Improving Home Oxygen Therapy In Patients With Interstitial Lung Diseases (ILDs): Application Of A Portable Non-Invasive Ventilation (NIV) Device

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Research

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Abstract

Background: Proper adjustment of arterial oxygen saturation (SaO_2) during daily activities in interstitial lung disease (ILD) patients requiring long-term oxygen therapy (LTOT) is challenging. Given the multifactorial nature of the limited exercise tolerance in patients with ILDs, the isolated use of oxygen therapy may not be enough. As demonstrated previously in COPD patients, the use of a portable non-invasive ventilation (NIV) device combined with oxygen therapy may prevent the falling of oxygen saturation during exercise, due to an increased activation of respiratory muscles that could lead to an improvement of exercise tolerance. We sought to assess in patients diagnosed with ILD who are in need of oxygen therapy, the effect of associating a portable NIV to improve oxygen parameters and the distance covered during the 6 minutes walking test (6MWT).

Methods: We conducted a prospective observational study in patients with ILDs. After a clinical characterization, we performed 6MWT in two different situations: using a portable oxygen concentrator with the regular flow used by the patient during their daily life activities and afterwards adding the additional support of a NIV. The oxygen saturation parameters were registered with a portable oximeter.

Results: We included 16 patients with different ILDs who have oxygen therapy prescribed. The use of NIV associated with oxygen therapy in comparison with the use of oxygen therapy alone showed an increase of the average SaO_2 [91% (88-93) vs 88% (86-90); $p=0.0005$] and a decrease in the percentage of time with oxygen saturation $<90\%$ (CT90): 36% (6-56) vs 58% (36-77); $p<0.0001$. There were no changes in the 6MWT distance: 307m (222-419) vs 316m (228-425); $p=0.10$

Conclusions: In our study the use of a portable NIV system associated with LTOT during exercise showed beneficial effects, especially improvement of oxygen saturation.

Background

Diffuse interstitial lung diseases (ILDs) are a heterogeneous group of respiratory pathologies characterized by inflammation and subsequent fibrosis of the space located between the basal membrane of the alveolar epithelium and the capillary endothelium. Their natural history entails, in most cases, a progressive clinical, radiological and functional deterioration, progressing to lung fibrosis over the subsequent years. ILD incidence is 26–32 cases/100,000 and they are associated with high morbidity and mortality [1]. Dyspnea is the most common symptom and, for most patients the most crippling one, [2] often accompanied by unproductive cough. The onset of the symptoms is slow but usually presents a progressive worsening over the years.

The presence of dyspnea of multifactorial origin is the main symptom presented by patients that limits the performance of their daily activities and involves a significant deterioration of their quality of life, affecting their social and personal environment. This is explained by a limitation on exercise, generated

by an impaired arterial oxygenation [3]. The main mechanism causing pulmonary arterial hypoxemia in patients with ILDs is the imbalance in the ventilation-perfusion ration (VA/Q) due to the interstitial space occupation and progressive destruction of alveolar units, as well as the limitation of oxygen diffusion from the alveoli into the capillaries [4]. Patients with ILDs present an excessive increase in respiratory rate during exercise, with less recruitment of tidal volumen (Vt), in addition to an increased dead space/tidal volume ratio (RV/Vt). All these factors lead to a worsening of the ventilation-perfusion relationship, as well as a decrease in the diffusion and consequently of the partial pressure of oxygen in mixed venous blood. These factors explain the drop in PaO₂ induced by exercise in patients with ILDs and is one of the main factors related to poor prognosis [5, 6].

The Royal College of Physicians recommends LTOT in patients with ILDs presenting a PaO₂ < 60 mmHg at rest (FiO₂ 0.21) or those showing an oxygen saturation by pulse oximetry of less than 90% during the 6-min walking test (6MWT) [7]. Oxygen therapy has also been recommended by the international guidelines of diagnosis and treatment for idiopathic pulmonary fibrosis (IPF) based on pathophysiological concepts and data extrapolated from patients with chronic obstructive pulmonary disease (COPD). A retrospective study of patients with different ILDs showed that home oxygen increased exercise tolerance and decreased dyspnea [8, 9]. Recently, a clinical trial (the AmbOx study) has demonstrated that ambulatory oxygen could improve health-related quality of life [10]

Moreover, given the multifactorial nature of the low exercise tolerance in patients with ILDs, the standard use of home supplemental oxygen therapy could not solve the whole problem. In COPD patients, multiple therapies have been described to solve this aspect. Porszasz and colleagues [11] evaluated the physiological effects of a portable non-invasive ventilator (NIV) device, designed to be used in conjunction with home oxygen therapy, in COPD patients presenting significant falls in SaO₂ during exercise. This device was designed to facilitate ambulation and activities of daily living, allowing its routine use. This study showed that the use of a NIV connected to oxygen increased exercise tolerance and significantly decreased dyspnea compared to traditional nasal prongs. The mechanism by which this device could improve respiratory dynamics was related to achieving a low respiratory rate, substantial activation of the respiratory muscles, and higher mean SaO₂ compared to standard devices [11].

Accordingly, we consider that the use of a portable ventilator could lead to an improvement in respiratory dynamics in ILD patients due to a greater activation of respiratory muscles and an increase in oxygenation in patients with ILDs. This would imply a substantial improvement in tolerance to physical exertion, a decrease in the patient's sensation of dyspnea, and could possibly enhance the effect of rehabilitation in patients with ILDs who require oxygen therapy. Our aim in this study is to assess whether the additional support provided by a NIV system could improve oxygenation parameters and exercise tolerance in patients with ILDs and home supplemental oxygen therapy.

Materials And Methods

Study design and population

This is a prospective observational study carried out at the ILD Unit at Hospital Clínic, Barcelona. This study was approved by the Ethics Committee of our institution (HCB/2014/0480). Each patient was asked for written informed consent to participate in the study.

We included ILD patients who were under LTOT for at least 12 weeks prior to the onset of the study. We excluded patients for the following reasons: inability to conduct a 6MWT or a previous one with a distance achieved lower than 150 meters; pulmonary hypertension requiring specific drug treatment or systolic pulmonary artery pressure estimated by echocardiography greater than 50 mmHg; severe cardiac disease or systemic muscle disease that may limit the effort of the patients; history of neoplastic disease treated with chemotherapy and/or accompanied by cachexia in the previous 2 years; concomitant diagnosis of chronic obstructive respiratory disease (COPD or asthma) and/or spirometry with $FEV_1/FVC < 0.70$; prior hospitalization for acute worsening of their lung condition in the last 12 weeks prior to the onset of the study; respiratory infection in the last 4 weeks prior to the study. All the patients were presented in our multidisciplinary discussion (MDD) session. All diagnoses were established following the standard guidelines [12–14].

Study protocol

We scheduled an initial visit for eligible patients at the ILD Unit in which we collected information about clinical and functional variables. The characteristics of the study and how the pulse oximeter worked were explained. The patient's baseline dyspnea was assessed with the mMRC scale and their quality of life with the Sant George's Respiratory Questionnaire test (Spanish version) [15]. Subsequently two interventions were performed: (a) 6MWT with oxygen therapy (O_2), using the same flow prescribed at home and (b) 6MWT with oxygen therapy and the additional support of a non invasive ventilator (O_2 + NIV). Previous to the second exercise patients had a rest period of at least 1 hour between the two 6MWT and underwent an adaptation period of about 30 minutes with the ventilator. Borg scale was used at the beginning and the end of the 6MWT to determine the level of dyspnea and muscle fatigue of the patients. As we wanted to avoid the effect of carrying the NIV and oxygen system by the patients on 6MWT, in both tests they were carried by an additional respiratory physician during the 6MWT.

Monitoring of arterial oxygenation was performed using a wrist pulse oximeter that comfortably allows continuous monitoring of SaO_2 for the patient during daily living activities (NONIN WristOx2 3150; Noning Medical). The system also has a large memory and the ability to download information from the study using the software for further analysis. Mean O_2 saturation (SaO_2), initial and final, percentage of time with oxygen saturation $< 90\%$ (CT90), and 85% (CT85) were calculated. ΔSaO_2 was the difference between final and initial SaO_2 in each patient.

For the second 6MWT, a non-invasive two-level positive pressure ventilator (BIPAP) model Stellar 150 ResMed ® was connected to a standard oxygen tank using a T piece located at the end of the tube

closest to the ventilator. Expiratory pressure (EPAP) of 4 cmH₂O and a variable inspiratory pressure (IPAP) were set to achieve approximately a tidal volumen (Vt) of 8–10 ml/kg, adjusted according to patient comfort. The respiratory mode was spontaneous (S) with a range of inspiratory time between 0.5 seconds (T insp minimum) and 2 seconds (T insp maximum). An oronasal mask was the interface used for all the patients.

Statistical analysis

The primary endpoint of our study was oxygen saturation parameters (mean SatO₂ and CT90) while performing the 6-min walking test. Assuming that with NIV, it would be possible to reduce 20±26% the percentage of CT90 in patients with ILD, at least 16 patients would be necessary. A significance level of 5% and a power of 80% were assumed

Categorical variables were summarized with counts and percentages. For continuous variables, the median (25th -75th percentile) were presented. Wilcoxon non-parametric tests were used for paired comparisons. The level of significance was set in all tests at 0.05 (all two-tailed). The graphs and the statistical analyses were performed using Prism 8 for MacOS (version 8.3.0), ©1994–2019, GraphPad Software, LLC.

Results

A total of 16 patients with different ILDs were included in the study, IPF being the most frequent (31%). Additionally, six patients also presented with connective tissue disease (CTD). From these patients, 3 patients were classified as CTD-ILD (NSIP associated with systemic sclerosis, NSIP associated with antisintetase syndrome and UIP associated with rheumatoid arthritis). All patients were functionally limited and needed LTOT for daily activities. Baseline characteristics of all patients are shown in Table 1.

Table 1
Baseline characteristics of patients (n = 16)

M/F	9/7
Age, years	72,88+/-8,18
Tobacco, n (%):	6 (37,5)
- Non-smokers	10 (62,5)
- Ex-smokers	
Chronic pathologies, n (%):	5 (31,3)
-Hypertension	5 (31,3)
-Diabetes	3 (18,8)
-Heart disease	3 (18,8)
-Lung disease other than ILD	6 (37,5)
-CTD	5 (31,2)
-Neoplasia	
ILD diagnosis, n (%):	2 (12,5)
- CHP	5 (31,3)
- IPF	2 (12,5)
- NSIP	2 (12,5)
- COP	3 (18,8)
- ILD-CTD	1 (6,3)
-Fibrosis-emphysema	1 (6,3)
-DIP	
Treatment, n (%):	4 (25)
-Oral corticosteroids	1 (6,3)
-IS	5 (31,3)
-Corticosteroids + IS	3 (18,8)
-Nintedanib	2 (12,5)
-Pirfenidone	1 (6,3)
-None	
PFTs:	58,37+/-16,50
-FVC (%)	64,12+/-19,61
-FEV ₁ (%)	62,67+/-16,12
-TLC (%)	35,80+/-7,97
-DLCO (%)	64,52+/-7,39
-PaO ₂ (mmHg)	
Oxygen therapy type of use, (%)	10 (62,5)
- Continuous	6 (37,5)
- At physical effort only	

Baseline characteristics of patients including pathological background, ILD diagnosis, functional parameters, current treatment and hours of oxygen therapy. Abbreviations: CHP: Chronic hypersensitivity pneumonitis, COP: Chronic organizing pneumonia, CTD: Connective tissue disease, DIP: Desquamative interstitial pneumonia, DLCO: lung diffusion capacity for carbon monoxide, FVC: forced vital capacity, FEV1: forced expiratory volume in one second, IPF: Idiopathic Pulmonary Fibrosis, IS: Immunosuppressants, NSIP: non-specific interstitial pneumonia; PFTs: pulmonary function tests, TLC: Total Lung Capacity. Plus-minus values represent means and standard deviation.

M/F	9/7
Dyspnea (mMRC),	1 (6,3)
-I	8 (50)
-II	7 (43,8)
-III	48,62+/-14,61
SGRQ score	
Baseline characteristics of patients including pathological background, ILD diagnosis, functional parameters, current treatment and hours of oxygen therapy. Abbreviations: CHP: Chronic hypersensitivity pneumonitis, COP: Chronic organizing pneumonia, CTD: Connective tissue disease, DIP: Desquamative interstitial pneumonia, DLCO: lung diffusion capacity for carbon monoxide, FVC: forced vital capacity, FEV1: forced expiratory volume in one second, IPF: Idiopathic Pulmonary Fibrosis, IS: Immunosuppressants, NSIP: non-specific interstitial pneumonia; PFTs: pulmonary function tests, TLC: Total Lung Capacity. Plus-minus values represent means and standard deviation.	

The majority of patients developed similar physical exercise in both 6MWT independently if they were using the NIV on top of the LTOT, as suggested by the similar distance walked [O_2 : 316 m (228–425), O_2 + NIV: 307 m (222–419); $p = 0.10$] (Fig. 1) and the similar changes in physiological parameters in both tests (Fig. 2). However, it is remarkable that there was an improvement in all the parameters associated with oxygen saturation: (a) a decrease in CT90 [O_2 : 58% (36–77), O_2 + NIV: 36% (6–56); $p < 0.0001$] and CT85 [O_2 : 25% (2–65), O_2 + NIV: 20% (0–39); $p = 0.0007$] after the use of NIV; (b) a lower fall of SaO_2 [$\Delta SaO_2 = O_2$: -12% (-20-8), O_2 + NIV: -7% (-18-3); $p = 0.0009$] and (c) an increase of mean SaO_2 [O_2 : 88% (86–90), O_2 + NIV: 91% (88–93); $p = 0.0005$] (Fig. 1). As both tests were performed using the same oxygen flow, these data suggest an optimization of the oxygen therapy effect on oxygen saturation.

Dyspnea were similar in both tests (Fig. 2), although in the O_2 + NIV test there was a tendency to a lower final Borg scale [4 (2–4,75), $p < 0.0001$] compared to the O_2 test [4 (2–5), $p < 0.0001$]; [$\Delta Borg = O_2$: 4 (1.5-5), O_2 + NIV: 3 (2-4.5); $p = 0.43$].

The median IPAP used under NIV in our study was 12 (10–16) cmH_2O . In all patients, an improvement in respiratory parameters was observed with an increase in median tidal volume [from 654 ml (500–770) to 870.5 ml (729–1076), $p < 0.0001$] and minute volume [from 14.03 L/min (12.07–17.83) to 26.96 L/min (24.41 to 35.38), $p < 0.0001$] with the support of the NIVpared to basal conditions.

Discussion

The results obtained in our study seems to demonstrate the favorable effect of associating a NIV with oxygen therapy to improve the oxygen saturation parameters during exercise without increasing the oxygen flow.

Current home supplemental oxygen devices have specific limitations, specially in patients with ILDs that characteristically develop a significant fall of SaO_2 during exercise and need higher flows of oxygen to

maintain an adequate level of SaO_2 [3]. The flow administered by portable oxygen devices are limited and sometimes do not satisfy patients needs [16, 17].

We hypothesized the improvement of oxygen saturation parameters to the additional effect of positive pressure in the airway, which accomplishes an enhanced activation of the ventilatory muscles as well as diminishing the respiratory rate and improving the recruitment of tidal volume, similarly to the studies of Porszasz and colleagues in COPD [11]. In their study, 15 patients diagnosed with COPD (FEV1 : $32 \pm 12\%$) performed an exercise test using a cycloergometer with a progressive increase in exercise intensity up to 80% of the peak load in several situations: ambient air, with oxygen therapy support, NIV with ambient air and NIV combined with oxygen therapy. The results showed a significant improvement of the average oxygen saturation in the group of NIV associated with oxygen therapy in comparison with oxygen therapy alone (97.4 ± 1.8 vs 91.2 ± 4.2), as well as a greater tolerance to exercise assessed by a sustained physical activity over a longer period of time (17.6 ± 5.7 min vs 11.4 ± 6.8 min). In our case, using 6MWT with a similar walking distance in both tests, patients also showed an improvement in oxygen saturation parameters. It is remarkable that in our study we observed an improvement of CT90 during 6MWT. No studies have previously assessed the relevance of CT90 in ILDs, but in COPD, CT90 is a useful parameter to monitor oxygen saturation during exercise [18]. As 6MWT is the current method to titrate oxygen flow for daily activities, the potential use of NIV to optimize flow titration in exercise could be relevant as a future application.

Several limitations should be addressed. Firstly, due to the characteristics and the physical exercise needed to perform the 6MWT, we excluded those patients with physical limitations derived from their lung disease as well as severe cardiac condition or muscle involvement. This may lead to a selection bias since the most severely affected patients could not be included. However, we hypothesized that the results obtained might also apply to them. Secondly, this is a pilot study to assess the potential use of NIV with ambulatory oxygen during 6MWT. However, these results should be confirmed during ambulatory daily activities with a NIV + O_2 system that could be easily and routinely used by patients. We think that their combined use could be helpful to improve patient oxygen saturation during physical exercise as well as their quality of life during the performance of their usual daily life activities. It would also have a potential role in rehabilitation programs to increment the effects of respiratory physiotherapy.

In conclusion, our study has shown that the additional use of a NIV device associated with oxygen therapy during the performance of the 6MWT may prove useful to improve the average oxygen saturation in patients with ILD during exercise. The future clinical application of these devices needs further assessment in prospective home studies.

List Of Abbreviations

CHP: chronic hypersensitivity pneumonitis, COP: chronic organizing pneumonia, CTD: connective tissue disease, COPD: chronic obstructive pulmonary disease, DIP: desquamative interstitial pneumonia, DLCO: lung diffusion capacity for carbon monoxide, FVC: forced vital capacity, FEV1: forced expiratory volume

in one second, ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, IS: immunosuppressants, LTOT: long-term oxygen therapy, NIV: non-invasive ventilation, NSIP: non-specific interstitial pneumonia, PFTs: pulmonary function tests, RV/Vt: dead space/tidal volume ratio, SaO₂: arterial oxygen saturation, TLC: total lung capacity, VA/Q: ventilation-perfusion ration, Vt: tidal volumen, 6MWT: 6 minutes walking test.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of our institution (HCB/2014/0480). Each patient was asked for written informed consent to participate in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests with the manuscript.

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Authors' contributions

Dra. SC took care of the initial assessment of the patients, obtained their informed consent, collected clinical and study data, and finally performed the walking test with the support of nurse MP. As committee members of the Interstitial Disease Unit of our hospital Dr. JF, NA and Dr. FH contributed to the assessment of the patients included. Dr. CE, IB and Dr. JS contributed to the study design, data analysis and interpretation of the results as well as the writing of the text. All co-authors reviewed and approved the submitted manuscript.

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Figures

Fig 1

Figure 1

Comparison of oxygen saturation parameters and total meters covered during the 6MWT, between oxygen therapy alone and with additional support of a non-invasive ventilator.

Fig 2

Figure 2

Comparison of physiological parameters (heart and respiratory rate) and dyspnea level assessed with Borg scale in patients with ILD with oxygen therapy alone and with additional support of a non-invasive ventilator.