The unresolved issue of oxygen therapy in lung fibrosis: Some clues from a Spanish cohort

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Abstract. Indication of oxygen therapy in fibrotic interstitial lung diseases is not standardized and its specific requirements are not well defined. The objective of this study was to evaluate ambulatory oxygen therapy features in lung fibrotic patients. Clinical and exploratory data, including 6-minute walking test and pulmonary hypertension, from one hundred and seven patients with fibrotic interstitial lung disease that received ambulatory oxygen treatment were studied. In up to 40% of cases the prescription of oxygen therapy was made after performing a 6-minute walking test. Patients who required ambulatory oxygen only during exercise presented a mild to moderate reduction of the predicted %FVC (62.1 ± 19) and DLCO (49 ± 14.4) while patients who had respiratory failure at rest (mean PaO2 51.9 ± 6.7) presented a moderate reduction of %FVC (56.8 ± 15.6) but a severe decrease of %DLCO (31.67 ± 12). Pulmonary hypertension (PH) was evaluated in 47.7% of patients and occurred in 60.8% of them. In conclusion, there is no pulmonary functional predictor of oxyhaemoglobin desaturation during exercise. PH is frequently associated with interstitial lung diseases, mainly when respiratory failure at rest appears. The heterogeneity of the patients and limitation of retrospective studies could be the cause of the tributes for potential benefits of oxygen treatment in interstitial lung diseases.

Keywords: Interstitial lung disease, oxygen therapy, 6-minute walking test, pulmonary hypertension

Introduction
Interstitial lung diseases (ILD) refer to a heterogenous group of pulmonary rare diseases with varying degrees of lung inflammation and fibrosis [1-5]. A common feature of fibrotic ILD patients is that they often progress and develop significant oxygen desaturation during exercise, exercise limitation, exertional dyspnea and reduced quality of life. Idiopathic pulmonary fibrosis (IPF) is the most frequent and lethal fibrotic ILD. Recently, advances have been developed in order to improve the clinical management of these patients, however non-pharmacological treatment remains poorly evaluated. Nowadays, the indication of oxygen therapy in lung fibrosis is done following the established rules for obstructive lung disease (COPD), although IPF and other less frequent lung fibrotic disorders are completely different in clinical and pathogenic features [1, 2]. Few studies that evaluate the benefits of oxygen treatment in IPF have been published, most of them are based on ambulatory oxygen treatment at rest, with a few number of patients and huge variability in oxygen conditions. On the other hand, comorbidities associated to continuous or repeated oxygen desaturation (SatO2<90%) are widely recognized. Specifically, pulmonary hypertension (PH) (defined as the main pulmonary arterial pressure ≥ 25 mmHg) is frequently associated with lung fibrosis [6] and has an adverse effect on the prognosis, directly related to its severity [6]. Although hypoxemia has been described as the main cause of associated PH, recent studies suggest that it could also result of vascular remodeling associated to the fibrotic process. Detecting early hypoxemia during exertion is crucial to elucidate the implication of this effect on the progression of the disease. The 6-minute walking test (6MWT) is an easy and non-invasive test, recently

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included in the clinical setting to monitor the progression and pharmacological effects in lung fibrosis, that can
detect oxygen desaturation during walking from early
stages [7-11]. Recent data suggest that ambulatory oxygen
improves exercise tolerance in patients with lung fibrosis
[12, 13]. Also, the updated guidelines recommended the
use of supplemental oxygen in IPF with respiratory failure.
However, the level of evidence for its benefit was very low
and no clear indication was included for oxygen therapy
during exercise [2]. Before conducting a prospective study
about the possible benefits of oxygen therapy in lung
fibrosis, basic questions in this field should still be
answered such as specific requirements of supplemental
oxygen treatment in lung fibrotic patients, or when and
how the treatment is usually prescribed in these patients.
The aims of the present study were: a) to evaluate the
current management and specific requirements of patients
with IPF and other lung fibrotic disorders who are
prescribed ambulatory oxygen therapy, b) to assess the
possible predictor factors to suspect oxygen desaturation
and the relationship with the presence of PH in these
patients.

Method
This multicenter and observational study included 8
hospitals that integrate the multidisciplinary clinical-
radiological-pathological expert group for the study of ILD
in Catalonia, Spain (CRAMPID). A total of 107 patients
with ILD who required ambulatory oxygen therapy were
included in this study during 2011. All patients accepted
the use of their data for epidemiological studies and
provided written informed consent. This study was
approved by the Ethics Committee of Clinical
Investigation of each hospital. Patients who presented with
respiratory failure because of an acute exacerbation were
excluded. Different entities were diagnosed based on the
ATS/ERS multidisciplinary consensus statement [1, 2].
Time from diagnosis to oxygen prescription, anthropometric, radiological, and lung functional features
were included. Data related to the 6MWT such as
limitation of tolerance to exercise or oxyhaemoglobin
saturation was recorded. The overall characteristics of
domiciliary oxygen therapy included were: type of oxygen
devices, flow rates used both at rest and under effort, and
prevalence in the use of valve system. In terms of co-
morbidity, the information about associated PH was also
included. These were prevalence of echocardiography
performed at the time of oxygen prescription, and the
presence or absence of associated PH and its reported
values.

Statistical analysis
The results of analyses are expressed as mean ±
standard deviation (SD) for quantitative variables and as
percentages for qualitative variables. Chi-square analysis
and Fisher exact test were used to compare the frequency
of binomial variables. Statistical significance was set at p <
0.05 in all cases. Data analysis was performed with SPSS
program V.19.0.

Results
The anthropometric, radiological and functional data of
the patients included in the study can be seen in Table 1
and Table 2, respectively.

| TABLE 1
| ANTHROPOMETRIC AND RADILOGICAL DATA |
|-----------------|-----------------|
| Characteristics  | Value           |
| Gender          |                 |
| Men             | 51 (48%)        |
| Women           | 56 (52%)        |
| Age             | 71±13           |
| Radiological UIP|                 |
| Pattern         | 48              |

Data are presented as mean ± SD. UIP: Usual interstitial pneumonia.

| TABLE 2
| FUNCTIONAL DATA |
|----------------|----------------|
| Variable       | Diagnosis       | Oxygen Therapy  |
|                |                 | Initiation      |
| %FVC           | 62 ± 17         | 53 ± 17         |
| %TLC           | 71 ± 19         | 63 ± 20         |
| %DLCO          | 46 ± 18         | 31 ± 15         |
| PaO2mmHg       | 65 ± 12         | 59 ± 10         |
| AaPaO2 mmHg    | 36 ± 15         | 48 ± 23         |

Data are presented as mean ± SD. UIP: Usual interstitial pneumonia.

The patients’ diagnoses included IPF (n=46), chronic
hypersensitivity pneumonitis (n=18), lung fibrosis
associated with connective tissue disease (n=18), combined
pulmonary fibrosis with emphysema (n=7), fibrotic
nonspecific interstitial pneumonia (n=6), and non-
classifiable lung fibrosis (n=13). All patients were carriers
of ambulatory oxygen therapy. Time from diagnosis to
prescription of ambulatory oxygen was 29.5 ± 24 months.
In 40% of patients (n=43) the prescription of this therapy
was made after performing a 6MWT, which evidenced
desaturation of arterial oxyhaemoglobin induced by
exercise (SpO2 < 90%). In this group, the mean partial
arterial oxygen pressure (PaO2) at rest was 71.9 ± 4.8.
Effort limitation observed at the moment of prescribing
oxygen therapy was 259 ± 121 meters. Minimum
saturation of arterial oxyhaemoglobin observed during
performance of 6MWT was 82 ± 6 % SpO2 (from 98% up
to 66%). Oxygen flows required at rest and during exercise
were 2 ± 1L (from 0 to 4L) and 3 ± 2 L (from 2 to 6L),
respectively. No significant differences in the lower mean
values of SpO2 during 6MWT and oxygen flow
requirements during the effort were found among the
included entities. The oxygen device more frequently used
was the portable liquid one (58%). Almost all the
prescribed oxygen devices had no valve system (n=104).
The mean percentage (%) of predictive value of forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO) when ambulatory oxygen was required was 53 ± 17 and 31 ± 15, respectively. Patients who required ambulatory oxygen only during exercise presented a mild to moderate reduction of predicted % FVC (62, 1 ± 19) and DLCO (49 ± 14.4), while patients with respiratory failure at rest (mean PaO2 51.9 ± 6.7) presented a moderate reduction of %FVC (56.8 ± 15.6) and a severe decrease of %DLCO (31.67 ± 12). There was no statistically significant relationship between FVC or DLCO values and the ambulatory oxygen requirement. However, when data was analyzed separately depending on the reason of oxygen prescription, a positive correlation between %FVC and PaO2 (r = 0.94, p = 0.02) was observed in patients with oxygen treatment only during exercise, while patients with respiratory failure at rest only during exercise presented a positive correlation between %DLCO and PaO2 (r = 0.77, p=0.06).

Echocardiography was performed in 51 patients (47.7%). PH was occurred in 30 patients (60.8%), of whom 19 had a systolic arterial pulmonary pressure (sPAP) ≥50 mmHg. Twenty-one patients (39.2%) that developed oxygen desaturation during exercise did not present HP. Mean values of sPAP observed were 53.50 ± 16.57 mmHg (from 26 up to 114). Right heart catheterization was performed when the estimated sPAP was ≥50 mmHg. There was a statistically significant association between the presence of HP and DLCO below 50% of predictive value (p = 0.036), with a sensitivity of 76% and a specificity of 56.3%. A predictor of HP development based on values of DLCO below 35% improves specificity (93.8%) but it loses sensitivity (32%, see Table 3). The mean value of HP at the time of oxygen prescription because of respiratory failure at rest was 64.8 ± 18.8 mmHg, while patients who required oxygen treatment only during exercise had a mean value of about 34 ± 9 mmHg. No significant association was found between the presence of associated PH and oxyhaemoglobin desaturation during exercise. However, a predictor of PH development based on desaturation of arterial oxyhaemoglobin of <82% would have a sensitivity of 54.5% and a specificity of 66.7%.

### Discussion

Our study shows some characteristics of patients with IPF and other fibrotic lung diseases that require ambulatory oxygen therapy, which differ from those of COPD patients. The prescription of ambulatory oxygen in fibrotic lung patients was performed after a few years from diagnosis. Almost in a half part of these patients oxygen treatment was needed only during exercise and the flux rate was commonly higher than for COPD patients [14]. Our results indicated that oxygen desaturation during exercise can be observed at early stages of the disease. Moreover, patients with effort desaturation demonstrated a correlation between PaO2 and FVC while PaO2 was only correlated with DLCO in patients with respiratory failure at rest. In the natural course of patients with lung fibrosis there is a period in which arterial oxygen desaturation occurs in response to a significant stress. During exercise the imbalance between the ventilation-perfusion ratio increases, oxygen diffusion worsens and partial oxygen pressure in mixed venous blood decreases [15, 16].

Previous studies have shown that the adverse prognostic significance of 6MWT desaturation may reflect either progression of fibrotic disease or the presence of early PH [17]. So, it is highly advisable that the 6MWT is very important in the follow up from the time of the IPF diagnosis to better determine not only oxygen requirement but also to monitor some signs of disease progression [4, 18, 19]. On the other hand, the present cohort showed a high prevalence of associated PH, mainly when respiratory failure at rest appears. Neither oxyhaemoglobin desaturation during exercise nor respiratory failure at rest had a statistically significant association with PH. However, higher risk for associated PH was observed when DLCO was under 50% of predictive value or desaturation of arterial oxyhaemoglobin was below 82%. DLCO, a non-specific marker that can be altered because of multiple factors, is reduced in fibrotic diseases [20].

In 2007, Hamada et al [21] showed a negative correlation between DLCO <40% of predicted value and sPAP (sensitivity 65% and specificity 94%). These data together with our results suggest that the screening for associated PH based on DLCO values present a high sensitivity when DLCO is below 50% of predicted value. This sensitivity decreases when DLCO declines down to 35% of predicted value, while specificity improves. Moreover, not all patients presenting desaturation at effort develop PH, suggesting that although hypoxia may play an important role, it is not the only cause of PH. Historically, the relevance of PH associated with underlying lung disease has been under-recognized. Nowadays there is a better known entity more commonly present when underlying fibrosis is severe [6], but it may appear at any stage of the IPF. The presence of PH is a worse prognostic determinant in fibrotic lung patients [2].

The sPAP >50mmHg on echocardiography has been associated with a median survival of 0.7 years compared to 4.1 years for a sPAP of 36-50mmHg [22]. Our results show that patients with respiratory failure usually present a sPAP >50 mmHg and only patients with a severe decline of oxyhaemoglobin desaturation (<82%) during exercise develops HP but with lower sPAP. Exercise-induced hypoxia occurs in patients with overt PH but may also precede and contribute to the development of PH in fibrotic lung patients [17]. Because of this, severe hypoxemia at rest or during exercise should be corrected to avoid worsening of PH. Therefore, the screening for oxyhaemoglobin desaturation during exercise and for

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**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%DLCO &lt;35</td>
<td>32</td>
<td>93.8</td>
<td>0.052</td>
</tr>
<tr>
<td>%DLCO &lt;50</td>
<td>76</td>
<td>56.3</td>
<td>0.036</td>
</tr>
</tbody>
</table>

DLCO: Carbon monoxide diffusion capacity
associated PH should be performed not only in advanced stages of the fibrotic lung disease, a good prognostic marker to suspect it could be a decrease of DLCO under 50% of the predictive value.

This study has several limitations due to its retrospective nature that could introduce restrictions in the analysis of the collected data. First of all, the pathogenic heterogeneity of the recruited cases and the limited number of patients for each specific rare disease does not allow comparing the results analyzed by the different groups. However, the common factor was that all the included fibrotic lung patients developed a fibrotic progression that required ambulatory oxygen treatment and there were common characteristics observed for all patients that differed from COPD patients. It could be possible that patients included because of oxygen failure at rest would first developed oxygen desaturation during exercise, but only a prospective study could evaluate this context. Secondly, the lack of some data in some cases such as for HP evaluation has limited the power of the obtained results, so the conclusions in these cases are preliminary. However, almost all previous studies evaluating oxygen treatment in fibrotic lung patients were also retrospective in nature, which is the main reason for the very low evidence in the oxygen treatment recommendation in IPF patients.

In summary, this study shows the specific oxygen requirements that IPF and other rare fibrotic lung diseases present and points to the relevance to prospectively test the potential benefits of an optimal oxygen therapy in IPF patients.

Acknowledgements
The authors want to thank Daniel Cuadras, from Statistical Support Services (CAIBER-UCICEC-IDIBELL) for his help in statistical analyze of the data report, and also Actelion© for its support to the CRAMPID study group meetings from 2008 to 2012.

Conflict of Interest
The authors declare that they have no competing interests.

References