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**HYPOXEMIC SLEEP RESPIRATORY DISORDERS IN
PRECAPILLARY PULMONARY HYPERTENSION: PREVALENCE
AND MECHANISMS**

Journal:	CHEST
Manuscript ID:	CHEST-11-3124
Manuscript Type:	Original Research
Date Submitted by the Author:	20-Dec-2011
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Keywords:	PULMONARY HYPERTENSION, SLEEP-DISORDERED BREATHING, HYPOXEMIA

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ABBREVIATIONS LIST

AHI: Apnea-hypopnea index

BMI: Body mass index

BNP: Brain natriuretic peptide

CI: cardiac index

CSA: Central sleep apnea

CSR: Cheyne Stokes respiration

CTEPH: Chronic thrombo-embolic pulmonary hypertension

DLco: Diffusion lung capacity for carbon monoxide

D90%: Duration of sleep time spent with SpO₂ < 90%

ESS: Epworth sleep scale

FEV_{25/75}: Forced expired volume between 25 and 75% of forced vital capacity

FEV₁: Forced expired volume in 1 second

FRC: Functional residual capacity

Ht: Hematocrit

IPAH: Idiopathic pulmonary arterial hypertension

mPAP: Mean pulmonary arterial pressure

mPWP: Mean pulmonary wedge pressure

NYHA: New York Heart Association

NH: Nocturnal hypoxemia

OSA: Obstructive sleep apnea

ODI: Oxygen desaturation index

PaO₂: Arterial pressure of oxygen

PH: Precapillary pulmonary hypertension

PVR: pulmonary vascular resistance

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5 SpO₂: Pulse oxygen saturation

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7 6MWT: Six minute walking test

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13 TcPCO₂: Transcutaneous pressure for carbon dioxide

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15 VA/Q: Ventilation/perfusion
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Word count

Abstract: 241

Body of paper: 2427

3 HYPOXEMIC SLEEP RESPIRATORY DISORDERS IN PRECAPILLARY PULMONARY

4 HYPERTENSION: PREVALENCE AND MECHANISMS

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 7 *Xavier Jaïs^{1,3,4}, MD; Marc Humbert^{1,3,4}, MD, PhD; Gabriel Roisman^{1,2}, MD, PhD*

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34 Running head: *pulmonary hypertension and sleep hypoxemia*

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36 Authors declare not to have any actual or potential conflict of interest

37
38 **ABSTRACT**

39 Background

40 The prevalence and mechanisms of nocturnal hypoxemia (NH) in precapillary pulmonary
41 hypertension (PH) are not clearly defined.

42 Methods:

43 In an observational prospective and transversal design, we studied 46 clinically stable PH
44 patients with BMI < 35 kg/m², FEV₁ > 60% of predicted and diagnosis of idiopathic
45 pulmonary arterial hypertension (IPAH, n=29) or chronic thrombo-embolic PH (CTEPH,
46 n=17). They underwent nocturnal polysomnography with transcutaneous capnography.

47 Results:

48 Most patients were in NYHA functional class II (69.6%). Mean pulmonary arterial pressure
49 was 44 ± 13 mmHg and cardiac index 3.2 ± 0.6 L/min/m². The time spent below a saturation
50 of 90% (D90%) was 48.9 ± 35.9% of sleep time and 38 out of 46 (82.6%) patients had NH.
51 Mean apnea hypopnea index (AHI) was 24.9 ± 22.1/ hour and 41 patients (89%) had sleep
52 apnea. The major mechanism of NH was ventilation/perfusion mismatch alone or associated
53 with obstructive apneic events. D90% was correlated with diurnal PaO₂ ($\rho = 0.60$, $P <$
54 0.05), alveolo-arterial gradient ($\rho = 0.49$, $P < 0.05$), and with FEV_{25/75} ($\rho = 0.53$, $P <$
55 0.05). AHI was also correlated with diurnal PaO₂ ($\rho = 0.36$, $P = 0.02$) and alveolo-arterial
56 gradient ($\rho = 0.40$, $P < 0.05$). Clinical symptoms or hemodynamics were not predictive of
57 NH.

58 Conclusions:

59 The prevalence of NH is high in PH and should be systematically screened for. Further
60 studies are needed to determine the impact of NH on the outcome of patients with PH.

ClinicalTrials.gov Identifier:	NCT01371669
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- 61 Key-words: pulmonary hypertension, sleep apnea, nocturnal hypoxemia, ventilation/perfusion
- 62 mismatch.

Privileged Communication

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6364 **ABBREVIATIONS LIST**

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66 BMI: Body mass index

67 BNP: Brain natriuretic peptide

68 CI: cardiac index

69 CSA: Central sleep apnea

70 CSR: Cheyne Stokes respiration

71 CTEPH: Chronic thrombo-embolic pulmonary hypertension

72 DLco: Diffusion lung capacity for carbon monoxide

73 D90%: Duration of sleep time spent with SpO₂ < 90%

74 ESS: Epworth sleep scale

75 FEV_{25/75}: Forced expired volume between 25 and 75% of forced vital capacity76 FEV₁: Forced expired volume in 1 second

77 FRC: Functional residual capacity

78 Ht: Hematocrit

79 IPAH: Idiopathic pulmonary arterial hypertension

80 mPAP: Mean pulmonary arterial pressure

81 mPWP: Mean pulmonary wedge pressure

82 NYHA: New York Heart Association

83 NH: Nocturnal hypoxemia

84 OSA: Obstructive sleep apnea

85 ODI: Oxygen desaturation index

86 PaO₂: Arterial pressure of oxygen

87 PH: Precapillary pulmonary hypertension

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97 **INTRODUCTION:**

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99 Idiopathic pulmonary arterial hypertension (IPAH) is associated with remodelling and
100 obliteration of small pulmonary arterioles, while chronic thrombo-embolic pulmonary
101 hypertension (CTEPH) is the consequence of persistent pulmonary artery obstruction due to
102 chronic thrombo-embolic disease ^{1,2}. Most patients with precapillary pulmonary
103 hypertension (PH) are not hypoxemic during daytime, but some studies on small cohorts
104 found an increase in sleep-related hypoxemia prevalence in PH, accounting for up to 77% of
105 cases ³. Although hypoxemia was not related to respiratory events like hypopnea or apnea in
106 one study ⁴, other studies mentioned Cheyne Stokes respiration (CSR) which is usually
107 observed in severe heart failure ^{5,6} and recently, Prisco et al reported an increased prevalence
108 of obstructive sleep apnea-hypopnea (OSA) accounting for 50% of PH patients ³.
109 Thus, all these studies revealed an increased frequency of nocturnal hypoxemia (NH) in PH,
110 but failed to agree on its mechanisms. Since chronic hypoxemia may promote pulmonary
111 artery vasoconstriction and remodelling ⁷⁻⁹, it may contribute to the pathogenesis of
112 pulmonary vascular remodelling in PH. The purpose of our study was therefore to evaluate
113 the prevalence and the mechanisms of hypoxemic respiratory sleep disturbances in patients
114 with IPAH or CTEPH.

115

116 **MATERIAL AND METHODS**

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118 This is an observational, prospective and transversal study, proposed to patients with already
119 diagnosed and treated IPAH or CTEPH, hospitalized for follow up in the pulmonary

120 department of Antoine Bécclère Hospital, which is the national referral center for PH in
121 France.

122 PH was defined by right heart catheterization with a mPAP >25 mmHg and a mean
123 pulmonary wedge pressure (mPWP) \leq 15mmHg¹. In IPAH, there was no identified cause
124 for the disease, but in CTEPH, contrast-enhanced spiral computed tomography of the chest
125 and pulmonary angiography confirmed chronic thrombo-embolic disease. Other types of PH
126 were not included in the study.

127 Patients were hospitalized in the pulmonary department for a standard follow-up. PH had
128 already been diagnosed in all patients on cardiac catheterization and treated to achieve the
129 best functional New York Heart Association (NYHA) class and hemodynamics parameters.
130 To participate in the study, patients had to be also in a stable clinical condition for at least
131 the three preceding months, as defined by NYHA functional class and a walking distance
132 difference within 10% of the previous three months measurement at the 6-minute walking
133 test (6MWT). Moreover, no change in medical therapy could have occurred during this
134 period. Other exclusion criteria were age > 75 years, moderately severe and severe
135 restrictive or obstructive pulmonary diseases with a TLC and a FEV₁ < 60% of the predicted
136 value, severe obesity defined by a BMI \geq 35 kg/m² or previously diagnosed sleep breathing
137 disorder.

138 All recruited patients provided written informed consent for the study approved by the
139 Comité de Protection des Personnes Ile de France VII (N: 10-008). They had a physical
140 examination evaluating NYHA functional class and clinical symptoms of PH. They also
141 completed a specialized auto-questionnaire for sleep symptoms including an Epworth
142 Sleepiness Scale (ESS) ranging from 0 to 24 points, with values >10 considered as reflecting
143 excessive daytime sleepiness¹⁰. Patients were selected regardless of their answers to the
144 sleep questionnaire.

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3 145 Other tests done for routine follow-up included a right heart catheterization, a 6MWT, lung
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5 146 function tests, arterial blood gas analysis, brain natriuretic peptide (BNP) and hematocrit
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7 147 (Ht). A one-night polysomnography (CIDELEC, France) was also performed during the
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9 148 patient's hospital stay. It recorded three electroencephalogram channels, two
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11 149 electrooculogram channels, submental and pretibial electromyograms, airflow with a nasal
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13 150 canula, thoracic and abdominal inductance belts, tracheal sounds, sleeping position, pulse
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15 151 oximetry and transcutaneous capnography (TOSCA 500, Radiometer, Denmark). Scoring
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17 152 was done visually by a sleep specialist in accordance with the French Clinical Practice
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19 153 guidelines¹¹. For definitions of sleep breathing abnormalities see the Online Supplement (e-
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21 154 Appendix and e-Figures 1, 2 and 3).

22 155 The duration of total sleep time (TST) spent at a SpO₂ < 90% (D90%) was derived from a
23
24 156 cumulative frequency curve of pulse oximetry. Desaturation was considered significant if
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26 157 D90% was ≥ 60 min or oxygen desaturation index (ODI) was ≥ 20/h.

27 158 Comparisons between groups, (IPAH and CTEPH, nocturnal desaturator and non-desaturator
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29 159 patients) were made using unpaired Student's *t* test. Nonparametric Mann-Whitney U test
30
31 160 was used for variables as appropriate. Comparisons of proportions were made using the Fisher
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33 161 exact test. Nonparametric correlations between data were made using Spearman's rank
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35 162 analysis. *P* values were based on two-side tests, and a *P* value ≤ 0.05 was considered
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37 163 significant. Results were expressed as mean ± SD.

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39 165 **RESULTS:**

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41 167 The charts of 218 patients admitted to the Antoine Bécclère referral center for PH between
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43 168 June 2010 and July 2011 were examined. The study was proposed to 81 patients fulfilling the
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45 169 inclusion criteria. Final analyses were done on 46 out of 50 eligible patients (Fig.1).

170 Baseline characteristics of the studied population are detailed in Table 1. Right-heart
171 catheterization confirmed PH with mPAP of 44 ± 13 mmHg and cardiac index (CI) of $3.2 \pm$
172 0.6 L/min/m². The group included 29 patients with IPAH and 17 with CTEPH. Five out of the
173 17 CTEPH patients had already underwent a thrombo-endarterectomy in the past but had
174 persistent PH related to surgically inaccessible endovascular lesions. The remainder of the
175 CTEPH patients were inoperable and were treated medically. Parameters reported in Table 1
176 (6 minutes walking distance, BNP levels, NYHA functional class, and hemodynamics with CI
177 within normal range) allowed highlighting the characteristics of a stable PH population. All
178 patients were on optimal medical treatment for PH, the majority being on a combination of
179 drugs (Table 1).

180 NH was observed in 82.6% of the whole population (38 out of 46 patients). Characteristics of
181 patients with desaturation (desaturators) and patients with normal nocturnal saturation (non-
182 desaturators) are presented in Table 2. The two groups differed by diurnal PaO₂, alveolo-
183 arterial gradient, SpO₂ prior to the 6MWT (resting SpO₂) and FEV_{25/75}: desaturators were
184 more hypoxemic than non-desaturators at daytime and they had significant distal narrowing of
185 small airways. When excluding smoking as a confounding factor for distal airways
186 obstruction (13 patients), the difference in mean FEV_{25/75} between the two groups remains
187 statically significant as shown in Table 2 ($P = 0.038$).

188 Other variables such as pulmonary hemodynamics, BNP or Ht did not show any significant
189 differences between the two groups.

190 The major mechanism identified for NH was ventilation/ perfusion (VA/Q) mismatch of 76%
191 (29 out of 38 patients, Fig. 2a). Sleep apneas were also common (89% of patients), with a
192 severe AHI (AHI ≥ 30 /h) in 28 % of cases, moderate ($15 \leq$ AHI < 30 /h) in 39% of cases, and
193 mild in the remaining 22% (Fig. 2b). Their mechanism was obstructive in the majority of

194 cases as > 50% of the respiratory events were obstructive. It was the only mechanism of NH
195 in 21% of cases, and was associated with VA/Q mismatch in the others (45%).

196 A single case of alveolar hypoventilation associated with a moderate OSA was identified:
197 TcPCO₂ increased by more than 30 mmHg during sleep with a marked decrease in SpO₂. The
198 cause of the alveolar hypoventilation observed in this patient is not clear, although it seemed
199 not to be associated to the apneic events. His AHI was 22/h, which is not usually sufficient to
200 induce alveolar hypoventilation in patients with normal respiratory drive. Although the
201 ventilatory response to hypercapnia was not measured, this patient had periods of clear
202 alveolar hypoventilation in the absence of apneic events (e-Figure 3).

203 Central respiratory events were rare, always associated with VA/Q mismatch periods (e-
204 Figure 2a). CSR was found in 3 out of the 4 patients with central sleep apnea (CSA). These
205 patients were in NYHA class III and had a mean CI of 2.7 ± 0.8 L/min/m².

206 D90% was correlated with diurnal PaO₂ ($\rho = 0.60$, $P < 0.05$, Fig. 3a), alveolo-arterial
207 gradient ($\rho = 0.49$, $P < 0.05$), resting SpO₂ ($\rho = 0.44$, $P < 0.05$), walking SpO₂ ($\rho =$
208 0.32 , $P = 0.03$) and with FEV_{25/75} ($\rho = 0.53$, $P < 0.05$, Fig. 3b, correlation done on non-
209 smoker patients).

210 AHI was also correlated with diurnal PaO₂ ($\rho=0.36$, $P = 0.02$) and alveolo-arterial gradient
211 ($\rho= 0.40$, $P < 0.05$). All other clinical, functional and hemodynamic variables did not show
212 significant correlations with sleep hypoxemia parameters (AHI, D90% and ODI). The two
213 most relevant correlations are presented in Fig. 3.

214 Comparisons between non-desaturator and desaturator patients were performed irrespective of
215 the type of PH. In fact, the distribution of non-desaturators and desaturators was similar
216 among both IPAH and CTEPH even if there were some differences in terms of age and
217 6MWT, CTEPH patients being older and having a more limited exercise performance (Table
218 3). Hemodynamic measurements showed identical pulmonary vascular resistances (PVR)

219 between the 2 groups with a greater mPAP in IPAH patients associated with a higher CI as
220 compared to CTEPH.

221

222 **DISCUSSION:**

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224 The relevant findings of this study are: 1) NH is common in stable IPAH and CTEPH
225 patients, being observed in more than 80% of cases, 2) the most frequent mechanisms
226 responsible for this hypoxemia were VA/Q mismatch alone or associated with apneic events,
227 present in 76% of desaturator patients.

228 We studied a well-defined population with two major causes of PH, namely IPAH and
229 CTEPH, at a steady state for at least three months without any confounding factors inducing
230 hypoxemia such as severe obesity or other respiratory diseases, which was not the case in
231 previous studies^{3,4,6,12,13}.

232 Our results extend data from the literature regarding the high prevalence of NH in PH.
233 Rafanan et al mentioned a prevalence of NH of 77%, recorded on 13 patients with IPAH, and
234 Minai et al observed a prevalence of 69.7% on 43 patients with IPAH and PH associated with
235 connective tissue diseases^{4,13}.

236 Sleep apneas were frequent in our study, being present in 89% of cases and considerably more
237 prevalent than in the general population for the 30–60-year age range (reported in around
238 24% of males and 9% of females¹⁴). Our results are in line with the findings of Prisco et al
239 who observed an increased prevalence of OSA and the absence of central events in patients
240 with PH, but the prevalence of OSA in our patients was higher (89% vs 50%) while the
241 severity of PH was similar (mPAP 44 ± 13 vs 40.9 ± 15.8 mmHg, respectively)³.

242 Schulz et al and Ulrich et al found 30% and 45% of periodic breathing (CSR) in respectively
243 20 and 38 patients with PH, studied by polysomnography^{5,6}. Periodic breathing is usually

244 observed in the setting of severe congestive heart failure¹⁵⁻¹⁸. Indeed, Schulz and Ulrich
245 reported patients manifestly more severe than ours, in NYHA functional class III-IV and
246 above all, with clinical stability defined over a shorter period of only 4 weeks. The mean CI
247 of their patients was respectively 2.4 L/min/m²⁶ and 1.96 L/min/m²⁵, whereas in our stable
248 patients mean CI was normal at rest (3.2 ± 0.6 L/min/m²) and similar to mean CI (2.9 ± 0.8
249 L/min/m²) observed by Prisco et al. Therefore, the higher prevalence of CSR observed by
250 these authors is most probably the result of heart failure rather than the consequence of PH by
251 itself.

252 Changes in ventilation during sleep such as mild hypoventilation^{19,20}, decreased FRC²¹,
253 blunted responses to hypoxemia and hypercapnia²² and increased airway resistance are well
254 established²³. Such ventilatory perturbations are mild and well-tolerated in normal
255 individuals but may exhibit more profound gas exchange abnormalities in patients with PH,
256 given the already elevated alveolo-arterial gradient present in wakefulness and at exercise, in
257 particular in CTEPH²⁴.

258 Sleep-related alveolar hypoventilation due to a possible reduction of FRC in the supine
259 position and to predisposing respiratory muscle weakness as previously described in patients
260 with PH was not evident in our population²⁵⁻²⁷. In fact, TcPCO₂ recorded overnight did not
261 show any significant increase (≥ 10 mmHg), except in one patient with normal BMI and
262 moderate OSA (AHI of 22/h). Moreover, this patient did not have any daytime
263 hypoventilation at rest or at exercise and was successfully treated with oxygen
264 supplementation which corrected NH and hypercapnia.

265 Another possible explanation for long desaturation periods recorded during sleep was
266 perturbation in VA/Q ratio. This abnormality may be secondary to the obliteration of small
267 pulmonary arterioles which increases pulmonary physiological dead space, but also to
268 narrowed distal airways as already described in patients with PH²⁸⁻³⁰. The relationship

269 between FEV_{25/75} and D90% found in our study suggests that small airway obstruction may
270 contribute to VA/Q mismatch by increasing the shunt effect.

271 No predicting factor of NH was found in our study. A relationship was observed between NH
272 and diurnal PaO₂ but it is somewhat expectable that patients with lower diurnal PaO₂ could be
273 more prone to desaturation at night. Although small airways obstruction was more frequent in
274 desaturator patients, it was not a discriminating factor for NH.

275 Clinical symptoms were also not reliable in the evaluation of sleep related breathing disorders
276 in our population. Sleep apnea was not clinically suspected as patients did not complain of
277 typical symptoms such as excessive daytime sleepiness whereas snoring was reported in 59%
278 of cases, as in the normal population of the same age range. This lack of clinical symptoms of
279 sleep apnea was outlined in previous studies^{3,6}.

280 Our study had some limitations. Our sample was restricted to 46 patients which is small for a
281 prevalence study. However, to our knowledge this is to date the largest and the most
282 homogeneous population of patients with stable PH studied for sleep-related disorders. We
283 cannot exclude an underestimation of central events due to the absence of the gold standard
284 which is the esophageal pressure measurements, but our choice was not to use this invasive
285 technique because of sleep disturbance and the potential risk in anticoagulated patients³¹. Our
286 evaluation of VA/Q mismatch was based upon the occurrence of long desaturation periods
287 without concomitant increase in TcPCO₂. The validity of such measurements using these
288 kinds of devices was questioned in the past³². But the TOSCA device that we use has shown
289 good accuracy in adult patients compared to blood gas analysis³³⁻³⁵.

290

291 In conclusion, sleep-related hypoxemia is frequent in IPAH and CTEPH. It is likely due to
292 major VA/Q mismatch but also to OSA. As there is no clear predicting factor for sleep-related
293 hypoxemia in PH, it is reasonable to screen all patients to diagnose and treat any other

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3 294 additional possible factor compromising pulmonary hemodynamics. The guidelines
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5 295 recommending polysomnography only in PH patients with clinical suspicion of sleep apnea
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7 296 certainly need to be reconsidered. Further studies are needed to evaluate whether management
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9 297 of hypoxemic sleep respiratory disorders may improve outcome in PH patients.
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5 299 **ACKNOWLEDGMENTS:**

6
7 300 *The sponsor was Assistance Publique – Hôpitaux de Paris (Département de la Recherche*

8
9 301 *Clinique et du Développement.*

10
11 302 *The authors thank the patients who participated to this study and Kaixian Zhu, MSc, Gérald*

12
13 303 *Simonneau, MD, Olivier Sitbon, MD, PhD, Florence Parent, MD, David Montani, MD, PhD,*

14
15 304 *and Laurent Savale, MD, PhD for their contribution.*

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28 309 Xavier Jaïs, MD: assistant writer.

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30 310 Marc Humbert, MD, PhD: assistant writer.

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32 311 Gabriel Roisman, MD, PhD: senior co-investigator, writer and guarantor of the entire

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34 312 manuscript.

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6 394 **FIGURE LEGENDS**

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8 **Fig. 1: Patients Flow Chart:** The charts of 218 patients were examined Twenty-seven patients
9 refused to participate and 4 could not undergo the polysomnography for logistic reasons due
10 to a short hospital stay. Fifty eligible patients were enrolled in the study and underwent a one-
11 night polysomnography. Four out of the 50 polysomnographies were not conclusive for
12 technical reasons. Analyses were done on the remaining 46 patients. IPAH: idiopathic
13 pulmonary arterial hypertension. CTEPH: chronic thrombo-embolic pulmonary hypertension.
14 PSG:
15 polysomnography.
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4 404 **Fig. 2a:** Identified nocturnal hypoxemia mechanisms (n=38). VA/Q mismatch was a prevalent
5 405 nocturnal abnormality, frequently associated with sleep apnea. VA/Q: ventilation-perfusion.
6 406 OSA: obstructive sleep apnea. CSA: central sleep apnea.
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8 408 **Fig. 2b:** AHI (apnea-hypopnea index) severity and prevalence in PH (n=46). Moderate and
9 409 severe AHI represent 67% of PH patients, with a predominance of obstructive forms. SAS:
10 410 sleep apnea.
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412 **Fig. 3a:** Correlation between D90% (sleeping period in minutes spent with a SpO₂ < 90%)
413 and diurnal PaO₂ (mmHg) obtained on arterial blood gas analysis in PH patients (N=46). *rho*
414 =0.60, *P* < 0.05. D90% ≥ 60 min was considered as a significant nocturnal hypoxemia
415 (dashed line).

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417 **Fig.3b:** Correlation between D90% and FEV_{25/75} (% of predicted) in non-smokers PH patients
418 (N=35). *rho* = 0.53, *P* < 0.05

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TABLES

	PH	
	N (%)	mean \pm SD
Age (yrs)	46	53 \pm 13.6
BMI (kg/m²)	46	24.6 \pm 4.2
Gender		
F	25 (54.4)	
M	21 (45.6)	
Race		
Caucasian	39 (84.8)	
Black	7 (15.2)	
IPAH	29 (63)	
CTEP	17 (37)	
Dyspnea (NYHA)		
I	3 (6.5)	
II	32 (69.6)	
III	11 (23.9)	
Snorers	27 (58.7)	
Epworth Sleepiness Scale (/24)	39	6.1 \pm 4.7
PH treatment		
Prostacyclin analogues	12 (26)	
Endothelin receptor antagonists	30 (65.2)	
5-Phosphodiesterase inhibitors	26 (56.5)	
Calcium channel blockers	11 (24)	
anticoagulation	42 (91.3)	
Combined therapy (2 or 3)	27 (58.7)	
Pulmonary function (% predicted)		
FEV ₁	44*	88.8 \pm 16
FVC	44*	93.4 \pm 17.1
Dlco	38*	69.1 \pm 18
TLC	44*	95.3 \pm 14.2
FEV _{25/75}	44*	73.2 \pm 24
Arterial blood gas		
PaO ₂ (mmHg)	43*	73.7 \pm 11.1
PaCO ₂ (mmHg)	43*	32.6 \pm 4.0
Alveolo-arterial gradient	43*	34.6 \pm 13.5
6MWT		
Walking distance (m)	46	496.3 \pm 92.7
Resting SpO ₂ (%)	46	94.6 \pm 2.7
Walking SpO ₂ (%)	46	87.9 \pm 6
BNP(ng/L)	46	95.5 \pm 144.6
Right heart catheterization		
RAP (mmHg)	46	5.1 \pm 3.7
mPAP (mmHg)	46	44 \pm 13.0
CI (L/min/m ²)	46	3.2 \pm 0.6
PVR (Woods U)	44*	6.5 \pm 2.4
mPWP	44*	8.1 \pm 2.8

Polysomnography		
TST (min)	46	354.8 ± 73.3
Sleep Efficiency (%)	46	80.6 ± 12.9
Arousals index (events/h)	46	21.7 ± 14
N3 stage (min)	46	75.6 ± 39.7
REM stage (% of TST)	46	20.2 ± 7.0
D90% (min)	46	176.2 ± 136.5
D90% (% of TST)	46	48.9 ± 35.9
AHI (events/h)	46	24.9 ± 22.1
ODI (events/h)	46	24.6 ± 24.1

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Table 1. Baseline characteristics of the population. *: Not all patients could execute correctly spirometry manoeuvres, especially DLco which requires holding breath for at least 10 sec. Some patients refused blood gas analysis, considering it very painful. In 2 patients, mPWP could not be technically measured (and so resulting PVR could not be calculated). RAP: right atrial pressure. PVR: Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency: ratio of total sleep time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement AHI: apnea-hypopnea index. ODI: oxygen desaturation index (other abbreviations in the text).

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	Non Desaturators		Desaturators		P
	N (%)	mean ± SD	N (%)	mean ± SD	
Age (yrs)	8	43.9 ± 21.4	38	54.9 ± 11.0	0.213†
BMI (kg/m ²)	8	22.2 ± 3.2	38	25.2 ± 4.1	0.058
Dyspnea NYHA I	1 (12.5)		2 (5.3)		
II	7 (87.5)		25 (65.8)		
III	0		11 (28.9)		
Snorers	5(62.5)		22(57.9)		
Epworth Sleepiness Scale (/24)	7	7.6 ± 3.7	29	5.6 ± 5	0.340
Pulmonary function (% predicted)					
TLC	8	90.7 ± 13.6	36	96.3 ± 14.3	0.322
FEV ₁	8	90.9 ± 16.1	36	88.4 ± 16.1	0.695
FVC	8	89.5 ± 15.3	36	94.3 ± 17.6	0.530
Dlco	8	68.1 ± 20.1	30	69.4 ± 17.7	0.858
FEV _{25/75}	8	95.2 ± 23.6	36	68.3 ± 21.5	0.003*
FEV _{25/75} (non smokers)	7	93 ± 24.5	25	77.5 ± 22.8	0.038*
Arterial blood gas					
PaO ₂ (mmHg)	8	83.2 ± 6.7	35	71.6 ± 10.8	0.006*
PaCO ₂ (mmHg)	8	32.9 ± 4.9	35	32.8 ± 3.9	0.812
Alveolo-arterial gradient	8	25.8 ± 14.2	35	36.6 ± 12.7	0.039*
6MWT					
Walking distance (m)	8	522.4 ± 21.3	38	490.8 ± 86.5	0.387
Resting SpO ₂ (%)	8	96.5 ± 1.1	38	94.3 ± 2.8	0.019*†
Walking SpO ₂ (%)	8	91.5 ± 4.2	38	87.2 ± 6.1	0.067
Biological analysis					
Hemoglobin (g/dl)	8	15.0 ± 0.9	35	15.0 ± 1.6	0.942
Ht (%)	8	45.0 ± 2.6	35	45.0 ± 4.8	0.989
BNP (ng/L)	7	42.1 ± 58.2	36	95.6 ± 143.7	0.342
Right heart catheterization					
RAP (mmHg)	8	4.1 ± 2.2	38	5.3 ± 4	0.418
mPAP (mmHg)	8	38.0 ± 15.6	38	45.2 ± 12.3	0.156
CI (L/min/m ²)	8	3.2 ± 0.7	38	3.2 ± 0.6	0.922
PVR (Woods U)	8	5.7 ± 2.0	36	6.7 ± 2.4	0.332
Polysomnography					
TST (min)	8	324.3 ± 75.9	38	361.2 ± 72.1	0.200
Sleep efficiency (%)	8	77.0 ± 17.5	38	81.3 ± 11.9	0.393
Arousals index (events/h)	8	18.1 ± 11.4	38	22.4 ± 14.5	0.440
N 3 stage (min)	8	85.4 ± 21.2	38	73.5 ± 42.5	0.445
REM stage (% of TST)	8	19.1 ± 9.6	38	20.4 ± 6.5	0.654
D90% (min)	8	13.2 ± 17.3	38	210.5 ± 25.1	<0.05*

AHI (events/h)	8	9.5 ± 6.2	38	28.2 ± 22.9	0.028*
ODI (events/h)	8	4.7 ± 3.0	38	28.8 ± 24.5	<0.05*

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Table 2. Comparisons between patients without nocturnal hypoxemia (non desaturators) and patients with significant nocturnal hypoxemia (desaturators). p was considered significant if < 0.05 (*) with *t* test or Mann-Whitney test (†). RAP: right atrial pressure. PVR: Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency: ratio of total sleep time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement. AHI: apnea-hypopnea index. ODI: oxygen desaturation index. (other abbreviations in the text).

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	IPAH		CTEPH		P
	N	mean ± SD	N	mean ± SD	
Age (yrs)	29	48.5 ± 13.7	17	60.6 ± 10	0.003*
BMI (kg/m²)	29	24.4 ± 4.7	17	25.1 ± 3.0	0.566
Pulmonary function (% predicted)					
TLC	28	94.7 ± 13.6	16	96.3 ± 15.6	0.724
FEV ₁	27	88.4 ± 15.1	16	88.7 ± 17.8	0.962
FVC	28	94.1 ± 16.7	16	92.2 ± 18.3	0.720
Dlco	26	67.6 ± 18.1	12	72.6 ± 17.9	0.432
FEV _{25/75}	28	75.3 ± 25.8	16	69.4 ± 20.7	0.438
Arterial blood gas					
PaO ₂ (mmHg)	28	74.3 ± 11.7	15	72.7 ± 10.2	0.667
PaCO ₂ (mmHg)	28	33 ± 4.3	15	31.7 ± 3.4	0.325
Alveolo-arterial gradient	28	33.7 ± 13.8	15	36.3 ± 13.3	0.549
6MWT					
Walking distance (m)	29	521.0 ± 83.1	17	454.1 ± 95.2	0.016*
Resting SpO ₂ (%)	29	94.8 ± 3.2	17	94.5 ± 1.9	0.675
Walking SpO ₂ (%)	29	88.9 ± 6.0	17	86.3 ± 5.9	0.155
BNP(ng/L)	27	66.4 ± 78.3	16	121.6 ± 194.9	0.900†
Right heart catheterization					
RAP (mmHg)	29	5.6 ± 4.1	17	4.2 ± 2.8	0.198†
mPAP (mmHg)	29	47.9 ± 13.3	17	37.3 ± 9.6	0.006*†
CI (L/min/m ²)	29	3.5 ± 0.6	17	2.8 ± 0.4	<0.001*
PVR (Woods U)	29	6.6 ± 2.3	15	6.3 ± 2.6	0.693
Epworth Sleepiness Scale (/24)	23	7.2 ± 5.4	13	3.8 ± 2.3	0.060†
Polysomnography					
TST (min)	29	370 ± 59.1	17	328 ± 88.5	0.064
Sleep Efficiency (%)	29	84.4 ± 8.2	17	74.0 ± 16.6	0.043*†
Arousals index (events/h)	29	21.6 ± 15.4	17	21.8 ± 11.8	0.967
N3 stage (min)	29	76.0 ± 38.4	17	74.8 ± 43.1	0.919
REM stage (% of TST)	29	21.4 ± 7.4	17	18.1 ± 5.9	0.123
D90% (min)	29	181.9 ± 147.7	17	166.4 ± 118.6	0.715
AHI (events/h)	29	26.9 ± 25.8	17	21.6 ± 13.7	0.435
ODI (events/h)	29	27.6 ± 27.5	17	19.4 ± 16.5	0.268

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443 Table 3. Comparisons of IPAH and CTEPH groups. Clinical and functional differences did

444 not reflect nocturnal oxygen saturation differences. RAP: right atrial pressure. PVR:

445 Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency: ratio of total sleep

446 time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement. AHI: apnea-hypopnea

447 index. ODI: oxygen desaturation index (other abbreviations in the text).

TABLE 1

	PH	
	N (%)	mean \pm SD
Age (yrs)	46	53 \pm 13.6
BMI (kg/m ²)	46	24.6 \pm 4.2
Gender F	25 (54.4)	
M	21 (45.6)	
Race Caucasian	39 (84.8)	
Black	7 (15.2)	
IPAH	29 (63)	
CTEP	17 (37)	
Dyspnea (NYHA) I	3 (6.5)	
II	32 (69.6)	
III	11 (23.9)	
Snorers	27 (58.7)	
Epworth Sleepiness Scale (/24)	39	6.1 \pm 4.7
PH treatment		
Prostacyclin analogues	12 (26)	
Endothelin receptor antagonists	30 (65.2)	
5-Phosphodiesterase inhibitors	26 (56.5)	
Calcium channel blockers	11 (24)	
anticoagulation	42 (91.3)	
Combined therapy (2 or 3)	27 (58.7)	
Pulmonary function (% predicted)		
FEV ₁	44*	88.8 \pm 16
FVC	44*	93.4 \pm 17.1
Dlco	38*	69.1 \pm 18
TLC	44*	95.3 \pm 14.2
FEV _{25/75}	44*	73.2 \pm 24
Arterial blood gas		
PaO ₂ (mmHg)	43*	73.7 \pm 11.1
PaCO ₂ (mmHg)	43*	32.6 \pm 4.0
Alveolo-arterial gradient	43*	34.6 \pm 13.5
6MWT		
Walking distance (m)	46	496.3 \pm 92.7
Resting SpO ₂ (%)	46	94.6 \pm 2.7
Walking SpO ₂ (%)	46	87.9 \pm 6
BNP(ng/L)	46	95.5 \pm 144.6
Right heart catheterization		
RAP (mmHg)	46	5.1 \pm 3.7
mPAP (mmHg)	46	44 \pm 13.0
CI (L/min/m ²)	46	3.2 \pm 0.6
PVR (Woods U)	44*	6.5 \pm 2.4
mPWP	44*	8.1 \pm 2.8

Polysomnography		
TST (min)	46	354.8 ± 73.3
Sleep Efficiency (%)	46	80.6 ± 12.9
Arousals index (events/h)	46	21.7 ± 14
N3 stage (min)	46	75.6 ± 39.7
REM stage (% of TST)	46	20.2 ± 7.0
D90% (min)	46	176.2 ± 136.5
D90% (% of TST)	46	48.9 ± 35.9
AHI (events/h)	46	24.9 ± 22.1
ODI (events/h)	46	24.6 ± 24.1

4
5 Table 1. Baseline characteristics of the population. *: Not all patients could execute correctly
6 spirometry manoeuvres, especially DLco which requires holding breath for at least 10 sec.
7 Some patients refused blood gas analysis, considering it very painful. In 2 patients, mPWP
8 could not be technically measured (and so resulting PVR could not be calculated). RAP: right
9 atrial pressure. PVR: Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency:
10 ratio of total sleep time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement
11 AHI: apnea-hypopnea index. ODI: oxygen desaturation index (other abbreviations in the
12 text).

TABLE 2

	Non Desaturators		Desaturators		P
	N (%)	mean ± SD	N (%)	mean ± SD	
Age (yrs)	8	43.9 ± 21.4	38	54.9 ± 11.0	0.213 [†]
BMI (kg/m ²)	8	22.2 ± 3.2	38	25.2 ± 4.1	0.058
Dyspnea NYHA I	1 (12.5)		2 (5.3)		
II	7 (87.5)		25 (65.8)		
III	0		11 (28.9)		
Snorers	5(62.5)		22(57.9)		
Epworth Sleepiness Scale (/24)	7	7.6 ± 3.7	29	5.6 ± 5	0.340
Pulmonary function (% predicted)					
TLC	8	90.7 ± 13.6	36	96.3 ± 14.3	0.322
FEV ₁	8	90.9 ± 16.1	36	88.4 ± 16.1	0.695
FVC	8	89.5 ± 15.3	36	94.3 ± 17.6	0.530
Dlco	8	68.1 ± 20.1	30	69.4 ± 17.7	0.858
FEV _{25/75}	8	95.2 ± 23.6.	36	68.3 ± 21.5	0.003*
FEV _{25/75} (non smokers)	7	93 ± 24.5	25	77.5 ± 22.8	0.038*
Arterial blood gas					
PaO ₂ (mmHg)	8	83.2 ± 6.7	35	71.6 ± 10.8	0.006*
PaCO ₂ (mmHg)	8	32.9 ± 4.9	35	32.8 ± 3.9	0.812
Alveolo-arterial gradient	8	25.8 ± 14.2	35	36.6 ± 12.7	0.039*
6MWT					
Walking distance (m)	8	522.4 ± 21.3	38	490.8 ± 86.5	0.387
Resting SpO ₂ (%)	8	96.5 ± 1.1	38	94.3 ± 2.8	0.019* [†]
Walking SpO ₂ (%)	8	91.5 ± 4.2	38	87.2 ± 6.1	0.067
Biological analysis					
Hemoglobin (g/dl)	8	15.0 ± 0.9	35	15.0 ± 1.6	0.942
Ht (%)	8	45.0 ± 2.6	35	45.0 ± 4.8	0.989
BNP (ng/L)	7	42.1 ± 58.2	36	95.6 ± 143.7	0.342
Right heart catheterization					
RAP (mmHg)	8	4.1 ± 2.2	38	5.3 ± 4	0.418
mPAP (mmHg)	8	38.0 ± 15.6	38	45.2 ± 12.3	0.156
CI (L/min/m ²)	8	3.2 ± 0.7	38	3.2 ± 0.6	0.922
PVR (Woods U)	8	5.7 ± 2.0	36	6.7 ± 2.4	0.332
Polysomnography					
TST (min)	8	324.3 ± 75.9	38	361.2 ± 72.1	0.200
Sleep efficiency (%)	8	77.0 ± 17.5	38	81.3 ± 11.9	0.393
Arousals index (events/h)	8	18.1 ± 11.4	38	22.4 ± 14.5	0.440
N 3 stage (min)	8	85.4 ± 21.2	38	73.5 ± 42.5	0.445
REM stage (% of	8	19.1 ± 9.6	38	20.4 ± 6.5	0.654

TST)					
D90% (min)	8	13.2 ± 17.3	38	210.5 ± 25.1	<0.05*
AHI (events/h)	8	9.5 ± 6.2	38	28.2 ± 22.9	0.028*
ODI (events/h)	8	4.7 ± 3.0	38	28.8 ± 24.5	<0.05*

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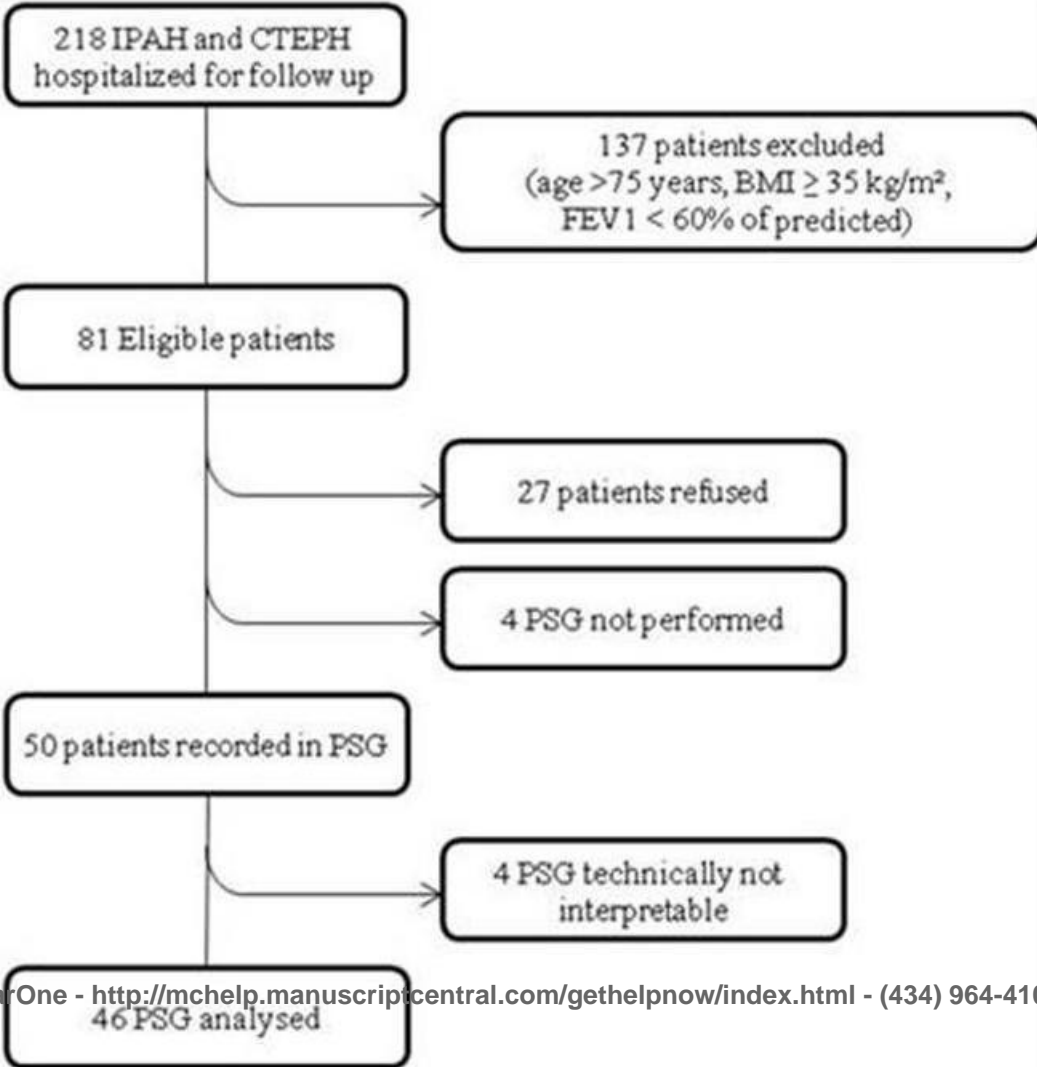
Table 2. Comparisons between patients without nocturnal hypoxemia (non desaturators) and patients with significant nocturnal hypoxemia (desaturators). p was considered significant if < 0.05 (*) with *t* test or Mann-Whitney test (†). RAP: right atrial pressure. PVR: Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency: ratio of total sleep time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement. AHI: apnea-hypopnea index. ODI: oxygen desaturation index. (other abbreviations in the text).

TABLE 3

	IPAH		CTEPH		<i>P</i>
	N	mean ± SD	N	mean ± SD	
Age (yrs)	29	48.5 ± 13.7	17	60.6 ± 10	0.003*
BMI (kg/m ²)	29	24.4 ± 4.7	17	25.1 ± 3.0	0.566
Pulmonary function (% predicted)					
TLC	28	94.7 ± 13.6	16	96.3 ± 15.6	0.724
FEV ₁	27	88.4 ± 15.1	16	88.7 ± 17.8	0.962
FVC	28	94.1 ± 16.7	16	92.2 ± 18.3	0.720
Dlco	26	67.6 ± 18.1	12	72.6 ± 17.9	0.432
FEV _{25/75}	28	75.3 ± 25.8	16	69.4 ± 20.7	0.438
Arterial blood gas					
PaO ₂ (mmHg)	28	74.3 ± 11.7	15	72.7 ± 10.2	0.667
PaCO ₂ (mmHg)	28	33 ± 4.3	15	31.7 ± 3.4	0.325
Alveolo-arterial gradient	28	33.7 ± 13.8	15	36.3 ± 13.3	0.549
6MWT					
Walking distance (m)	29	521.0 ± 83.1	17	454.1 ± 95.2	0.016*
Resting SpO ₂ (%)	29	94.8 ± 3.2	17	94.5 ± 1.9	0.675
Walking SpO ₂ (%)	29	88.9 ± 6.0	17	86.3 ± 5.9	0.155
BNP(ng/L)	27	66.4 ± 78.3	16	121.6 ± 194.9	0.900†
Right heart catheterization					
RAP (mmHg)	29	5.6 ± 4.1	17	4.2 ± 2.8	0.198†
mPAP (mmHg)	29	47.9 ± 13.3	17	37.3 ± 9.6	0.006*†
CI (L/min/m ²)	29	3.5 ± 0.6	17	2.8 ± 0.4	<0.001*
PVR (Woods U)	29	6.6 ± 2.3	15	6.3 ± 2.6	0.693
Epworth Sleepiness Scale (/24)	23	7.2 ± 5.4	13	3.8 ± 2.3	0.060†
Polysomnography					
TST (min)	29	370 ± 59.1	17	328 ± 88.5	0.064
Sleep Efficiency (%)	29	84.4 ± 8.2	17	74.0 ± 16.6	0.043*†
Arousals index (events/h)	29	21.6 ± 15.4	17	21.8 ± 11.8	0.967
N3 stage (min)	29	76.0 ± 38.4	17	74.8 ± 43.1	0.919
REM stage (% of TST)	29	21.4 ± 7.4	17	18.1 ± 5.9	0.123
D90% (min)	29	181.9 ± 147.7	17	166.4 ± 118.6	0.715
AHI (events/h)	29	26.9 ± 25.8	17	21.6 ± 13.7	0.435
ODI (events/h)	29	27.6 ± 27.5	17	19.4 ± 16.5	0.268

Table 3. Comparisons of IPAH and CTEPH groups. Clinical and functional differences did not reflect nocturnal oxygen saturation differences. RAP: right atrial pressure. PVR: Pulmonary vascular resistances. TST: total sleep time. Sleep efficiency: ratio of total sleep time over time in bed. N3: stage 3 of sleep. REM: rapid eye movement. AHI: apnea-hypopnea index. ODI: oxygen desaturation index (other abbreviations in the text).

Figure 1



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Figure 2a

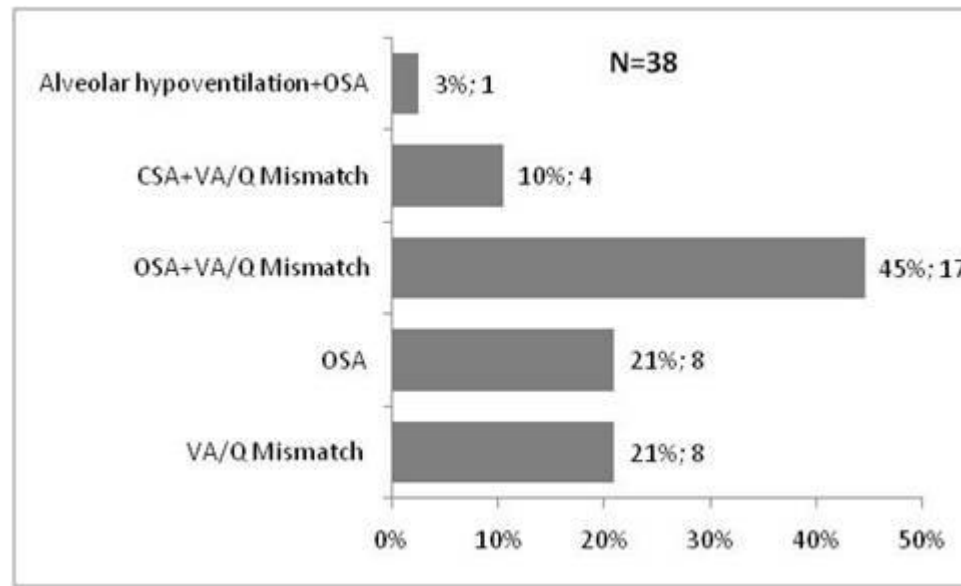
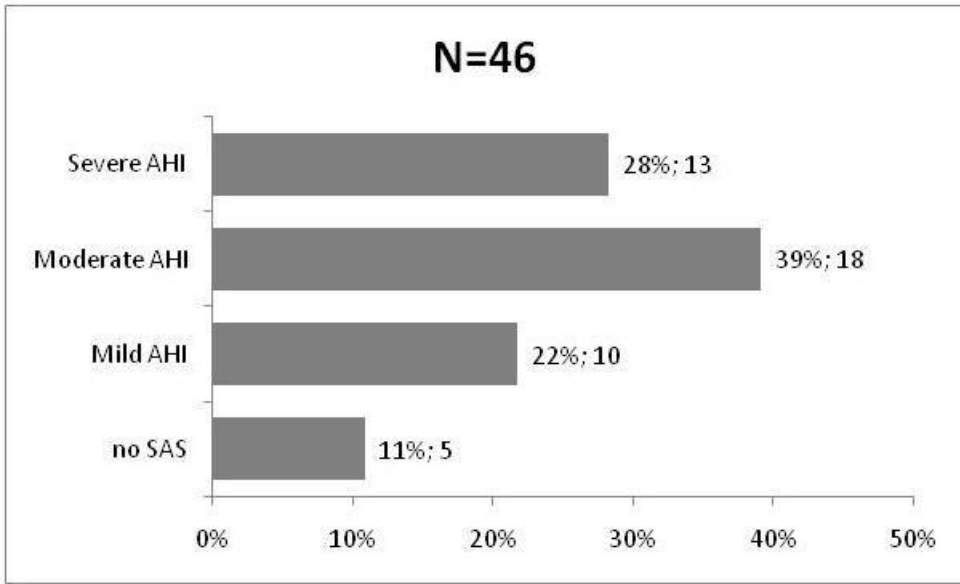


Figure 2b



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Figure 3a

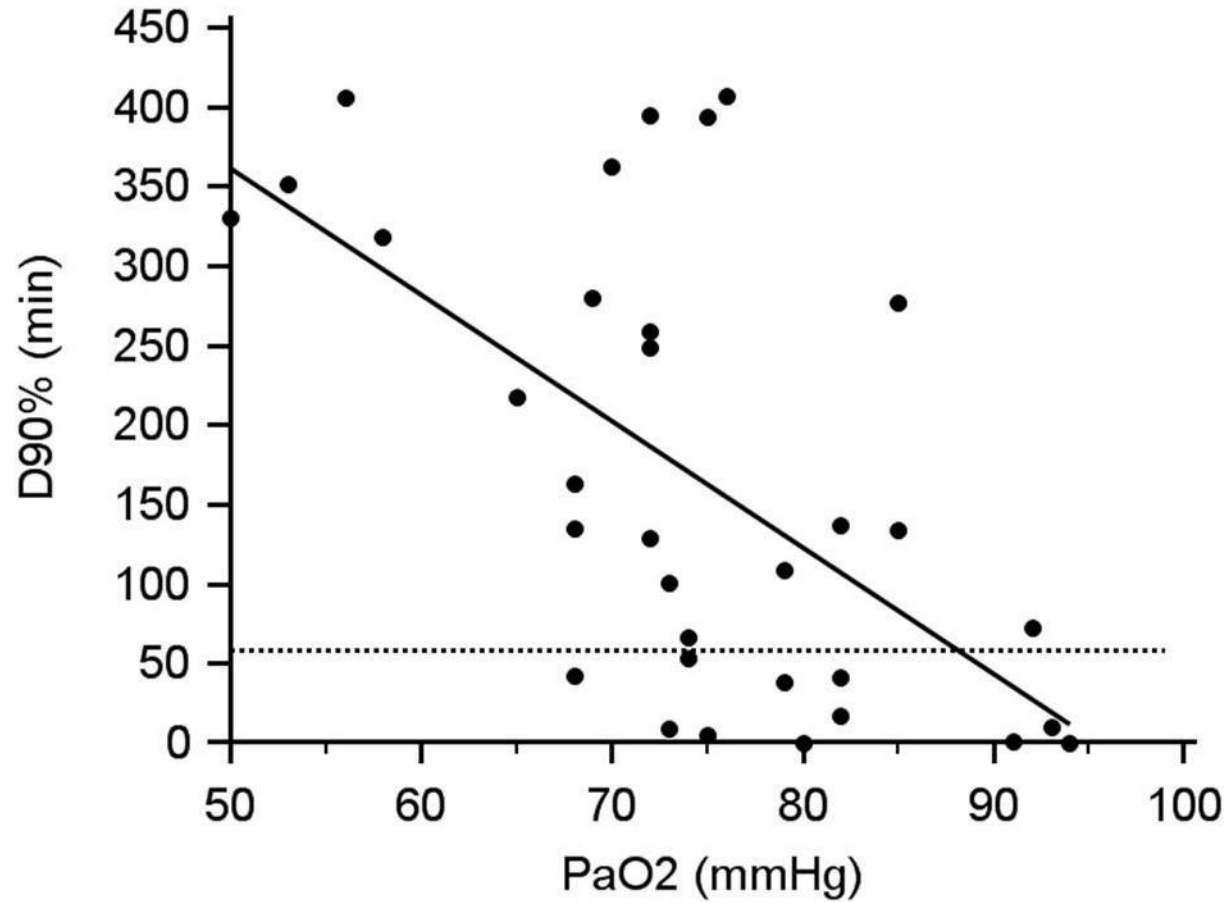
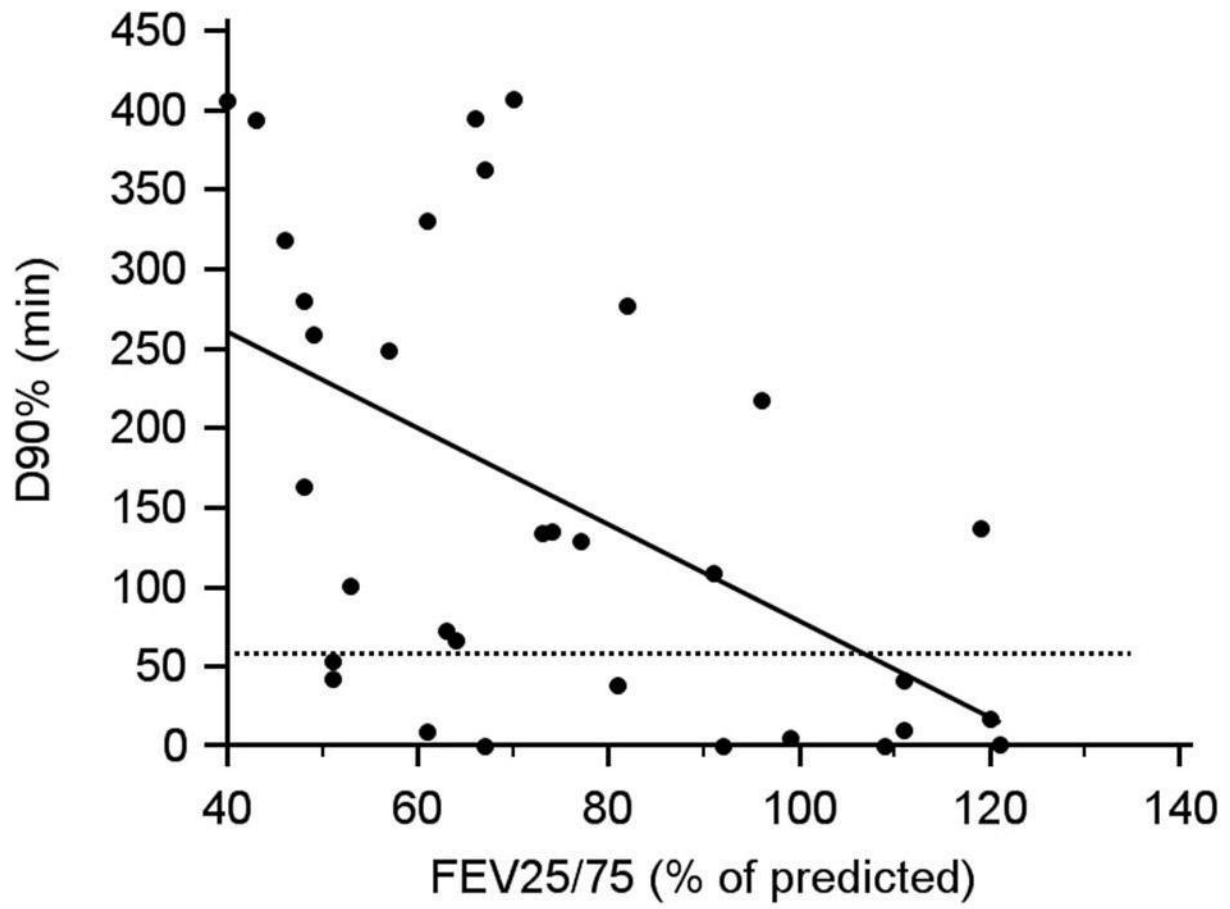


Figure 3b



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Web-only supplement

HYPOXEMIC SLEEP RESPIRATORY DISORDERS IN PRECAPILLARY PULMONARY

HYPERTENSION: PREVALENCE AND MECHANISMS

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e-Appendix 1

Definition of sleep breathing abnormalities

An apnea was defined as a 90% or greater reduction of airflow lasting 10 sec or longer.

Apneas were defined as obstructive when there was evidence of persistent respiratory effort,

and central in the absence of any respiratory effort. Hypopneas were defined as a reduction

in airflow by more than 50% of baseline, lasting at least 10 sec, or a lower reduction in

airflow associated with a desaturation $\geq 3\%$ and/or an arousal. Apnea-hypopnea index (AHI)

was considered mildly elevated when ranging between 5 and 15/h, moderately elevated

when between 15 and 30/h and severely elevated if ≥ 30 /h. Periodic respiration like CSR

consisted of at least 3 crescendo and decrescendo pattern changes in breathing amplitude,

lasting more than 10 consecutive minutes or associated with a central AHI ≥ 5 /h¹. Sleep

apnea-hypopnea-related hypoxemia was recognized by its typical intermittent pattern (“Saw-

tooth” pattern) which is characterized by periodic falls $\geq 3\%$ in SpO₂ following airflow

obstruction or central apnea, with a return to baseline or near baseline level (e-Figure 1).

Sustained hypoxemia periods in the absence of simultaneous apneic events or alveolar

hypoventilation pattern were considered to be the consequence of a worsening in ventilation-

perfusion heterogeneity. Thus, ventilation/perfusion (VA/Q) mismatch-related hypoxemia

was defined as sustained hypoxemia periods lasting for at least 10 consecutive minutes

24 without any concomitant increase in TcPCO₂ suggestive of alveolar hypoventilation nor the
25 presence of apneas or hypopneas (e-Figure 2).

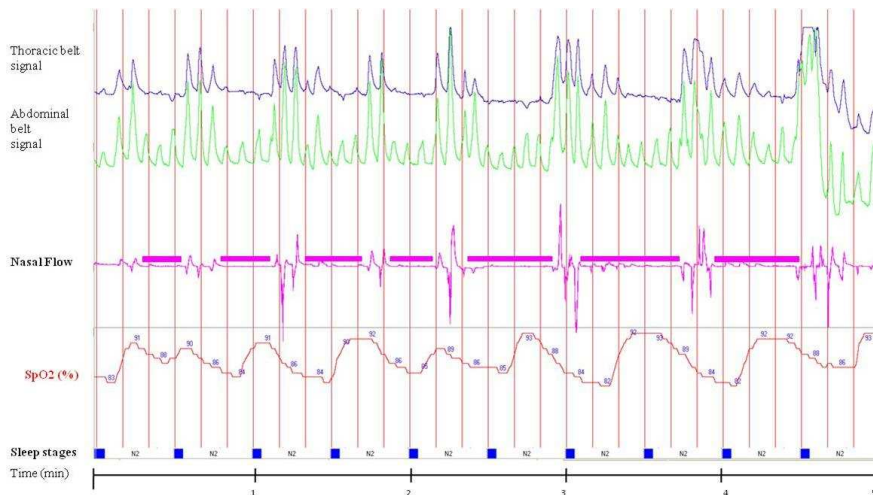
26 Alveolar hypoventilation-related hypoxemia was defined as an increase in PaCO₂ during
27 sleep from awake supine values with a simultaneous sustained oxyhemoglobin desaturation
28 not explained by apnea or hypopnea events¹². We used transcutaneous PCO₂ (TcPCO₂) as
29 surrogate measures of PaCO₂ since the TOSCA device that we use has shown good accuracy
30 in adult patients compared to blood gas analysis¹³⁻¹⁵. Actually, apnea and hypopnea events
31 induce intermittent hypoxemia and hypercapnia. However, TcPCO₂ monitors have a slower
32 reaction time than SpO₂ monitors and show usually a trend rather than breath-to-breath
33 changes. Thus, duration of alveolar hypoventilation should be sufficient to account for the
34 effects of response time of the TcPCO₂ monitor. For this reason, apnea- and hypopnea-
35 induced PaCO₂ fluctuations are not usually detected by TcPCO₂ devices and should not be
36 considered as a cause of prolonged alveolar hypoventilation (e-Figure 3).

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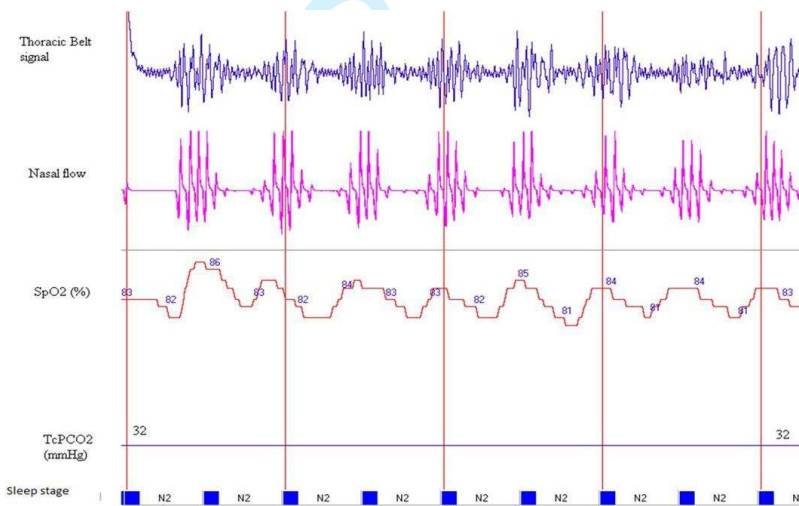
53 **e-Figure 1**

54 **1a**



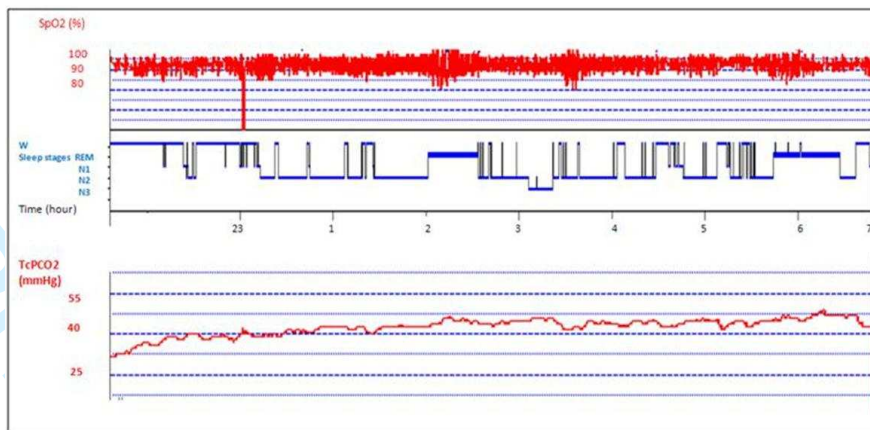
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56 **1b**



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58 **1c**



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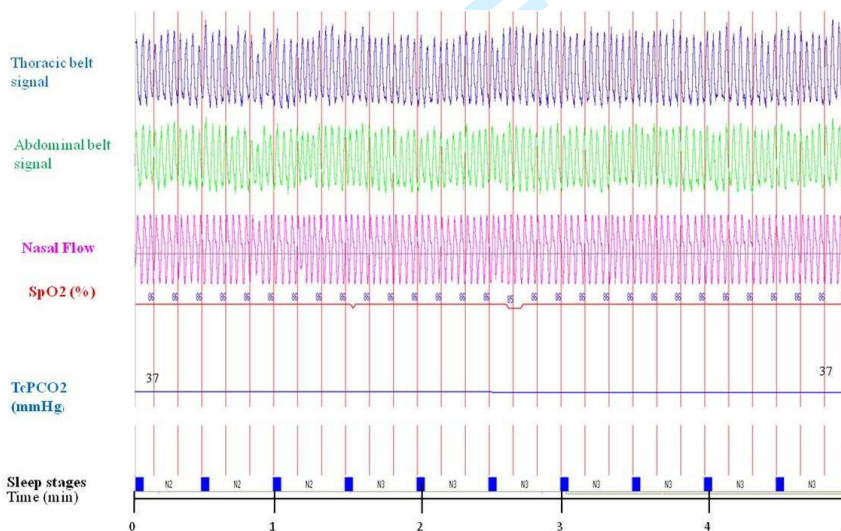
60 **e-Fig. 1.a:** Obstructive sleep apneas with intermittent desaturation. Thick horizontal lines on
 61 the flow nasal signal are obstructive apneas.

62 **e-Fig. 1.b:** Cheyne Stokes respiration with intermittent SpO₂ variation concomitant with
 63 central apneic events.

64 **e-Fig. 1.c:** Sleep apnea-hypopnea characterized by intermittent fluctuations in SpO₂ over the
 65 night without significant increase in TcPCO₂.

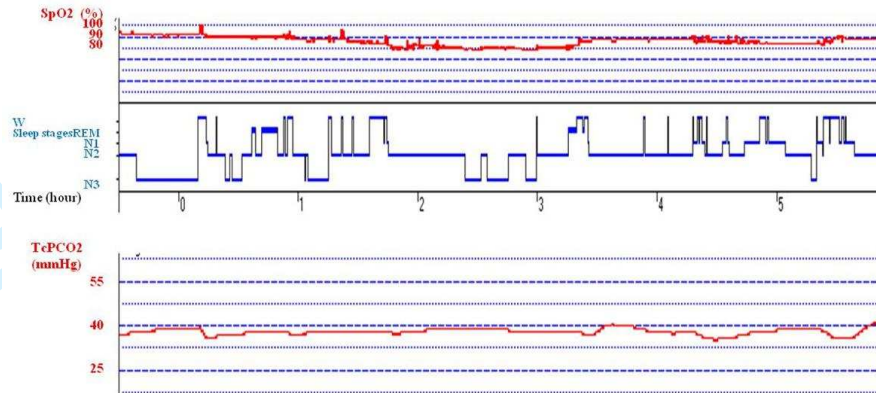
66 **e-Figure 2**

67 **2a**



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69 **2b**



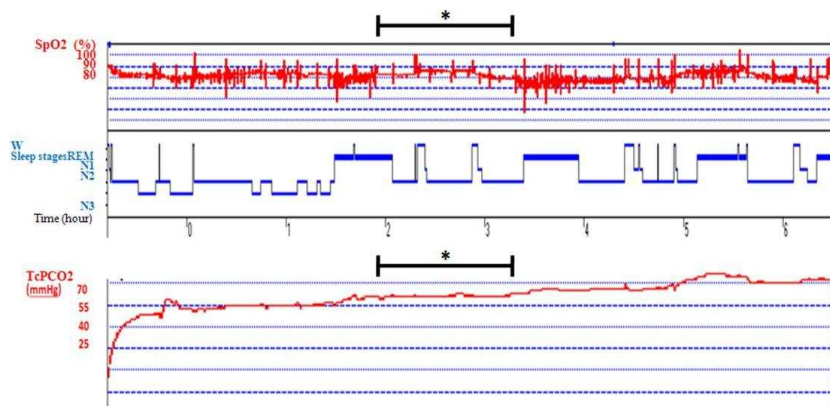
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71 **e-Fig.2.a** shows 5 minutes trend of nocturnal VA/Q mismatch: persistent desaturation without
 72 any increase in TcPCO₂ suggestive of alveolar hypoventilation, nor any change in nasal flow
 73 indicating apnea-hypopnea events. SpO₂ in wakefulness was 95%.

74 **e-Fig .2b:** shows long desaturation periods during sleep (between 1:00 AM and 3:30 AM, and
 75 4:30 AM and 5:30 AM) without significant increase in TcPCO₂

76

e-Figure 3



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78 **e-Fig. 3:** Sleep hypoventilation: long nocturnal desaturation with a concomitant increase in
 79 TcPCO₂ (from 45 to over 70 mmHg), associated to intermittent fluctuations in SpO₂ due to a
 80 moderate obstructive sleep apnea-hypopnea syndrome (AHI = 22/h). *: period of isolated
 81 alveolar hypoventilation (stable SpO₂ of 86-88%, elevated TcPCO₂ of 58 mmHg) without
 82 significant AHI (AHI=2/h calculated between 1:55 AM and 3:20 AM)