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Elevated nocturnal desaturation index predicts mortality in interstitial lung disease

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Abstract. *Background:* Nocturnal desaturation may contribute to long-term pulmonary vascular stress in interstitial lung disease (ILD). We study the prevalence, severity and prognostic utility of nocturnal desaturation across ILD. *Methods:* ILD patients with overnight oximetry (June 2006-August 2008) were reviewed (n=134). Significant nocturnal desaturation was considered as ≥10% of sleep with SpO_2≤90%. Desaturation index (DI) was defined as the number of desaturation events >4%/hr. Covariates, including indices of nocturnal desaturation, were evaluated against mortality. *Results:* Nocturnal desaturation was present in 49 (37%) patients. 31% of patients had pulmonary hypertension (PH) on echocardiography. Increased DI was associated with higher mortality independent of age, gender and BMI (HR 1.04; 95% CI 1.00, 1.06; p=0.009). In separate models, DI and a) elevated brain natriuretic peptide (BNP; HR 1.04; 95% CI 1.00, 1.08; p=0.04); b) moderate-severe PH on echocardiography (HR 3.15; 95% CI 1.24, 8.00; p=0.02); and c) daytime resting SpO_2 (HR 0.92; 95% CI 0.85, 0.99; p=0.04) independently predicted mortality following adjustment for age, gender and BMI. *Conclusion:* Nocturnal desaturation is common and may be severe in ILD. Elevated nocturnal DI predicts higher mortality across ILD, independent of other vascular parameters. This finding may have important implications for the pathogenesis of PH in IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 41-50)*

Key words: nocturnal desaturation; mortality; overnight oximetry; pulmonary fibrosis; pulmonary hypertension

Introduction

Resting hypoxia is frequent in severe diffuse lung disease and is likely to be associated with and contribute to the development of pulmonary hypertension (PH) (1-3). However, PH may occur in early interstitial lung disease (ILD) in the absence of resting hypoxia (3). We have suggested that intermittent nocturnal and exercise-induced hypoxia may be instrumental in the pathophysiology of PH particularly in early ILD, where the PH is 'disproportionate' to the extent of the parenchymal lung disease (1). PH is associated with increased mortality in ILD (2, 4, 5), and markers of PH, such as elevated pulmonary vascular resistance (PVR), are strongly associated with early death (6). More recently, we have shown that elevation in serum brain natriuretic peptide (BNP) levels is a major determinant of mortality across ILD (7). Therefore, it follows that nocturnal hypoxia may be a marker for both mortality and PH in ILD patients.

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Although nocturnal hypoxia is thought to be common in ILD patients (8, 9), it has been traditionally considered to be mild, and of little clinical importance (10). In one small study, nocturnal hypoxia was less severe in ILD patients than in those with chronic obstructive pulmonary disease (COPD) or scoliosis (11). However, maximal fall in oxygen saturation (SpO_2) during sleep is greater in ILD patients than in normal subjects (12, 13), with one study reporting a maximum fall of 13.1% in ILD patients, compared to 4.8% in control subjects (14). Nocturnal hypoxia can occur in the absence of daytime hypoxia (12) and is not closely linked to the severity of the underlying ILD (8).

Thus, in this study we examined the prevalence and severity of nocturnal hypoxia in ILD patients. We explored the role of nocturnal hypoxia as a marker of mortality, and studied its relationship with PH across the ILD population.

Methods

Patient Selection

All ILD patients who had undergone overnight oximetry between June 2006 and August 2008 (n=139) were studied. It is our practice to perform overnight oximetry on all new ILD referrals (n=53) and for oxygen supplementation assessment (n=86). All patients with corresponding pulmonary function, and echocardiography (n=134) were included. Most patients also had serum BNP concentration (n=119), and six-minute walk testing (6MWT, n=99) performed. Ethics approval was in place for local retrospective analysis of clinical data. Demographic and clinical data was collected.

Patients were followed to death, last follow-up or to 19th March 2009. Mortality was determined from hospital patient databases, and confirmed with local physicians when appropriate. Mean follow up was 355 (12months) ± 189 days. Twenty-two deaths occurred (16%) during follow up.

Investigations

a) Overnight Oximetry

The Konica-Minolta Pulsox-300i oximeter was used in all cases. Data was interpreted using Download 2001 (version 2.8.0; *Stowood Scientific Instruments* Ltd) software. Oximetry was performed on room air (n=103), unless patients were using continuous oxygen supplementation (n=31; range 1-6L/min). The Epworth Sleepiness Score was measured in a subset (n=53) of patients (15). Significant nocturnal desaturation was considered present when ≥10% of sleep with SpO_2 <90% (16). DI was defined as the number of desaturation events >4%/hour of sleep. Nocturnal desaturation was considered disproportionate to the severity of the ILD when significant desaturation was present in the presence of relatively preserved pulmonary function (DLco ≥35%) (17).

b) Pulmonary Function Testing

Pulmonary function measurements included total lung capacity, spirometric volumes and DLco. The composite physiologic index (CPI) was calculated as previously described (18). Predicted values calculated according to ATS/ERS guidelines (Jaeger Masterscreen; Cardinal Health UK 240 Ltd) (19-22). End capillary (ear-lobe) blood gas analysis was performed on room air (n=129). Resting hypoxia was considered present if daytime resting SpO_2 <92%.

c) Echocardiography

Trans-thoracic echocardiography was performed in all 134 patients. Right atrial pressure was estimated on the basis of inferior vena cava size and movement on respiration (23). The modified Bernoulli equation was used to calculate right ventricular systolic pressure (RVSP) (24). PH was defined as the presence of either RVSP ≥40mmHg or right heart dilatation, and moderate-severe PH was defined as either RVSP ≥50mmHg or right heart dilatation.

d) Six Minute Walk Testing

6MWT was performed in 99 patients in accordance with ATS/ERS guidelines (25), on supplemental oxygen if patients were on continuous oxygen therapy. Resting and six-minute heart rate and SpO_2 and six-minute walk distance (6MWD) were recorded. Exercise-induced hypoxia was considered present when 6MWT end SpO_2 was ≤88% (26).

Statistical Analysis

All analyses were performed using STATA statistical software (version 10.0; Stata Corp., College

Station, TX). The prevalence of nocturnal hypoxia was determined for the entire cohort, and for patients with resting and exercise-induced hypoxia. The chi-squared test was used for population comparisons.

Severity of nocturnal desaturation was described with regard to duration of desaturation (time with SpO_2 <90%) and degree of desaturation, as previously evaluated in PAH patients (16). The following categories of severity were used:

1. Severity of desaturation by duration of desaturation (time with SpO_2 <90%)
   a) Mild: 11-20% of sleep with SpO_2 <90%
   b) Moderate: 21-50% of sleep with SpO_2 <90%
   c) Severe: >50% of sleep with SpO_2 <90%
2. Severity of desaturation by degree of desaturation
   a) Mild: >10% of sleep SpO_2 86-90%
   b) Moderate: >10% of sleep SpO_2 80-85%
   c) Severe: >10% of sleep SpO_2 <80%

Indices were evaluated against overall mortality using Cox regression analysis. Covariates were chosen *a priori,* and included:

a) Nocturnal hypoxia parameters (DI, total number of desaturation events <90%, minimum nocturnal SpO_2);
b) Cardiovascular Noninvasive Biomarkers (BNP, RVSP and PH on echocardiography);
c) Potential vascular makers (DLco%, KCO%, resting and 6MWT end SpO_2, 6MWD);
d) Other variables (age, gender, body mass index (BMI), FVC% and CPI).

Multivariate survival analysis was performed, adjusting for age, gender and BMI. In order to determine that overall trends were not influenced by a single ILD subgroup, analyses were repeated for the largest subgroup of patients, primary fibrosing ILD (n=63), and following the exclusion of each diagnostic sub-groups in turn (6, 7).

Population comparisons were performed for patients with and without limited fibrosis and with and without PH on echocardiography using Student's t-test or Wilcoxon's ranksum test as appropriate. Markers of nocturnal hypoxia were evaluated against markers of severity of ILD and PH using Pearson's or Spearman's correlation.

Results

Patient Characteristics

Seventy-five (56%) patients were male. Mean age was 59 ± 14 years, and mean BMI 28 ± 7kg/m^2. ILD diagnoses included: primary fibrosing ILD [idiopathic pulmonary fibrosis (IPF, n=27), idiopathic non-specific interstitial pneumonia (NSIP, n=14), fibrotic hypersensitivity pneumonitis (HP, n=22)], sarcoidosis (n=18), organising pneumonia with fibrosis (n=5), connective tissue disease-associated ILD (n=29) and other ILD (n=19). Seventy-two patients were life-long non-smokers, 55 were ex-smokers and seven current smokers (mean pack years 23 ± 16). Baseline parameters are shown in Table 1.

Twenty-three patients (17%) had significant daytime resting hypoxia. Forty-two patients (31%) had PH on echocardiography. Forty-seven (47%) of patients had significant desaturation on 6MWT. Of the 55 who completed the sleep survey, the median Epworth Sleepiness score was eight (range 0-24), 21 (38%) complained of snoring, and ten (18%) of daytime sleepiness.

Patients with significant nocturnal desaturation had significantly lower daytime resting SpO_2, 6MWT end SpO_2 and lower baseline spirometry (Table 1). There was no difference in BNP levels or echocardiographic parameters in patients with or without significant nocturnal hypoxia.

Prevalence of Nocturnal Desaturation

Significant nocturnal desaturation occurred in 49 of 134 (37%) patients. Thirty-eight of 49 (78%) patients with significant nocturnal desaturation did not have resting daytime hypoxia (Table 2). Fifteen of 36 (42%) patients had significant nocturnal desaturation in the absence of exercise desaturation (Table 3). e demonstrate an association between daytime, resting SpO_2 and minimum nocturnal SpO_2 (R=0.33, p=0.0002), but no link between 6MWT end SpO_2 and minimum nocturnal SpO_2. Neither the presence of daytime, resting hypoxia (p=0.22) nor the presence of 6MWT oxygen desaturation (p=0.10) was associated with significant nocturnal desaturation.

Table 1. Baseline Characteristics

Investigations*	Total Cohort‡	Significant Nocturnal Desaturation	No Significant Nocturnal Desaturation	P value *f*
Nocturnal Oximetry				
Desaturation Index	4.18 (0.1 to 83.7)			
Resting SpO_2 (%)	95.4 ± 2.6			
Minimum SpO_2 (%)	76.2 ± 9.9			
% Sleep time with SpO_2 <90%	5.15 (0 to 98.9)			
% Sleep time with SpO_2 <86%	0.94 (0 to 48.7)			
% Sleep time with SpO_2 <82%	0.17 (0 to 36.75)			
SpO_2 dips <90%	2.51 (0 to 81.4)			
Maximal Heart rate	114.0 ± 22.1			
Pulmonary function				
DLco (% predicted)	37.4 ± 16.1	37.4 ±18.1	37.5 ± 15.0	0.98
KCO (% predicted)	67.0 ± 20.9	69.3 ± 21.9	65.7 ± 20.3	0.35
TLC (% predicted)	68.8 ± 18.0	67.8 ± 16.2	69.3 ± 19.0	0.67
FEV_1 (% predicted)	63.8 ± 19.8	58.8 ± 21.6	66.7 ± 18.2	0.03
FVC (% predicted)	65.5 ± 21.3	60.0 ± 21.2	68.7 ± 20.8	0.03
SpO_2 (%)† (n=129)	93.4 ± 5.3	92.1 ± 7.0	94.0 ± 3.9	0.05
PaO_2 (kPa) † (n=129)	9.5 ± 1.8	8.9 ± 1.6	9.8 ± 1.8	0.004
$PaCO_2$ (kPa) † (n=129)	5.2 ± 0.7	5.3 ± 0.8	5.2 ± 0.6	0.46
Composite physiologic index	53.5 ± 14.6	54.4 ± 15.8	52.9 ± 14.0	0.59
Echocardiography				
RVSP (mmHg) (n=86)	41 ± 13	42 ± 13	40 ± 13	0.31 ∫
Pulmonary acceleration time (ms) (n=78)	106 ± 31	98 ± 29	111 ± 32	0.06
Fractional shortening (n=122)	37 ± 8	38 ± 9	36 ± 7	0.28
BNP (pmol/L) (n=119)	6 (1-228)	5 (1-228)	6 (1-177)	0.57 ∫
6 minute walk test (n=99)				
6MWT end SpO_2 (%)	88.0 ± 7.3	85.7 ± 8.5	89.3 ± 6.1	0.02
6MW distance (m)	327 ± 123	331 ± 117	324 ± 128	0.68 ∫

* n=134, unless otherwise specified
† Arterial blood gases performed at rest on room air
‡ Mean ± standard deviation or Median (range) as appropriate
∫ Student's t-test or Wilcoxon rank-sum test (∫) as appropriate.

Table 2. Prevalence of Significant Nocturnal Desaturation in patients with and without Daytime Resting Hypoxia (SpO_2<92%)

	Awake, Resting Normoxia*	Awake, Resting Hypoxia*
No Significant Nocturnal Desaturation	73	12
Significant Nocturnal Desaturation	38	11

* Chi^2 test for population comparisons, p=0.22

Table 3. Prevalence of Significant Nocturnal Desaturation in patients with and without Desaturation on 6MWT (SpO_2≤88%)

	No Desaturation on 6MWT*	Desaturation on 6MWT*
No Significant Nocturnal Desaturation	37	26
Significant Nocturnal Desaturation	15	21

* Chi^2 test for population comparisons, p=0.10

Severity of Nocturnal Desaturation

When severity of nocturnal desaturation was assessed with regard to percentage of sleep time with SpO_2 <90%, 71% patients with nocturnal desaturation had mild or moderate desaturation, but 29% of patients met the criteria for severe desaturation. Similarly, when severity of nocturnal desaturation was assessed by the degree of oxygen desaturation, 88% patients with nocturnal desaturation had mild to moderate desaturation, but 12% had severe disease (Table 4). There was 68.8% agreement between these two severity scales (Weighted Kappa 0.42; p=0.0002).

Table 4. Severity of Nocturnal Desaturation: a) Classified by % of sleep time with SpO_2<90% and b) Classified by Degree of Nocturnal desaturation

Severity of Nocturnal Desaturation	Number of patients (%) *
Duration of Sleep time with SpO_2 <90%	
- Mild: 11-20%	16 (32.6%)
- Moderate: 20-50%	19 (38.7%)
- Severe: >50%	14 (28.6%)
Degree of Nocturnal Desaturation	
- Mild: >10% of sleep with SpO_2 86-90%	33 (67.3%)
- Moderate: >10% of sleep with SpO_2 80-86%	10 (20.4%)
- Severe: >10% of sleep with SpO_2 <80%	6 (12.2%)

* Percentage given of patients with nocturnal desaturation (n=49)

Survival Analysis

Increased mortality was associated with elevated nocturnal DI and number of SpO_2 dips <90%, following adjustment for age, gender and BMI (Table 5). Higher mortality was also linked to the established cardiovascular non-invasive biomarkers, BNP and moderate to severe PH on echocardiography. There was no link between mortality and markers of severity of the underlying ILD (including FVC and CPI).

On bivariate analysis, a) elevated DI (HR 1.04; 95% CI 1.00, 1.08; p=0.04) and BNP (HR 1.01; 95% CI 1.00, 1.02; p=0.03); and b) elevated DI (HR 1.04; 95% CI 1.01, 1.06; p=0.006) and the presence of moderate to severe PH on echocardiography (HR 3.15; 95% CI 1.24, 8.00; p=0.02) and c) elevated DI (HR 1.05; 95% CI 1.01, 1.09; p=0.01) and daytime resting SpO_2 (HR 0.92; 95% CI 0.85, 0.99; p=0.04) were independently associated with increased mortality following adjustment for age, gender and BMI.

Using stepwise, multivariate regression, the combination of variables most strongly associated with increased mortality was the model including elevated DI and moderate to severe PH on echocardiography.

These findings remained significant following adjustment for the use of supplemental oxygen. Our results remained significant for the largest diagnostic subgroup (primary fibrosing ILD) and following the exclusion of each smaller ILD subgroup in turn, in-

Table 5. Predictors of Mortality: Cox regression analysis

	Hazard Ratio	P value
Nocturnal Oximetry		
Desaturation index	1.03 (1.00, 1.05)	0.03*†‡∫§
Number of SpO_2 dips <90%*	1.03 (1.01, 1.06)	0.02†‡∫§
Minimum SpO_2	0.97 (0.93, 1.01)	0.10
Maximum fall in SpO_2	1.02 (0.97, 1.07)	0.47
Cardiovascular Noninvasive Biomarkers		
Brain Natriuretic Peptide	1.01 (1.00, 1.02)	0.04*§
Right Ventricular Systolic Pressure	1.02 (0.99, 1.06)	0.18
Moderate-Severe PH on echocardiography	2.64 (1.13, 6.20)	0.03*§
Potential Vascular Markers		
DLco %	0.99 (0.97, 1.02)	0.74
KCO %	1.00 (0.98, 1.02)	0.94
Daytime, resting SpO_2	0.94 (0.88, 1.01)	0.10
6MWT end SpO_2	0.95 (0.90, 1.01)	0.13
6MWT distance	1.00 (0.997, 1.01)	0.61
Other		
Age	0.99 (0.96, 1.02)	0.62
Male Gender	0.92 (0.40, 2.14)	0.85
Body Mass Index	0.96 (0.89, 1.04)	0.35
FVC %	0.99 (0.97, 1.01)	0.32
Composite Physiologic Index	1.01 (0.97, 1.04)	0.71

* Remains significant following adjustment for age, gender and body mass index.
† Remains significant following adjustment for age, gender and body mass index and brain natriuretic peptide.
‡ Remains significant following adjustment for age, gender and body mass index and moderate-severe PH on echocardiography.
∫ Remains significant following adjustment for age, gender and body mass index and daytime, resting SpO_2.
§ Remains significant following adjustment for age, gender and body mass index and the use of supplemental oxygen.

dicating that results were not overly influenced by a specific ILD subgroup.

Nocturnal Hypoxia and PH

In order to determine whether nocturnal hypoxia is linked to disproportionate PH, we studied patients with limited ILD (DLco>35%), in whom nocturnal desaturation is disproportionate to the underlying ILD. Significant nocturnal desaturation was present in 21 (32%) of the 65 patients with limited fibrosis. There was no difference in any nocturnal oximetry parameters between patients with limited and extensive fibrosis. In patients with limited fibrosis, PH on echocardiography was associated with markers of nocturnal hypoxia, including increased DI and number of SpO_2 dips <90% (Table 6).

In order to study whether the severity of nocturnal hypoxia reflected the degree of vascular impairment or the severity of the underlying ILD, we studied the correlation between parameters of nocturnal hypoxia and tricuspid regurgitant jet velocity (TRJV) and CPI levels in patients with limited fibrosis. Parameters of nocturnal hypoxia correlated significantly with TRJV measurements (Table 7). However, no association between nocturnal hypoxia and the severity of the underlying ILD (as judged by CPI) was found.

Table 7. Correlation of Parameters of Nocturnal Hypoxia in patients with Limited Fibrosis

	Desaturation Index		Number of SpO_2 dips <90%		Minimum SpO_2	
	R*	p	R*	p	R*	p
TRJV	0.33	<0.05	0.33	<0.05	-0.34	0.04
CPI	0.14	0.29	0.10	0.47	-0.01	0.93

* Spearman's Non-parametric Correlation Coefficient (R)

Discussion

In this study, we show in ILD patients, that nocturnal desaturation is common, can be severe, and is unrelated to daytime, resting or exercise-induced hypoxia. We have previously shown across ILD, that pulmonary vascular disease (PVD) is predictive of increased mortality (6, 7). In the current study, we show that elevated nocturnal DI is linked to increased mortality across ILD subgroups, and that in limited ILD, nocturnal desaturation is linked to the severity of the PVD, rather than the severity of the pulmonary fibrosis. These findings suggest a link between intermittent nocturnal desaturation and PVD, and its associated mortality. Although our findings cannot immediately be applied to clinical practice without prospective evaluation, they may

Table 6. Comparison of patients with limited fibrosis with and without PH

	Pulmonary Hypertension (n=12)	No Pulmonary Hypertension (n=57)	P value*
Nocturnal Oximetry			
Desaturation index	16.5 ± 5.8	7.5 ± 10.7	0.03†
Number of SpO_2 dips <90%	14.1 ± 21.4	5.4 ± 8.6	0.03†
Minimum SpO_2	73.0 ± 10.7	78.4 ± 9.6	0.05†
Maximum nocturnal fall in SpO_2	20.7 ± 7.9	17.2 ± 9.6	0.10†
Cardiovascular Noninvasive Biomarkers			
BNP	29.2 ± 61.3	8.0 ± 10.5	0.03†
Potential Vascular Markers			
DLco %	44.6 ± 7.8	51.4 ± 12.4	0.04†
KCO %	76.2 ± 12.9	79.8± 17.4	0.50
PaO_2	9.7 ± 1.9	10.3 ± 1.6	0.24
6MWT end SpO_2	89.0 ± 6.6	92.2 ± 3.7	0.04
6MWT distance	332 ± 129	377 ± 104	0.34†
Other			
Age	63 ± 12	57 ± 12	0.07
BMI	29.1 ± 4.5	30.2 ± 7.2	0.59
FVC %	68.2 ± 23.0	75.9 ± 21.3	0.38†
CPI	47.4 ± 8.7	41.3 ± 11.9	0.10†

* Student's t-test used for population comparison except for non-parametric variables when Wilcoxon's ranksum test was used (†)

have profound implications with regard to the pathogenesis of PH in ILD.

Nocturnal Hypoxia is Common in ILD

We show that nocturnal desaturation is frequent in ILD patients, commonly occurring in the absence of resting or exercise-induced hypoxia. In our study, 37% had significant nocturnal desaturation, and the majority did not have resting (78%) or exercise-induced (42%) hypoxia. We found no association between nocturnal desaturation and resting or exercise desaturation, suggesting that nocturnal hypoxia cannot be excluded on the basis of resting or exercise normoxia. Our results confirm and extend observations of earlier studies, in which a high prevalence of nocturnal hypoxia in ILD has been reported (8, 9).

Severity of Nocturnal Hypoxia in ILD

In ILD, nocturnal hypoxia is often mild, and considered less important than in other conditions such as COPD, or scoliosis (10, 13, 27). Indeed, our results confirm that nocturnal desaturation is usually mild to moderate in severity. However, we also demonstrate the presence of a sub-group of ILD patients with severe nocturnal hypoxia. Striking nocturnal hypoxia may be due to the underlying ILD, when severe. However, nocturnal hypoxia may occur in the context of mild ILD and may be disproportionate to the extent of the underlying ILD. In our study, 49% of patients with significant nocturnal desaturation had extensive ILD, but the remainder had limited fibrosis and disproportionate nocturnal hypoxia.

Nocturnal hypoxia is associated with increased mortality across ILD

We show that nocturnal hypoxia (DI, and number of SpO_2 dips<90%) is associated with increased mortality across ILD, following adjustment for age, gender and BMI. In advanced ILD there appears to be a final common pathway across ILD disorders. In one study, survival did not differ between biopsy-proven IPF and NSIP in patients with DLco ≤35% (17), and in another study, patients with severe HP had similar outcomes to IPF patients (28). We have suggested that pulmonary vasculopathy may contribute to this final common pathway across the ILD population (6, 7). In support of this hypothesis, we have demonstrated that across ILD, mortality is strongly linked to parameters of PVD including increased PVR and serum BNP levels (6, 7). We have proposed that nocturnal hypoxia may precede and contribute to the development of PVD in ILD patients (1). Thus, it follows that the link between nocturnal hypoxia and mortality may reflect its link to PVD. This hypothesis is further supported by the fact that elevated BNP and moderate to severe PH at echocardiography were also associated with increased mortality. In fact, elevated DI provided additional, independent prognostic information over these vascular markers (BNP and echocardiography). Longer, prospective studies across unselected ILD patients are required to clarify the prognostic role of nocturnal hypoxia.

Nocturnal hypoxia is associated with PH in limited ILD

We show that parameters of nocturnal hypoxia correlate with markers of severity of PH (TRJV) but not with the underlying ILD (CPI). This finding supports our hypothesis that disproportionate nocturnal desaturation is a marker for PVD. This theory is further supported by a study of chronic lung disease patients (including 16 with ILD), in which nocturnal desaturation was linked to pulmonary hemodynamic impairment, but not to pulmonary function or arterial blood gases (29). In another ILD study, nocturnal hypoxia was not linked to the severity of pulmonary function impairment (8). In the current study, the correlation between markers of nocturnal hypoxia and TRJV was weak, with no R^2 value above 0.2, indicating that even in cases of limited fibrosis, nocturnal hypoxia is likely to be a non-specific marker, reflecting both pulmonary vascular, and interstitial disease processes.

Nocturnal Hypoxia and the pathogenesis of PH in ILD

Nocturnal hypoxia occurs commonly in patients with pulmonary arterial hypertension (16). We have suggested that in ILD, intermittent nocturnal hypoxia may play a role in the development of PH disproportionate to the underlying ILD (1). However, it should be noted that in patients with

underlying CTD, such as systemic sclerosis, pulmonary arterial hypertension is a frequent complication independent of concomitant hypoxia. There are several potential mechanisms whereby intermittent nocturnal hypoxia may contribute to the pathogenesis of PH in ILD. Repetitive episodes of acute hypoxia result in acute elevation in PVR (30) eventually leading to vascular remodelling. In ILD, episodes of nocturnal oxygen desaturation are associated with acute rises in arterial endothelin-1 (ET-1) levels (9), an important mediator in pulmonary vascular remodelling. Nocturnal hypoxia may lead to pulmonary vascular remodelling and established PH via intermittent nocturnal surges of ET-1, as well as hypoxia-mediated endothelial dysfunction. Intermittent nocturnal hypoxia may also result in the resetting of peripheral chemoreceptors, lowering the hypoxic drive, as seen in other nocturnal hypoventilation syndromes (31, 32). In some cases, disproportionate nocturnal hypoxia may be due to an underlying sleep disorder (such as obstructive sleep apnoea, OSA). It has been proposed that negative intra-thoracic pressures in ILD may lead to increased upper airway collapsibility, and subsequent OSA (33). However, the true prevalence of OSA in IPF is unknown, as the largest study exploring this issue is limited by selection bias (33). A recent study of 34 unselected IPF patients showed 59% prevalence of OSA (34). Larger studies in unselected patients are required to further characterise the role of sleep-disordered breathing in ILD.

Limitations

In this study, and as argued by Clark et al (8), we chose to study ILD in general, rather than a specific ILD subgroup such as IPF. We have previously shown that pulmonary vascular markers strongly predict mortality across ILD (6, 7) and so we hypothesised that other pulmonary vascular markers may also predict mortality across ILD. However, as in our earlier work, we considered it important to establish that our results were not dominated by a single ILD subgroup (6, 7). Thus, we analyzed the data for the largest sub-group (primary fibrosing ILD), and following exclusion of each diagnostic subgroup in turn (as the alternative strategy of examining each sub-group in isolation was precluded by small subgroup numbers). Results remain highly statistically significant, indicating that no ILD subgroup had overly influenced our findings.

Secondly, this study was limited by the lack of formal polysomnography. In the absence of polysomnography, it is not possible to distinguish those patients who desaturate due to concomitant OSA. Although the true prevalence of OSA in this population is unknown, it is likely to be higher than in the general population (33)(34). Further unselected studies of ILD patients with formal polysomnography are necessary to quantify the contribution of OSA in the nocturnal oxygen desaturation observed in these patients.

Our study was also limited by the lack of invasive pulmonary haemodynamic data. The definition of PH involves having a mean pulmonary artery pressure ≥25mmHg at right heart catheter (RHC) (35). Invasive testing also allows distinction between pre-capillary PH (pulmonary capillary wedge pressure, PCWP ≤15mmHg) and post-capillary PH (PCWP >15mmHg), which is not uncommon in ILD patients. However, it is not practicable for all ILD patients to undergo RHC as it is a moderately invasive procedure. In clinical practice, echocardiography is often used as a non-invasive surrogate to screen for PH. However, it is clear that echocardiography is moderately accurate at best in the context of ILD, overestimating pulmonary pressures in mild cases, and underestimating pulmonary pressures in more severe disease (36). Nevertheless, echocardiography remains the most accurate non-invasive method to assess the pulmonary vasculature, and our study reflects usual clinical practice (6). Serum BNP levels, another non-invasive marker frequently used in clinical practice (37), are also not specific for pulmonary vascular disease, as BNP levels may also be elevated in left heart disease. However the incidence of previous cardiac disease in our cohort was low, as 110 (82%) of our cohort had no cardiac history.

Finally, our study was necessarily limited by its retrospective nature, and patient selection. However, a wide range of disease severity was evaluated, and we suggest that the range of disease severity reflects real-life clinical practice. Nevertheless, exact clinical utility with reference to unselected ILD cases cannot be extrapolated from our data.

Conclusion

Nocturnal desaturation is common in ILD, and may be disproportionate to the underlying interstitial fibrosis. Elevated nocturnal DI strongly predicts increased mortality across ILD, providing additional prognostic information over other known cardiovascular noninvasive biomarkers, including BNP and the presence of PH on echocardiography. In patients with limited fibrosis, elevated DI is a marker for PH. These findings need to be confirmed in longer-term studies before widespread clinical application is recommended. Although our findings cannot immediately be applied to clinical practice, they may have profound implications with regard to the role of intermittent nocturnal hypoxia in the pathogenesis of PH in ILD.

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