Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis

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ABSTRACT The objectives of this prospective study were: 1) to determine the prevalence and determinants of obstructive sleep apnoea (OSA) in patients with newly diagnosed idiopathic pulmonary fibrosis (IPF); 2) to determine whether OSA was associated with cardiovascular disease (CVD) as well as increased oxidative stress and levels of IPF biomarkers in the blood.

A group of 45 patients with newly diagnosed IPF attended polysomnography. The prevalence of CVD and the severity of coronary artery calcification were investigated by high-resolution computed tomography. The levels of 8-hydroxydeoxyguanosine (8-OH-DG) and various IPF biomarkers in the blood were compared between patients with no or mild OSA (apnoea–hypopnoea index (AHI) <15 events·h^{-1}), with moderate OSA (15 ⩽AHI <30 events·h^{-1}) and with severe OSA (AHI ⩾30 events·h^{-1}).

The prevalence of moderate-to-severe OSA and severe OSA was 62% and 40%, respectively. AHI did not correlate with demographic or physiological data. All patients with severe OSA had a medical history of CVD, *versus* 41.2% and 40% of those with no or mild OSA, or with moderate OSA, respectively (p<0.0001). Ischaemic heart disease (IHD) and moderate-to-severe coronary artery calcifications were strongly associated with severe OSA. The 8-OH-DG and matrix metalloproteinase-7 serum levels were significantly increased in the severe OSA group.

Moderate-to-severe OSA is highly prevalent in incident IPF and severe OSA is strongly associated with the presence of CVD, particularly IHD.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare and fatal disease of unknown origin affecting mostly elderly people, characterised by the accumulation of extracellular matrix in the distal lung, leading to progressive loss of pulmonary function. The pathophysiology of IPF is not fully understood, but it could be due to aberrant repair following repetitive micro-injuries of the alveolar epithelium [1]. Recently, several studies have reported that moderate-to-severe obstructive sleep apnoea (OSA) syndrome defined by an apnoea–hypopnoea index (AHI) >15 events·h^{-1}, was particularly frequent in IPF patients [2–6].

The interrelationships between IPF and OSA are complex. On the one hand, physiological studies have shown that a decrease in lung volume increased upper airway instability. This suggests that lung restriction in IPF could potentially lead to OSA [7–9]. On the other hand, OSA promoting gastro-oesophageal reflux (GER) [10], or increasing lung oxidative stress through chronic nocturnal intermittent hypoxia [11] might *per se* favour the development of pulmonary fibrosis. Thus, it raises the important question whether OSA appears in the natural course of IPF as a consequence of lung function restriction, or whether it precedes (or occurs at the same time as) it.

Respiratory failure is the main cause of death in IPF [12]. However, IPF patients often present comorbid conditions including cardiovascular disease (CVD) and diabetes mellitus that may impact survival [13–18]. Moderate-to-severe OSA is a recognised risk factor for CVD [19–23] and glucose intolerance [24]. Oxidative stress and low-grade systemic inflammation induced by chronic intermittent hypoxia are likely to play a key role in this phenomenon [25]. It is currently not known whether severe OSA is associated with cardiovascular and metabolic comorbidities and whether or not it may increase systemic oxidative stress in IPF patients.

To address these issues, we prospectively recorded by nocturnal polysomnography (PSG) 45 consecutive patients at the time of IPF diagnosis. The main objectives of the study were 1) to determine the prevalence of OSA in incident IPF and to look for correlations between AHI and demographic and physiological variables; 2) to compare in IPF patients with no or mild OSA, with moderate OSA or with severe OSA the prevalence of comorbid conditions such as GER, CVD and diabetes, as well as oxidative stress and prognostic IPF biomarker peripheral blood levels.

Materials and methods

Subjects

This prospective study was part of a larger French national cohort study on IPF (the COFI study 2007–2014; principal investigator, Dominique Valeyre), and was approved by Aulnay-sous-Bois Comité de Protection des Personnes and CNIL (no. 908198). Five university pulmonary departments participated in the study between June 2009 and December 2010. Inclusion criteria were the following: age >18 years; ability to provide informed consent; stable dyspnoea; diagnosis of incident IPF according to ATS/ERS recommendations [26] (delay between diagnosis of IPF and inclusion <9 months). Non-inclusion criteria were prior diagnosis of OSA and unstable dyspnoea.

Study protocol

All patients attended nocturnal PSG (Morpheus Apparatus, Micromed, Mâcon-Loché, France, Dream Apparatus, Medatec, Brussel, Belgium or CID102L, CIDELEC, Sainte-Gemmes sur Loire, France) according to established standards [27]. Patients requiring nocturnal home oxygen therapy (n=4) at the time of the study received oxygen supplementation during PSG at their usual flow-rate (2–3 L·min^{-1}). Apnoeas, hypopnoeas and sleep staging were defined as outlined by the American Academy of Sleep Medicine [27] (rules for scoring respiratory events are summarised in the supplementary material). Subjects were asked to complete the Epworth Sleepiness Scale questionnaire. Comorbidities and cardiovascular risk factors were carefully registered by a chest physician based on information from medical records, paying special attention to the presence of GER, smoking status, hyperlipidaemia, prednisone treatment, obesity, diabetes mellitus, pulmonary hypertension, thromboembolic disease and CVD. CVD was defined as one or more of the following: hypertension, ischaemic heart disease (IHD,

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including history of myocardial infarction, coronary artery bypass or coronary artery stent), stroke/transient ischaemic attack, aortic aneurysm and peripheral arteriosclerosis. High-resolution computed tomography (HRCT) and pulmonary function testing (PFT) including spirometry, body box plethysmography and measurement of diffusing capacity of the lung for carbon monoxide (*D*LCO) were performed according to ATS/ERS guidelines within 3 months of PSG. Blood samples were obtained the day patients underwent PFT between 08:00 h and 10:00 h after one night of fasting, and serum was stored at −80°C in the tumour biobank of the Biological Hematology Laboratory before subsequent analysis.

HRCT analysis

Two radiologists independently reviewed HRCT scans and evaluated the extent of fibrosis representing the sum of the reticular pattern and honeycombing, according to SUMIKAWA *et al.* [28]. Coronary arteries from the mediastinal windows were screened for calcification and graded according to NATHAN *et al.* [29] as follows: 0=no visible calcification, 1=trace calcification, 2=mild calcification, 3=moderate calcification and 4=extensive calcification.

Serum biomarker analyses

DNA oxidative damage was assessed by determination of 8-hydroxy-deoxyguanosine (8-OH-DG) serum levels using an ELISA kit (Oxiselect, Cell Biolabs Inc, San Diego, CA). Serum levels of peripheral blood biomarkers proposed in IPF were measured using the following ELISA kits: Surfactant Protein A (SPA) (BioVender LM, Czech Republic), matrix metalloproteinase-7 (MMP-7) and intercellular adhesion molecule (ICAM)-1 (R&D Systems Europe, Lille, France).

Statistical analysis

Means and SD were reported for the continuous variables, except for blood biomarkers expressed as medians and interquartiles. Normally distributed continuous variables were analysed with one-way ANOVA and, when allowed by the F value, results were compared by the modified least significant difference (Fisher's PLSD), adjusted by the Bonferroni correction for multiple comparisons. The Kruskal–Wallis test with Dunn's correction was used in comparisons of non-normally distributed continuous variables. The Pearson correlation coefficient was employed to examine the relation between PFT variables, age, body mass index (BMI) and AHI. Categorical variables are reported as number and percentage, and were analysed by the Chi-squared test or Fisher exact test. For association between AHI groups (<15, 15–30 and ⩾30 events·h^{-1}), interactions between ischaemic heart disease and potential confounders were tested, and subgroup analyses were performed with the Bonferroni correction for multiple testing. A p-value <0.05 was considered as statistically significant. Analyses were carried out using R statistical software version 3.1.2.

Results

Study population

The diagnosis of incident IPF was made in 67 subjects during the inclusion period. Five subjects were not included because of prior diagnosis of OSA, and two subjects because of unstable dyspnoea. Among the 60 subjects eligible for the study, 45 were included and successfully completed PSG. Characteristics and treatments of the study population are given in table 1 (see supplementary material for the characteristics of non-included patients). Only 22.2% of included subjects received prednisone (mean duration of treatment before PSG: 5.2±2.7 months).

Polysomnography

Forty subjects (88.8%) had OSA as defined by an AHI >5 events·h^{-1} of sleep (table 2). Twelve subjects (26.6%) had mild OSA (5 ⩽AHI <15 events·h^{-1}), 10 subjects (22.2%) had moderate OSA (15 ⩽AHI <30 events·h^{-1}) and 18 subjects (40%) had severe OSA (AHI ⩾30 events·h^{-1}) (table 2). Apnoeas and hypopnoeas represented 35±26.2% and 62.9±26.7% of all respiratory events, respectively. Sleep apnoeas were mostly obstructive or mixed, central apnoeas representing less than 5% of sleep apnoeas (table 2). Careful analysis of respiratory tracings revealed no evidence for Cheyne–Stokes breathing (CSB), periodic breathing or sleep-related alveolar hypoventilation. Also, snoring was detected in all subjects with abnormal AHI, as well as features evoking upper airway obstruction such as airflow limitation or thoracoabdominal paradox. Mean nocturnal arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) was significantly decreased in the severe OSA group while the percentage of total sleep time spent with S_{pO_2}<90% and the oxygen desaturation index (ODI) were significantly increased (table 2). As shown in figure 1, there was no correlation between baseline S_{pO_2} in room air and AHI or ODI.

TABLE 1 Participant characteristics

Characteristic	Result
Subjects	45
Age years	68.8±8.7
Sex M/F	38/7
BMI kg·m^{-2}	28±3.5
BMI ⩽25	8 (17.8)
25 <BMI ⩽30	24 (53.3)
30 <BMI ⩽35	12 (26.7)
BMI >35	1 (2.2)
Ethnic origin	
Caucasian	33 (73.3)
North African	12 (26.7)
TLC % predicted	72.2±16.4
FVC % predicted	72.8±20.3
*D*LCO % predicted	45.1±18.9
Medications	
Sleeping pills	1 (2)
IPF medication	17 (37.7)
Prednisone[#]	10 (22.2)
N-Acetylcysteine	10 (22.2)
Immunosuppressive drug	6 (13.3)
Clinical trial	5 (11.1)
Supplemental oxygen therapy[¶]	6 (13.3)

Data are presented as n, n/n, n (%) or mean±SD unless otherwise stated. BMI: body mass index; TLC: total lung capacity; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; IPF: idiopathic pulmonary fibrosis. [#]Mean duration of prednisone treatment before polysomnography (PSG) was 5.2±2.7 months. [¶]: Four patients required nocturnal home oxygen therapy at the time of the study.

Correlation between demographic and PFT variables and PSG parameters

There was no significant difference between the four groups (no OSA, mild, moderate and severe OSA) regarding age, BMI (table 2), PFT and arterial blood gas variables (table 3). AHI did not correlate with age, BMI, FVC, TLC, FEV1 or *D*LCO (Supplementary figure S1).

Comorbidities

To analyse the prevalence of comorbidities and cardiovascular risk factors, the study population was divided into three groups: patients with no OSA or mild OSA (AHI <15 events·h^{-1}) (n=17; mean AHI 8.5 ±4.3 events·h^{-1}), patients with moderate OSA (15 ⩽AHI <30 events·h^{-1}) (n=10; mean AHI 22.6±3.4 events·h^{-1}), patients with severe OSA (AHI ⩾30 events·h^{-1}) (n=18; mean AHI 60.5±25.4 events·h^{-1}). There was no significant difference between groups regarding age, BMI, PFT variables, smoking status, the presence or absence of hyperlipidaemia or prednisone treatment (table 4). As shown in table 4, GER tended to be more frequent in the severe OSA group (p=0.08). The prevalence of diabetes was not significantly different between groups (p=0.41). All subjects with severe OSA suffered from at least one CVD among the following, hypertension, IHD, stroke/transient ischaemic attack, aortic aneurysm and peripheral arteriosclerosis, compared with 40% of subjects with moderate OSA and 41.2% of subjects with no/mild OSA (p=0.0001). When cardiovascular comorbidities were considered separately, IHD appeared to be highly prevalent in the severe OSA group, affecting 61.1% of subjects, significantly more frequent than in the moderate OSA group (30% of subjects) and in the no/mild OSA group (11.8% of subjects) (p=0.009, univariate analysis). Subgroup analysis showed that the association between severe OSA and IHD was independent of cardiovascular comorbidities, age, BMI, smoking history, hyperlipidaemia, but revealed an interaction with the presence of diabetes (p=0.04). All patients with diabetes and severe OSA (n=5) had a history of IHD.

HRCT findings

HRCT scans were reviewed in a subset of 34 subjects including 12 subjects with no/mild OSA, eight subjects with moderate OSA and 14 subjects with severe OSA, with no significant difference between groups regarding demographic variables and PFT data (Supplementary table E1). Mean fibrosis score was low in all groups consistent with early stage of IPF, with no difference between groups (table 5). Staging of coronary artery calcifications revealed that the percentage of subjects with moderate-to-severe (grade 3 and

TABLE 2 Demographic and polysomnographic data

Variable	No OSA[#]	Mild OSA[¶]	Moderate OSA[+]	Severe OSA[§]	p-value
Subjects	5	12	10	18	
Age years	61±10.9	67.6±7.5	72.1±7.7	69.8±8.6	0.11
Sex M/F	3/2	9/3	9/1	16/1	
BMI kg·m^{-2}	27.7±4.3	27.8±2.5	27.3±4	28.6±3.7	0.79
ESS	7±4.2	6.4±3.2	6.2±4.1	8.9±4	0.13
AHI events·h^{-1}	3±1.7	10.8±2.6	22.6±3.4	60.5±25	<0.0001
Apnoea index events·h^{-1}	0.5±0.6	1.4±2	8.2±4.7	33.7±30	0.0002
Obstructive and mixed apnoeas %	–	95±9.1	97.2±4.7	97.8±4	
Mean S_{pO_2} %	93.4±1.1	93.6±1.3	92.7±2.1	91.2±2.3	0.01
Time S_{pO_2} is <90% %TST	4.3±5.5	2.9±3.6	9.1±24.1	26.8±30.1	0.03
ODI (⩾3%) events·h^{-1}	1.7±1.4	5.1±5.4	10.1±4.4	50±35.1	<0.0001
TST min	381±130	389±99	398±85	387±89	0.99
Sleep efficiency %	64.6±26	66±17	70.9±16	69.6±11	0.83
Sleep stage					
N1 %TST	12.4±9.9	17±9.7	18.2±15.7	21.5±13.4	0.52
N2 %TST	50.9±9	46.9±12.8	44±8.8	51.6±16.3	0.49
N3 %TST	20.5±6.6	18.9±6	21±10.3	14.4±7.7	0.14
REM %TST	16.2±6.4	17.2±7.5	16.9±8.1	12.5±6.2	0.25
Arousal index events·h^{-1}	12.6±10.3	23.3±26.3	28.4±29.7	26.1±13.1	0.66
Periodic limb movement index events·h^{-1}	8.1±9.2	11.9±19.9	9.3±18.2	25.5±34.8	0.37

Data are presented as n, n/n or mean±SD unless otherwise stated. OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; BMI: body mass index; ESS: Epworth Sleepiness Scale; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; TST: total sleep time; ODI: oxygen desaturation index; REM: rapid eye movement. [#]: AHI <5 events·h^{-1}. [¶]: 5 ⩽AHI <15 events·h^{-1}. [+]: 15 ⩽AHI <30 events·h^{-1}. [§]: AHI ⩾30 events·h^{-1}.

4) calcifications was significantly higher in the severe OSA group (85.7%) than in the other groups (33.3% and 25% of subjects in the no/mild OSA group and the moderate OSA group, respectively) (p=0.002). The positive predictive value of having OSA with coronary artery calcifications higher than grade 2 was 0.78.

Oxidative stress and IPF biomarkers in peripheral blood

Blood samples were available in 29 patients, 13 patients with no/mild OSA, five subjects with moderate OSA and 11 patients with severe OSA, with no difference in demographic and PFT characteristics between groups (supplementary table E2). Serum 8-OH-DG levels (detecting DNA oxidative damage) were significantly increased in the moderate and severe OSA groups compared with the no/mild OSA group (p=0.03 and p=0.04, respectively) (figure 2A). Concerning IPF biomarkers (figure 2B–E), no difference between groups regarding SPA serum levels was observed (figure 2B). There was a trend to an increase in ICAM-1 levels in the severe OSA group (p=0.10 compared with the no/mild OSA group) (figure 2C). Finally, serum levels of MMP-7 were significantly increased in the severe OSA group compared with the no/mild OSA group (p=0.04) (figure 2D). Indeed, there was a positive correlation between ODI and MMP-7 serum levels (r=0.59; p=0.001) (figure 2E).

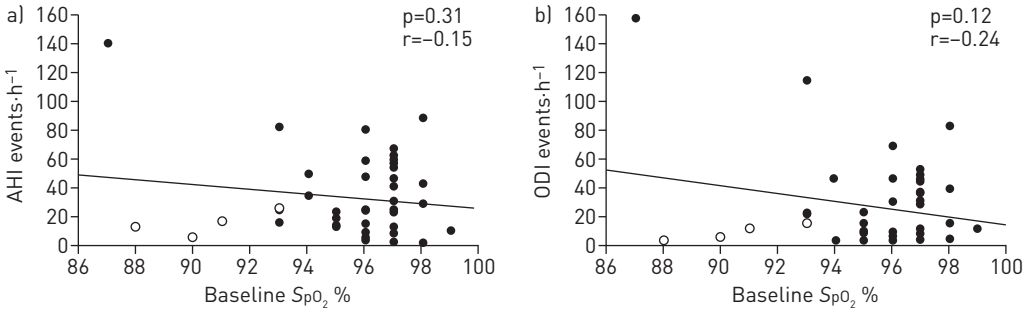

FIGURE 1 Scatter plots of baseline S_{pO_2} (arterial oxygen saturation measured by pulse oximetry) in room air with (a) apnoea–hypopnoea index (AHI) and (b) oxygen desaturation index (ODI). Each data point represents one study subject (n=45). Empty circles indicate subjects that received supplementary oxygen during polysomnography (PSG) (n=4). Regression lines (black lines) and Pearson correlation coefficients are indicated.

TABLE 3 Physiological characteristics. The GAP index (absolute and relative frequency) was calculated according to gender, age and physiologic data (% predicted FVC and D_{LCO}). The composite physiologic index (CPI) was calculated according to the formula CPI=91−(0.65×% predicted D_{LCO})−(0.53×% predicted FVC)+(0.34×% predicted FEV_1).

Variable	No OSA[#]	Mild OSA[¶]	Moderate OSA[+]	Severe OSA[§]	p-value
Subjects	5	12	10	18	
GAP index					0.97
Stage I	2 (40%)	5 (41.7%)	5 (50%)	6 (33.3%)	
Stage II	1 (20%)	6 (50%)	3 (30%)	9 (50%)	
Stage III	2 (40%)	1 (8.3%)	2 (20%)	3 (16.7%)	
CPI	51.7±20.07	46.1±14.44	47.9±17.16	50.1±14.31	0.86
FVC %	65.9±25.8	75.1±16	71.1±23.6	64.2±20.2	0.83
FEV_1 %	68.6±21.7	75.5±15.5	75.6±26.9	78.7±22	0.82
FEV_1/FVC	77.5±7.2	78.8±6.5	79±8.3	78.5±8.6	0.99
TLC %	66.1±18	71.7±14.3	73.2±16.3	73.8±18	0.83
D_{LCO} %	42.7±21.5	48.4±21.6	47.9±20.9	42.5±16.4	0.81
P_{aO_2} mmHg	83±17.6	78.2±12.9	79.7±10.1	79.2±11.7	0.91
P_{aCO_2} mmHg	37±2	38.3±4.2	41.1±4.1	39.8±8.3	0.57
S_{pO_2} %	95.6±3.4	95.6±3.1	95.5±1.8	96.2±2.7	0.92

Data are presented as n, n (%) or mean±SD unless otherwise stated. OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. [#]: AHI <5 events·h^{-1}. [¶]: 5 ⩽AHI <15 events·h^{-1}. [+]: 15 ⩽AHI <30 events·h^{-1}. [§]: AHI ⩾30 events·h^{-1}.

Discussion

The main findings of this prospective study are the following: 1) OSA, particularly severe OSA, was highly prevalent in a French population of patients with incident IPF, and AHI was not correlated with age, BMI and PFT variables; 2) cardiovascular comorbidities, particularly IHD, were more frequently found in IPF patients with severe OSA than in IPF patients with no OSA or mild-to-moderate OSA, and the presence of moderate-to-severe coronary artery calcifications on HRCT was strongly associated with severe OSA; 3) 8-OH-DG and MMP-7 serum levels were increased in patients with incident IPF and severe OSA, and there was a trend to an increase in ICAM-1 in this group.

TABLE 4 Comorbidities and cardiovascular risk factors at inclusion

Characteristic	No OSA or mild OSA[#]	Moderate OSA[¶]	Severe OSA[+]	p-value
Subjects	17	10	18	
GER	4 (23.5)	1 (10)	9 (50)	0.08
Cardiovascular disease[§]	7 (41.2)	4 (40)	18 (100)	<0.0001
Hypertension	6 (35.3)	3 (30)	10 (55.6)	0.37
Ischaemic heart disease	2 (11.8)	3 (30)	11 (61.1)	0.009
Stroke/transient ischaemic attack	0 (0)	0 (0)	3 (16.7)	0.23
Peripheral arteriosclerosis	0 (0)	0 (0)	3 (16.7)	0.22
Aortic aneurysm	0 (0)	0 (0)	1 (5.6)	1
Thromboembolic disease	1 (5.9)	2 (20)	1 (5.6)	0.43
Pulmonary hypertension	0 (0)	0 (0)	0 (0)	1
Diabetes mellitus	2 (11.8)	1 (10)	5 (27.8)	0.41
Hyperlipidaemia	5 (29.4)	3 (30)	9 (50)	0.42
Smoking status				0.06
Never a smoker	5 (29.4)	7 (70)	3 (16.7)	
Former smoker	8 (47.1)	3 (30)	12 (66.7)	
Current smoker	4 (23.5)	0 (0)	3 (16.7)	
Prednisone treatment	6 (35.3)	1 (10)	3 (16.7)	0.24

Data are presented as n or n (%) unless otherwise stated. OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; GER: gastroesophageal reflux. [#]: AHI <15 events·h^{-1}. [¶]: 15 ⩽AHI <30 events·h^{-1}. [+]: AHI ⩾30 events·h^{-1}. [§]: Some patients had more than one diagnosis.

TABLE 5 High-resolution computed tomography (HRCT) data

Data	No or mild OSA[#]	Moderate OSA[¶]	Severe OSA[+]	p-value
Subjects	12	8	14	
Fibrosis score	105.8±42.8	139.4±55.9	104.7±30.7	0.15
Coronary artery calcifications (grade >2)	4 (33.3)	2 (25)	12 (85.7)	0.005

Data are presented as n, n (%) or mean±SD unless otherwise stated. OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index. [#]: AHI <15 events·h^{-1}. [¶]: 15 ⩽AHI <30 events·h^{-1}. [+]: AHI ⩾30 events·h^{-1}.

Our results show that 62.2% of patients with incident IPF had a moderate-to-severe OSA defined by an AHI ⩾15 events·h^{-1}. This is clearly higher than the prevalence of moderate-to-severe OSA in adults older than 60 years, estimated to be approximately 20% by the Sleep Heart Health Study [30]. Indeed, 40% of our patients had severe OSA (AHI ⩾30 events·h^{-1}). Here, we did not classify hypopnoeas as obstructive or central events, as the American Academy of Sleep Medicine guidelines 2007 for scoring of respiratory events stated this classification should not be performed without a quantitative assessment of respiratory effort [27]. However, on careful examination, PSG tracings in patients with abnormal AHI were found to be typical of classical OSA. First, the proportion of obstructive or mixed apnoeas was very high, over 95% of total apnoeic events, and we did not observe any episode of CSB or periodic breathing. Second, snoring was always detected, and there was evidence of upper airway obstruction such as airflow limitation and/or thoracoabdominal paradox during hypopnoeic events. Another important methodological point is the fact that the number of respiratory events might be overestimated in patients with restrictive lung disease and low baseline S_{pO_2} when PSG is performed without nocturnal O_2 supplementation. In our population of

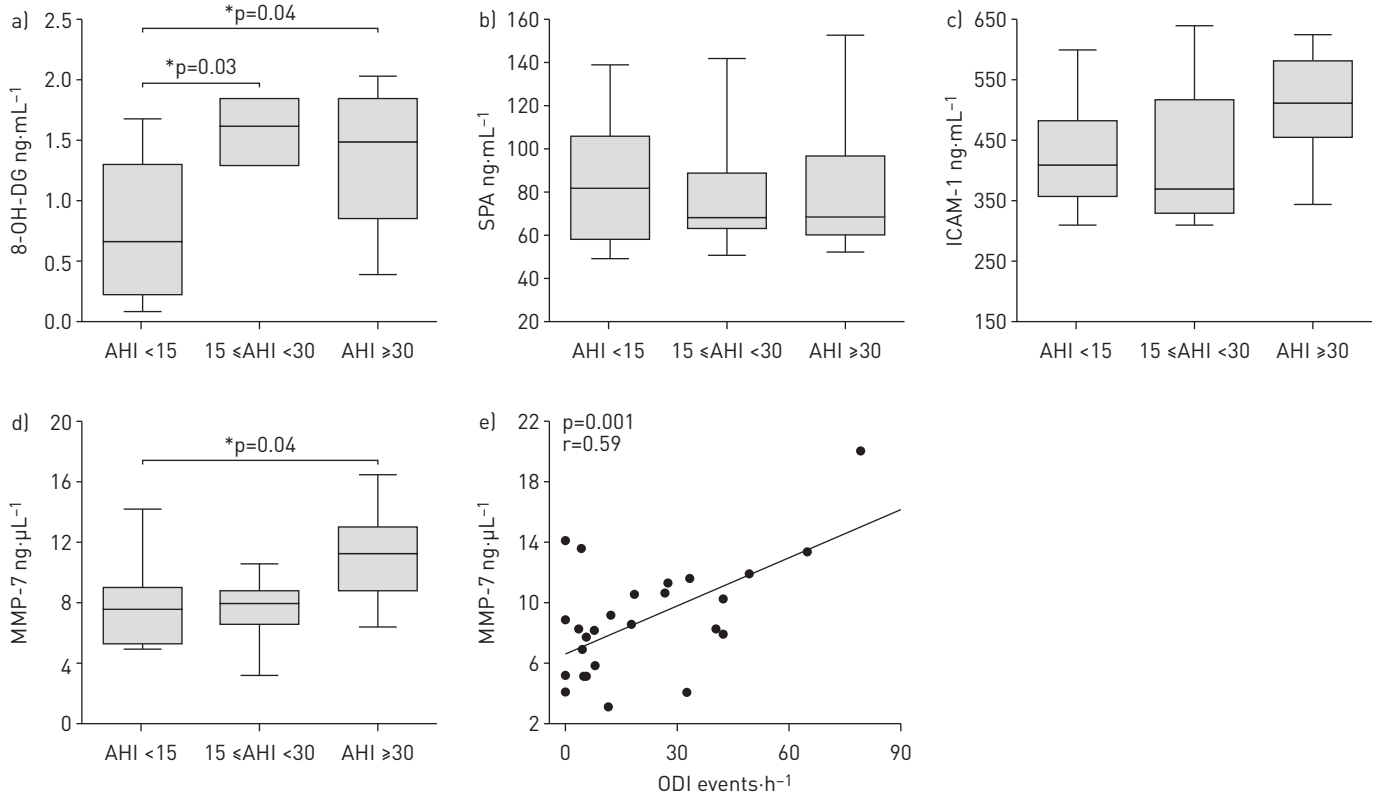

FIGURE 2 Peripheral blood biomarkers of oxidative stress and idiopathic pulmonary fibrosis (IPF). A box plot of 8-hydroxydeoxyguanosine (8-OH-DG) (a) illustrates oxidative DNA damage while plots of surfactant protein A (SPA) (b), intercellular adhesion molecule (ICAM-1) (c), and matrix metalloproteinase-7 (MMP-7) (d) illustrate potential IPF biomarkers in subjects with no/mild OSA (AHI <15 events·h^{-1}) (n=13), moderate OSA (15 ⩽AHI <30 events·h^{-1}) (n=5), and severe OSA (AHI ⩾30 events·h^{-1}) (n=11). Median values and interquartile ranges are represented by horizontal black lines and the upper and lower bounds of the box, respectively. A scatter plot of oxygen desaturation index (ODI) with MMP-7 serum level (e) is also shown with regression line and Pearson correlation coefficient as indicated. OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; *: p-values of <0.05 were determined by ANOVA and Bonferroni correction.

incident IPF, only four patients had a baseline S_{pO_2} (measured in room air) lower than 93%, and three of these patients received O_2 supplementation during PSG. The remaining patient without O_2 supplementation during PSG had a very high AHI (140 events·h^{-1}) but also a very high index of obstructive apnoeas (122·h^{-1}), consistent with severe OSA. Indeed, in the present study, baseline S_{pO_2} in room air correlated neither with AHI nor with ODI (figure 1), indicating that the high prevalence of OSA in this study was not due to overestimation of respiratory events.

The prevalence of moderate-to-severe OSA we observed in newly diagnosed IPF patients is similar to that reported in the cross-sectional study of LANCASTER *et al.* [3], studying patients at various stages of IPF severity. It is much higher than the prevalence previously reported in two smaller series of incident IPF by REID *et al.* [31] and MERMIGKIS *et al.* [4] (22% and 15%, respectively). Importantly, only 22.2% of our patients were receiving prednisone at the time PSG was performed (mean duration of treatment 5.2 months). Another interesting point is that AHI was not correlated with BMI, unlike previously reported [2, 3], suggesting that obesity was not a major risk factor for OSA in incident IPF. It has been proposed that restrictive lung diseases could favour OSA as the decrease in lung volume was experimentally shown to induce upper airway instability [7–9]. However, the relationship between lung function and AHI in IPF patients is controversial. MERMIGKIS *et al.* [2] reported that AHI negatively correlated with FEV1 but LANCASTER *et al.* [3] found no correlation between AHI, lung volume or *D*LCO. In the present study, lung volume was only mildly decreased and the mean lung fibrosis score on HRCT was low, consistent with early-stage IPF. There was no correlation between AHI, spirometry and *D*LCO values. Taken together, these data suggest that in our cohort of incident IPF, OSA was not likely to be the consequence of progressive lung restriction.

Because moderate-to-severe OSA is a well-recognised risk factor for cardiovascular and metabolic diseases [19–25], we wondered whether OSA was associated with comorbid conditions in our study population. The prevalence of comorbidities was compared among groups of patients with no/mild OSA, moderate OSA, and severe OSA. Patients with no OSA (n=5) and patients with mild OSA (n=12) were pooled in the same group for statistical analyses because mild OSA is highly prevalent in adults over 60 (affecting approximately one-third of the general population [30]) and most often asymptomatic. Furthermore, the association of mild OSA with cardiovascular/metabolic diseases remains unproven (see ref. [32] for review). Our data show that 100% of patients with severe OSA had a history of CVD *versus* 40–41% in other groups, but there was no significant difference among groups concerning diabetes mellitus. Among CVD patients, IHD was strongly associated with severe OSA, affecting 61% of patients, independently of cardiovascular comorbidities and cardiovascular risk factors (table 4), except diabetes. In line with this observation, 85% of IPF patients with severe OSA exhibited moderate-to-severe coronary artery calcifications (grade 3–4) on HRCT *versus* only 25–33% of patients with no/mild OSA or moderate OSA. Previous studies have reported a higher prevalence of IHD in IPF patients than in matched chronic obstructive pulmonary disease or emphysema patients for instance, independently of common coronary artery risk factors [13–17]. Patients with significant coronary artery disease at the time of IPF diagnosis appear to have worse outcomes than patients without [16]. Furthermore, the rate ratio of first-time IHD events was shown to be twice higher in IPF patients than in matched controls, even after adjusting for classical CVD risk factors [17]. Therefore, the strong association we observed between incident IPF, severe OSA and IHD suggests that severe OSA could be an important and underdiagnosed risk factor for IHD in IPF patients.

The pathophysiological mechanisms of cardiovascular and metabolic diseases in OSA include sympathetic activation as well as oxidative stress and inflammation because of chronic intermittent hypoxia, leading to endothelial and/or adipose tissue dysfunction [25]. Consistent with this, in IPF patients with moderate-to-severe OSA compared with those with no or mild OSA, we observed a significant increase in systemic oxidative stress as assessed by 8-OH-DG serum levels (reflecting oxidative DNA damage). Interestingly, oxidative stress has also been evidenced in the lung of IPF patients, and is likely to be involved in the pathophysiology of the disease [1]. We therefore compared a panel of selected blood biomarkers shown to have a prognostic value in IPF among groups, to evaluate whether they would be modulated by OSA and/or oxidative stress. We were particularly interested in biomarkers reflecting alveolar epithelial cell activation/injury such as MMP-7 and SPA, because alveolar epithelial cell injury is thought to play a key role in the pathophysiology of IPF [1]. Indeed, these cells are directly exposed to acute changes in alveolar gas composition (*i.e.* hypoxia–reoxygenation cycles) because of repeated sleep apnoeas, which could induce oxidative stress and subsequent cell injury. ICAM-1, a soluble adhesion molecule reflecting endothelial dysfunction, was also studied. Serum levels of ICAM-1 tended to be higher in patients with severe OSA than in other groups (p=0.10). Measurements of epithelial biomarkers provided discordant results: while MMP-7 serum levels were significantly increased in the severe OSA group and correlated well with ODI, SPA levels were not different between groups. Blood concentrations of ICAM-1, SPA and MMP-7 have been shown to be significantly and independently associated with

mortality/disease progression in IPF [33, 34]. However, ICAM-1 and MMP-7 are certainly not specific for IPF inasmuch as they can also be increased in OSA, especially as IHD is associated [35–37]. OSA and IHD may therefore represent potential confounding factors. The increase in MMP-7 (and to a lesser degree in ICAM-1) blood levels observed here might reflect the disease activity of IPF, the presence of OSA or IHD, or both. One limitation of the present study is the relatively small size of our cohort and the fact that blood samples were not available for all patients. It would certainly be interesting to assess whether additional blood biomarkers, such as KL-6 or Surfactant Protein D, may be more specific of alveolar epithelial cell activity/injury in IPF in a larger cohort of IPF patients with and without sleep apnoeas to determine whether their levels are affected or not by OSA.

In conclusion, severe OSA is highly prevalent in patients with newly diagnosed IPF, and is strongly associated with the presence of IHD. We advocate that nocturnal PSG should be performed at the time of IPF diagnosis to detect occult OSA, especially when moderate-to-severe coronary artery calcifications are observed on HRCT scan.

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