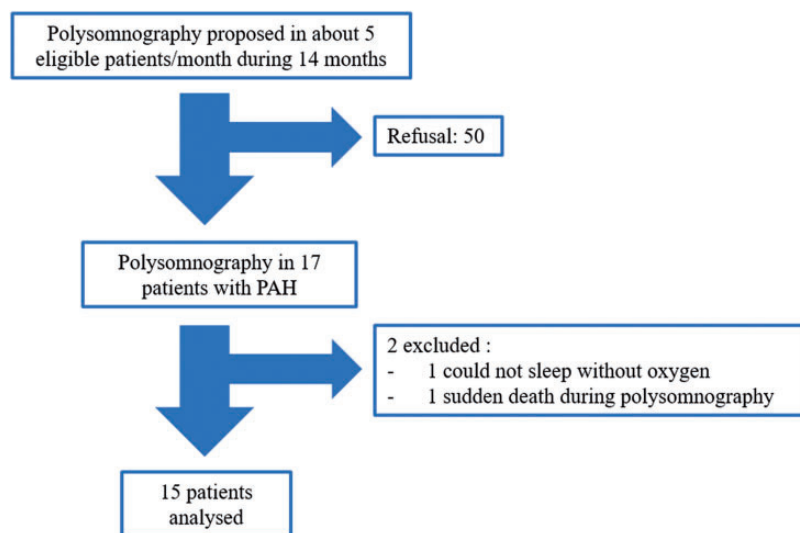
pulmonary function tests revealed normal lung volumes with moderate decrease in lung diffusion capacity. Arterial blood gases tests showed moderate hypoxemia and hypocapnia. The BNP was normal in the majority of patients. Hemodynamic of PAH was severe according to the measurement of mPAP and PVR, with a RAP slightly increased in favor of moderate fluid overload, but with preserved cardiac output. None had signs of right heart failure. Most of the patients received drug treatments approved for PAH in combined bi- or tri-therapy.

### Sleep characteristics

The most common sleep-related symptoms were snoring and sleepiness, reported by more than one-third of patients (Table 2, first column). The mean sleep duration was seven hours with a good sleep efficacy and an overall normal architecture without major sleep fragmentation and periodic leg movements. Only two patients (13%) had sleep apnea: one had a severe central sleep apnea (AHI: 39/h) without Cheyne–Stokes respiration and another had a moderate obstructive sleep apnea (AHI: 16/h). Eight (53%) patients had hypoxemia during sleep without sleep apnea and five (33%) had no sleep-related breathing disorders. The PtcCO<sub>2</sub> was low, indicating hyperventilation during both wakefulness and sleep. Bioelectrical impedance showed an overnight rostral fluid shift of 168 (118–263) mL per leg, which was accompanied by an overnight reduction in ankle, calf, and thigh circumferences, and a small overnight increase in neck circumference (Table 3, first column).

### Comparison between patients with and without hypoxemia during sleep

As per definition, in the comparison between patients without and with hypoxemia during sleep, the two patients with



**Fig. 1.** Flow chart of the study. PAH: pulmonary arterial hypertension.

**Table 1.** Clinical characteristics of the patients with PAH divided according to the presence of hypoxemia during sleep.

	All (N = 15)	Without hypoxemia during sleep (N = 5)	With hypoxemia during sleep (N = 8)	P Values
<b>Demographic data</b>				
Age, years	40 (32–61)	35 (20–43)	40 (33–59)	0.30
Gender, M/F (ratio)	2/13	1/4	1/7	1.00
BMI, kg/m <sup>2</sup>	23 (22–26)	22 (18–28)	24 (22–30)	0.35
Smoker or ex-smoker, n (%)	5 (33)	1 (20)	4 (50)	0.57
<b>PAH etiology</b>				
Idiopathic, n (%)	11 (73)	4 (80)	6 (80)	1.00
Heritable, n (%)	2 (13)	1 (20)	0	0.39
Anorexigenic, n (%)	1 (7)	0	1 (13)	1.00
Treated congenital heart disease, n (%)	1 (7)	0	1 (13)	1.00
<b>Functional parameters</b>				
NYHA functional class, n (%)				
I	4 (27)	1 (20)	3 (38)	0.54
II	7 (46)	2 (40)	3 (38)	
III	4 (27)	2 (40)	2 (24)	
Six-minute walk distance, m	499 (449–572)	449 (429–544)	505 (457–631)	0.30
FEV1/FVC	79 (71–82)	78 (69–96)	80 (72–82)	0.91
TLC, % theo	82 (77–98)	80 (78–98)	82 (77–96)	0.76
PaO <sub>2</sub> on room air, mmHg	72 (66–86)	85 (58–94)	69 (64–74)	0.11
PaCO <sub>2</sub> on room air, mmHg	33 (30–36)	29 (25–36)	32 (30–35)	0.71
<b>Biologic tests</b>				
Increased BNP, n (%)	4 (27)	2 (20)	2 (25)	1.00
<b>Hemodynamics</b>				
mPAP, mmHg	56 (46–68)	50 (42–77)	58 (53–68)	0.65
RAP, mmHg	9 (7–12)	8 (6–12)	11 (8–13)	0.37
PAWP, mmHg	11 (9–13)	11 (8–14)	12 (10–14)	0.64
CO, L/min	5.9 (4.5–6.7)	5.7 (5.0–7.0)	6.5 (4.4–6.7)	1.00
CI, L/min/m <sup>2</sup>	3.3 (3.0–4.1)	3.3 (3.2–4.1)	3.4 (2.7–3.8)	0.50
PVR, WU	8.8 (6.4–10.1)	7.6 (4.7–12.7)	8.0 (6.5–9.9)	1.00
<b>PAH approved drugs</b>				
ERA, n (%)	13 (87)	5 (100)	7 (88)	1.00
PDE5i, n (%)	12 (80)	5 (100)	5 (63)	0.23
IV prostanoid, n (%)	6 (40)	4 (80)	3 (38)	0.27
SC prostanoid, n (%)	1 (7)	1 (20)	0 (0)	0.39
PO prostanoid, n (%)	1 (7)	1 (20)	0 (0)	0.39
Calcic antagonists, n (%)	1 (7)	0 (0)	1 (13)	1.00
Bitherapy, n (%)	5 (33)	2 (40)	2 (25)	1.00
Tritherapy, n (%)	6 (40)	3 (60)	3 (38)	0.59
<b>Other treatments</b>				
Diuretics, n (%)	12 (80)	2 (40)	8 (100)	0.04
Anticoagulants, n (%)	13 (87)	4 (80)	7 (88)	1.00
Oxygen therapy, n (%)	1 (7)	0 (0)	1 (13)	1.00

Notes: Data presented as median (25th–75th percentile) and n (%). The P-values refer to a comparison between patients without and with hypoxemia during sleep. As per definition, in the comparison of patients without and with hypoxemia during sleep, the two patients with sleep apnea were excluded from the analysis. BNP was considered as increased when BNP > 50 ng/L or NT-proBNP > 300 ng/L.

BMI: body mass index; BNP: brain natriuretic peptide; CI: cardiac index; ERA: endothelin receptor antagonist; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; IV: intravenous; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PaO<sub>2</sub>: partial pressure of oxygen in arterial blood; PaCO<sub>2</sub>: partial pressure of carbon dioxide in arterial blood; PAWP: pulmonary arterial wedge pressure; PDE5i: phosphodiesterase 5 inhibitor; PO: per os; PVR: pulmonary vascular resistances; RAP: right atrial pressure; SC: subcutaneous; TLC: total lung capacity; WU: Wood unit.

sleep apnea were excluded from the analysis. Concerning the clinical and sleep characteristics (Tables 1 and 2, second and third column), there was no difference between the two groups, apart from greater sleepiness score and

larger use of diuretics in patients with hypoxemia during sleep. In accordance, the overnight rostral fluid shift measured by bioelectrical impedance was significantly higher in patients with hypoxemia than in those without hypoxemia

**Table 2.** Sleep-related characteristics of the patients with PAH divided according to the presence of hypoxemia during sleep.

	All (N = 15)	Without hypoxemia during sleep (N = 5)	With hypoxemia during sleep (N = 8)	P values
<b>Sleep symptoms</b>				
Nocturnal symptoms, n (%)				
Difficulties falling asleep	3 (20)	2 (40)	0 (0)	0.13
Nocturnal awakenings	2 (13)	0 (0)	1 (13)	1.00
Snoring	6 (40)	1 (20)	4 (50)	0.57
Breathing pauses	2 (13)	0 (0)	2 (25)	0.49
Nocturia	1 (7)	0 (0)	1 (13)	1.00
Legs muscular contractions	1 (7)	0 (0)	1 (13)	1.00
Non-restorative sleep	4 (27)	1 (20)	2 (25)	1.00
<b>Diurnal symptoms, n (%)</b>				
Morning headaches	4 (27)	0 (0)	4 (50)	0.11
Altered memory and attention	2 (13)	0 (0)	2 (25)	0.49
ESS	8 (6–13)	6 (5–10)	13 (7–16)	0.03
ESS > 10	6 (40)	1 (20)	5 (63)	0.27
<b>Polysomnography results</b>				
Total sleep time, min	434 (376–475)	376 (321–470)	447 (433–493)	0.09
Sleep efficacy, %	90 (83–95)	83 (77–96)	94 (88–95)	0.38
Sleep onset latency, min	14 (6–26)	35 (7–108)	13 (3–18)	0.22
N1-2 sleep stages, % of TST	59 (53–63)	61 (58–63)	56 (49–60)	0.17
N3 sleep, % of TST	19 (15–23)	20 (16–23)	19 (16–24)	1.00
REM sleep, % of TST	22 (19–24)	19 (17–23)	24 (22–28)	0.09
Arousal index, n/h	8 (6–13)	9 (8–11)	7 (4–9)	0.17
Periodic leg movement index, n/h	0 (0–0)	0 (0–4)	0 (0–2)	0.84
<b>Sleep breathing</b>				
Apnea-hypopnea index, n/h	2 (0–5)	0 (0–2)	2 (0–5)	0.22
Apnea-hypopnea index > 15/h, n(%)	2 (13)	–	–	–
Mean awake SpO <sub>2</sub> (%)	92 (90–94)	92 (91–93)	91 (89–94)	0.51
Mean sleep SpO <sub>2</sub> (%)	91 (90–92)	92 (91–92)	91 (88–91)	0.08
Time SpO <sub>2</sub> < 88 %, min	19 (0–47)	0 (0–0)	33 (9–174)	0.002
Mean awake PtcCO <sub>2</sub> , mmHg	34 (32–36)	34 (30–39)	33 (32–35)	0.90
Mean NREM sleep PtcCO <sub>2</sub> , mmHg	37 (35–39)	39 (36–42)	35 (35–37)	0.12
REM sleep PtcCO <sub>2</sub> , mmHg	38 (37–40)	39 (37–44)	38 (36–40)	0.41

Data presented as median (25–75th percentile) and n (%). The P-values refer to a comparison between patients without and with hypoxemia during sleep. As per definition, in the comparison of patients without and with hypoxemia during sleep, the two patients with sleep apnea were excluded from the analysis.

ESS: Epworth sleepiness score; NREM: non rapid eye movement; PtcCO<sub>2</sub>: transcutaneous CO<sub>2</sub> pressure; sleep efficacy: total sleep time/time in bed; REM: rapid eye movement; SpO<sub>2</sub>: pulsed oxygen saturation; TST: total sleep time.

**Table 3.** Overnight leg and neck circumferences changes divided according to the presence of hypoxemia during sleep.

	All (N = 15)	Without hypoxemia during sleep (N = 5)	With hypoxemia during sleep (N = 8)	P-values
<b>Overnight change in</b>				
Ankle circumference, cm	−0.6 (−0.8 to 0.4)	−0.6 (−0.7 to −0.5)	−0.6 (−0.8 to −0.5)	0.99
Calf circumference, cm	−1.0 (−1.3 to −0.7)	−1.0 (−1.3 to −0.4)	−1.0 (−1.4 to −0.7)	0.59
Thigh circumference, cm	−0.8 (−1.1 to −0.3)	−0.3 (−0.7 to −0.1)	−1.0 (−2.1 to −0.4)	0.04
Neck circumference, cm	0.2 (−0.2 to 1.2)	0.3 (−0.5–1.3)	0.1 (−0.6 to 1.3)	0.86

Notes: Data presented as median (25–75th percentile). The P-values refer to a comparison between patients without and with hypoxemia during sleep. As per definition, in the comparison of patients without and with hypoxemia during sleep, the two patients with sleep apnea were excluded from the analysis.

during sleep (Fig. 2), which was consistent with a higher difference in the overnight change in thigh circumferences (Table 3, second and third column).

Hemodynamic parameters were similar between patients with and without hypoxemia during sleep. Accordingly, there was no significant difference in the time with  $\text{SpO}_2 < 88\%$  during the night when we compared patients with lower mPAP (<median) versus higher mPAP (>median), lower PVR (<median) versus higher PVR (>median) and higher RAP (<median) versus higher RAP (>median) (see supplemental material and Figure S2).

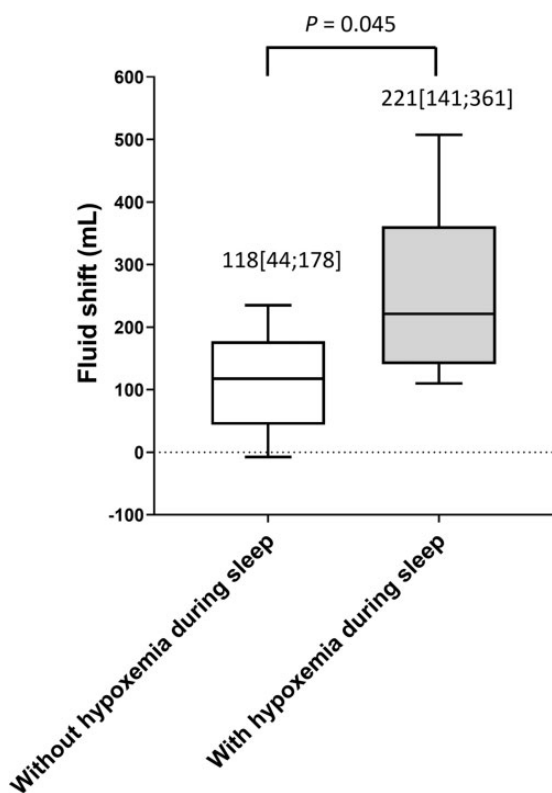
## Discussion

This pilot study confirms the results of the literature indicating that sleep-related breathing disorders are common in PAH, including mainly a high prevalence of hypoxemia during sleep, and demonstrates that patients with PAH and hypoxemia during sleep have an increased overnight rostral fluid shift.

To the best of our knowledge, this is the first study to suggest an association of hypoxemia during sleep with overnight rostral fluid shift in patients with PAH. Hypoxemia during sleep has been previously shown to be frequent in PAH, independently of sleep apnea, but the underlying mechanism remains unclear. The main suspected process

is ventilation–perfusion mismatch, probably secondary to the obliteration of small pulmonary arterioles (<500  $\mu\text{m}$ ) and to narrowed distal airways, which in turn increase pulmonary physiologic dead space.<sup>25–27</sup> Indeed, Jilwan et al. reported that, among 46 clinically stable patients with idiopathic PAH ( $N=29$ ) or chronic thromboembolic pulmonary hypertension ( $N=17$ ), the major mechanism of nocturnal hypoxemia is a ventilation/perfusion mismatch, alone or associated with obstructive apneas.<sup>7</sup> The ventilation/perfusion mismatch was defined by sustained hypoxemia periods without any concomitant increase in  $\text{PtcCO}_2$  and without apneas or hypopneas, as observed in our patients with hypoxemia during sleep. In most cases, this ventilation–perfusion mismatch is not associated with hypoxemia during wakefulness at rest in PAH, as in our study, but differently from veno-occlusive diseases, characterized by a more severe hypoxemia.<sup>28</sup> During sleep, the respiratory system undergoes major physiological changes (including a decline of functional residual capacity and in minute ventilation, and of the responsiveness to hypoxemia/hypercapnia, as well as an increase in upper airway resistance), which are well tolerated in healthy individuals, but might induce hypoxemia during sleep in patients with PAH. Sleep-related alveolar hypoventilation has also been previously reported as one of the causes of hypoxemia during sleep in PAH,<sup>29</sup> but this is not observed in our patients, who instead had hyperventilation. The present study suggests for the first time that overnight rostral fluid shift into the upper part of the body is feasibly a contributor of hypoxemia during sleep. This pathogenetic link may be explained by fluid accumulation in the distal airways wall and their subsequent narrowing, which determines reduced ventilation and ventilation-perfusion abnormalities.<sup>17,18</sup> Moreover, although this finding did not meet statistical significance, our patients with hypoxemia during sleep had a lower  $\text{PaO}_2$  at rest which could facilitate hypoxemia during sleep, as they were found to be closer to the steep part of the oxyhemoglobin dissociation curve.

Unlike other studies,<sup>3,6,9</sup> we observed a low prevalence of sleep apnea. This virtual absence of obstructive sleep apnea is consistent with the lack of significant overnight increase in neck circumference in our study, going against a significant distribution of fluid displaced from the legs into the neck. This may be partly due to the predominance of female gender in our population. Indeed, it has been shown that for a similar amount of fluid moving out of the legs, women accumulate more fluid in their abdomen than in their neck and have a smaller increase in neck circumference compared to men.<sup>30</sup> The low prevalence of central sleep apnea in our study may be due to less severe PAH. Our patients indeed have lower hemodynamic and functional alteration (more often I–II than III–IV NYHA class) than those in previous studies showing high prevalence of central sleep apnea.<sup>3,5</sup> The relatively young age of our population may also be a factor explicating such a low prevalence of both obstructive



**Fig. 2.** Overnight rostral fluid shift according to the presence of hypoxemia during sleep (without hypoxemia ( $N=5$ ) versus with hypoxemia during sleep ( $N=8$ )) in patients with PAH.

sleep apnea and central sleep apnea compared to other studies. In accordance, recent findings by Carvalho et al. revealed that 50% of PH patients have mild-to-moderate sleep apnea, but with a higher prevalence of men, elderly subjects and with more severe hemodynamic alterations, as well as greater fluid shift, in comparison with the patients in our study (220 versus 168 mL).<sup>19</sup> However, the authors evaluated a different population from ours, since besides patients with idiopathic PAH (31%), they also included subjects with connective tissue disease (31%), congenital heart disease (7%), portal hypertension (7%), pulmonary veno-occlusive disease (7%), and chronic thromboembolic pulmonary hypertension (17%).<sup>19</sup>

Currently, overnight polysomnography or oximetry are recommended in patients with PAH when sleep-related breathing disorders are clinically suspected.<sup>1</sup> Nevertheless, except for higher sleepiness levels, we did not find an elevated prevalence of the usual clinical signs of sleep-related breathing disorders, as previously shown in PAH.<sup>5,7,31</sup> For this reason, some authors indicate that sleep study should be systematic in PAH,<sup>32</sup> using nocturnal oximetry as a screening tool only when there is no sign of sleep apnea and in non-severe patients (NYHA functional class I or II patients whose hemodynamics do not show decreased cardiac output).<sup>33</sup> The identification of risk factors for sleep-related breathing disorders, such as overnight rostral fluid shift, may represent a helpful decision-making tool to submit patients with PAH to a sleep study. However, bioelectrical impedance measurement is difficult to perform routinely, so new and easier approaches to detect fluid shift are needed.<sup>34</sup>

The effect of hypoxemia during sleep on hemodynamic and on the outcome of patients with PAH is still poorly understood. In a retrospective study on 151 patients with PAH, Nagaoka et al report that 31 (21%) had hypoxemia during sleep, with an increased mortality rate.<sup>10</sup> Hypoxemia during sleep in PAH may promote hypoxic pulmonary vasoconstriction, enhance PVR and pulmonary vascular remodeling, as observed in pulmonary hypertension due to hypoxia (group 3).<sup>35</sup> Moreover, hypoxemia might trigger inflammation-driven vascular remodeling, with elevated circulating tumor necrosis factor- $\alpha$  levels, as observed in chronic thromboembolic pulmonary hypertension.<sup>36</sup> Nocturnal oxygen therapy may reverse hypoxemia, reduce PVR, and be beneficial for pulmonary vascular remodeling, but the currently available data are controversial. In a randomized study on 23 adult patients with PAH linked to congenital heart defect and Eisenmenger syndrome, nocturnal oxygen did not modify the natural history of the disease.<sup>37</sup> On the contrary, Ulrich et al. showed an improvement in 6MWD and in right ventricular ultrasound evaluation after one week of nocturnal oxygen therapy in a randomized, placebo-controlled, double-blind study in 23 patients with pulmonary hypertension, 13 of them with PAH.<sup>38</sup> However, to date, there is no randomized study

showing the positive effects of long-term oxygen therapy in PAH, whether in case of daytime or nighttime hypoxemia. The current guidelines recommend to prescribe oxygen therapy when diurnal PaO<sub>2</sub> is <60 mmHg (8 kPa) and to ensure that oxygen therapy covers the sleep periods with an adequate flow,<sup>1</sup> but there is no specific indication on nocturnal oxygen therapy in PAH.

This study has some limitations. First, because of the explorative nature of this pilot study, only a limited sample of patients was included and therefore we cannot rule out the contribution of some confounding factors in hypoxemia during sleep, like PaO<sub>2</sub> at rest or hemodynamic parameters. Second, the population was maybe not representative of all the patients with PAH, as few patients accepted to participate in the study in relation with the necessity to move to another hospital to undergo the polysomnography. Third, we could highlight an association, but the study design prevents us from drawing any firm conclusion on a possible causal link between overnight rostral fluid shift and hypoxemia during sleep. And finally, we demonstrated a fluid shift from the legs to the upper part of the body, but we could not assess precisely the amount of fluid distributed respectively in the abdomen, lungs, and neck, and we did not quantify urine volume during the night as well.

In conclusion, this pilot study provides for the first time some evidence for a novel mechanism that may contribute to the pathogenesis of hypoxemia during sleep in PAH: overnight fluid displacement from the legs to the upper part of the body. Our data might pave the way for the identification of overnight rostral fluid shift as a new potentially modifiable risk factor for hypoxemia during sleep in PAH. Further studies are needed to confirm this association, to identify new tools to easily detect overnight fluid shift and to assess the clinical benefits of correcting hypoxemia during sleep in PAH, either with nocturnal oxygen therapy or by targeting overnight rostral fluid shift.

## Conflict of interest

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### Ethical approval

The institutional review board for human studies approved the study (Comité de Protection des Personnes Ile de France VI, reference number 2015-A01947-42).

### Guarantor

Etienne-Marie Jutant is the guarantor of the content of the manuscript.

### Contributorship

E.M.J., D.M., C.S., S.G., O.S., G.G., I.A., M.H, T.S., and S.R. designed the initial concept. E.M.J., C.S., S.G., and S.R. made the inclusion of patients. E.M.J. made the measurement of overnight rostral fluid shift by impedancemetry. S.R. made the analysis of sleep exams. E.M.J., D.M., and S.R. performed the statistical analysis. E.M.J and S.R. wrote the manuscript. All the authors reviewed the manuscript.

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### ORCID iDs

Etienne-Marie Jutant  <https://orcid.org/0000-0002-1374-1890>  
David Montani  <https://orcid.org/0000-0002-9358-6922>

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### Supplemental Material

Supplemental material for this article is available online.

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