Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The Monaldi Archives for Chest Disease is, therefore, E-publishing PDF files of an early version of manuscripts that undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear on a regular issue of the journal. E-publishing of this PDF file has been approved by the authors.

Monaldi Arch Chest Dis 2021 [Online ahead of print]

To cite this Article:
Acute effect of oxygen therapy on exercise tolerance and dyspnea perception in ILD patients

Josuel Ora¹, Angelo Coppola², Andrea Perduno³, Gian Marco Manzetti³,
Ermanno Puxeddu¹,³, Paola Rogliani¹,³

1. Respiratory Medicine, Tor Vergata Hospital Foundation, Rome, Italy
2. Respiratory Medicine, San Filippo Neri Hospital, Rome, Italy
3. Respiratory Medicine, department of Experimental Medicine, “Tor Vergata University, Italy

Corresponding author: Dr. Josuel Ora, Respiratory Medicine, Tor Vergata Hospital Foundation, email address josuel.ora@ptvonline.it, telephone: +39 06 20904649, telephone: +39 06 20904669.

Keywords: Interstitial Lung Disease, dyspnea, oxygen supplementation, 6MWT

Acknowledgments: none.

Authors contributions: All authors contributed to the substantial conception and design of the work; AC, AP, GMM contributed in running the experiments and writing the paper; JO, EP and PR contributed to the interpretation of data for the work; JO, AC, PR drafted the work and revised it critically for important intellectual content; all authors approved the final version to be published, and agreed with all aspects of the work in ensuring the accuracy and integrity of all its parts.

Conflicts of interest: JO, AC, AP, GMM, EP, PR have no conflicts of interest concerning this topic. JO participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Novartis, Zambon. AC participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, and Zambon.

AP and GMM have no conflict of interest to declare. EP participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca, Boehringer Ingelheim, Chiesi
Farmaceutici, GlaxoSmithKline, Menarini Group, and Zambon. PR participated as a lecturer and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer ingelheim, Chiesi Farmaceutici, Edmond Phama, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis, and her department was funded by Almirall, BoehringerIngeiheim, Chiesi Farmaceutici Novartis, and Zambon.

Funding sources: No funding to declare

Statement of ethics: The study was conducted in accordance with the Declaration of Helsinki and approved by “Tor Vergata” Indipendent Ethic Board (prot.4678/2016)

Abstract

Ambulatory oxygen therapy (AOT) is commonly prescribed in Interstitial Lung Disease (ILD) patients, with the aim of reducing dyspnea and increasing exercise tolerance. Despite its frequent use and a reasonable physiological rationale, there is a lack of evidence supporting the effect of AOT on improving dyspnea during exercise. Moreover, dyspnea encompasses distinct sensory (intensity, quality) and affective (anxiety, fear) components with different underlying neurophysiological mechanisms. The aim of this study was to evaluate the effect of oxygen supplementation on exercise tolerance and dyspnea in ILD patients with exercise induced hypoxia (EIH). Forty-seven ILD patients performed a six minute walk test (6MWT) on room air (RA) and with oxygen supplementation (Ox). The 6MWT distance (6MWD) was significantly greater with oxygen supplementation (RA: 242±143 m vs Ox: 345±106 m p<0,01). With oxygen supplementation, the overall dyspnea and anxiety significantly decreased both at rest (1,1±1,4 Borg Unit (BU) vs 0,4±0,9BU , p.<0.01, and 1,1±1,6BU vs 0,5±1,3 BU, p.<0.05, respectively) and at the end of exercise (5,1±2,6 BU vs 3,7±2,5 BU, p.<0.001 and 3,4 ±2,9 vs 2,5 ±2,8, p.<0.01, respectively) despite a greater walked distance. In ILD patients with EIH, oxygen supplementation increases the exercise tolerance and reduces overall dyspnea perception and the anxiety component of breathlessness.

Introduction

Ambulatory Oxygen Therapy (AOT) is defined as the use of supplemental oxygen during exercise and activities of daily living and is used to optimise saturations and short-term exercise capacity (1). During exercise, patients with Interstitial Lung Diseases (ILDs) present a
significant widening of the alveolar-to-arterial O\textsubscript{2} gradient and profound arterial oxygen desaturation can occur causing greater ventilation and higher dyspnea perception (2). AOT is given to prevent oxygen desaturations and to reduce the dyspnea perception. The six-minute walk test (6MWT) is the simplest and most commonly used submaximal exercise test. Applied in patients with ILD (3), it has shown better ability compared to cardiopulmonary exercise test (CPET) on a bike in detecting oxygen desaturation (4,5). Although there is evidence that in Chronic Obstructive Pulmonary Disease (COPD) AOT improves exercise tolerance (6), there is a lack of evidence supporting the effectiveness of oxygen therapy in ILD (7–11). Visca et al. (9) showed in 52 ILD subjects a statistically significant improvement of 31 meters on 6MWT distance (6MWD) during oxygen supplementation, conversely Nishiyama et al. (7) showed that in 20 patients with Idiopathic Pulmonary Fibrosis (IPF) without resting hypoxemia the oxygen supplementation did not improve exercise tolerance (7–9). Similarly, despite the widespread use of oxygen to reduce dyspnea, a recent systematic review showed no effects of oxygen therapy on dyspnea during exercise in ILD (10).

Moreover, dyspnea is a multidimensional respiratory sensation and incorporates distinct sensory (intensity, quality) and affective (anxiety, fear) components, which may have different underlying neurophysiological mechanisms (2,12). Three main distinctive sensory components have been so far characterised: work/effort of breathing, tightness, air hunger/unsatisfied inspiration (12). In ILD patients dyspnea intensity is increased at any given exercise VO\textsubscript{2}, work rate or ventilation compared with healthy controls (13–15) and increased “effort/work” of breathing and “unsatisfied inspiration” are the most common qualitative descriptors at VO\textsubscript{2} peak during incremental CPET (14,15), but no information is provided about the affective component perceived by patients.

The aim of this study is to evaluate the effect of oxygen supplementation in ILD patients with EIH, and to explore which component of the perceived breathlessness is more affected. We hypothesize that oxygen supplementation would increase the 6MWD and reduce the dyspnea perception overall, although its effect can be blurred by the greater distance walked with oxygen supplementation.

**Materials and methods**

**Design of the study**

All subjects performed a first visit to familiarize with the pulmonary function tests (PFTs), 6MWT and the dyspnea questionnaires, and a second visit included PFTs, two 6MWTs on
Room Air (RA) and with oxygen supplementation (Ox) spaced by 30 minutes of rest and all the dyspnea questionnaires. The study was conducted in accordance with the Declaration of Helsinki and approved by “Tor Vergata” Independent Ethic Board (prot.4678/2016)

**Pulmonary function testing**

Complete PFTs, including forced vital capacity (FVC) and diffusing lung capacity (DL’CO), determined with the single breath technique, was carried out according to the ATS guidelines (16) on a Master Screen Body PFT (Jaeger, Wurtzburg, Germany) using European Coal and Steel Community reference spirometric values (17).

**Six minute walk test**

The 6MWT was performed in a 25 m, straight indoor hallway according to ATS guidelines (3). All patients were tested under standardized conditions by trained operators. Heart rate and oxygen saturation were measured at rest (baseline), every minute during the test and at the end of the test until recovery. A Nellcor N-20PATM Handheld Pulse Oximeter (Nellcor BS; Nellcor, Hayward, CA) was used. Supplemental oxygen was administered through a nasal cannula, using commercially available integrated E-cylinder, valve and regulator device (Rivoira, Milan, Italy) carried by the patient as recommended by guidelines (3,18). The 6MWD was expressed both as absolute value in meters and as %predicted value (%pr), using the Enright and Sherill equations (18).

**Questionnaires / Dyspnea evaluation**

The impact of dyspnea in daily life was evaluated by modified Medical Research Council Dyspnea Scale (mMRC), Oxygen Cost Diagram (OCD), Visual Analogue scale (VAS), Baseline Dyspnea Index (BDI) (19). The sensory perceptual intensity of respiratory discomfort was evaluated by the Borg’s 0-10 category ratio scale. Five different qualitative dimensions of dyspnea were explored: 1) overall dyspnea discomfort, 2) unsatisfied inspiration, 3) unsatisfied expiration, 4) anxiety, fear of breathing, 5) increased work of breathing. The sensory perceptual intensity of leg fatigue was evaluated by the Borg’s 0-10 category ratio scale as well. Before the 6MWT, subjects were familiarized with Borg’s 0–10 category ratio scale (20) and its endpoints were anchored such that “0” represented “no respiratory discomfort (leg discomfort)” and “10” was “the most severe respiratory discomfort (leg discomfort) they had ever experienced or could ever imagine experiencing”. By pointing to the Borg scale, subjects rated
their level of perceived respiratory and leg discomfort at rest and at exercise cessation.

**Statistical analysis**
Statistical analysis was carried out employing GraphPad Prism software. Group comparisons were made using Student’s T-test or one-way analysis of variance (ANOVA) as appropriate. A p value of less than 0.05 was considered statistically significant. Univariate correlations were examined using Pearson’s product moment-correlation. Data are presented as average ± standard deviation if not differently specified.

**Results**

**Subjects**
Subjects’ characteristics are shown in Table 1. Forty-seven ILD with exercise-induced hypoxemia were studied. Patients’ characteristics and pulmonary function tests are summarized in Table 1 and showed a mild restrictive pattern, but a moderate-severe DL’co impairment. All the subjects had no oxygen desaturation at rest.

**Six-minute walk test**
Subjects performed two 6MWT, on RA and with average Ox of 6 ± 3 l/min via nasal cannula. At the 6MWT with oxygen supplementation, SpO₂ was greater than 87% (SpO₂ nadir: 91% ± 3 vs 80% ± 5, Ox vs RA) and the walked distance was 103 m more compared to the 6MWD on RA (6MWD: 345 m ± 106 vs 242 m ± 43, Ox vs RA respectively).

**Dyspnea perception**
All the patients were symptomatic per dyspnea (mMRC: 2,4 ± 1,2; BDI: 5,1 ± 2,4; OCD: 55 ± 18) (Table 1).
During oxygen supplementation, overall dyspnea decreased significantly both at rest (0,4BU ±0,9 vs 1,1BU ±1,4, Ox vs RA respectively, p.<0.01) and at the end of exercise (3,7BU ±2 vs 5,1BU ±2,6 5, Ox vs RA respectively, p.<0.001) despite a greater distance walked. The other components of dyspnea (difficult expiration, difficult inspiration, increased effort/work of breathing) and the leg discomfort were not significantly different (Table 2). Twenty-one patients out of 47 experienced anxiety/fear of breathing during at least one of the two 6MWTs. The affective component was significantly reduced at rest (1,1 BU ±1,6 vs 0,5 BU ±1,3,
(p.<0.05) and at the end of exercise (3.4 BU ±2.9 vs 2.5 BU ±2.8, p.<0.01) (Figure 1). Dyspnea descriptors were asked and clustered at the end of exercise, but there was no difference between groups (Figure 2).

**Discussion**

The main findings of this study are as follows: 1) Oxygen supplementation increases exercise tolerance and decreases dyspnea perception both at rest and at the end of exercise in ILD subjects with EIH; 2) the main dyspnea component influenced by oxygen supplementation is anxiety; 3) perception of work/effort of breathing, difficult inspiration and expiration and the main descriptors of dyspnea at the end of exercise were similar with and without oxygen supplementation.

The results of the present study confirm that in ILD patients with EIH oxygen supplementation increases exercise tolerance at the 6MWT and, differently than the Bell et al.’ study, decreases overall dyspnea perception. Similarly to our findings, Visca et al. have already demonstrated in ILD subjects a significant increase of 31 m at the 6MWT with oxygen supplementation (9). In our study the increase by oxygen supplementation was 103 m. The main difference between our and the Visca et al.’ study was that the oxygen supplementation was provided to guarantee to all patients an SpO2 nadir ≥ 88%, while in the Visca et al.’ study the SpO2 nadir was 84.7%. Similarly, in the Nishiyama et al. study (7), oxygen flows provided did not prevent the oxygen desaturation, and at the end of exercise the oxygen saturation was 84% with oxygen supplementation instead of 80% without oxygen. The 4 l/min provided in that study were not sufficient to prevent the EIH and probably the negative results of AOT on exercise tolerance and dyspnea are due to this reason. …

In addition, our study shows an improvement in dyspnea perception with oxygen supplementation. Although oxygen is recommended by the main societies for the treatment of more severe patients (22,23), the effect of oxygen therapy on breathlessness is still controversial. Some studies failed to demonstrate a positive effect of oxygen supplementation in terms of dyspnea relief or increases in exercise tolerance (24–27), although other studies have demonstrated a reduction of ventilation at a similar work rate (9,28). … Just recently the Bell et al’ systematic review was not able to demonstrate any effects of oxygen therapy on dyspnoea during exercise in ILD …. These results are strongly contradicting the common clinical practice and the accepted recommendations of an extensive use of oxygen therapy in patients with ILD. … Our study clearly shows a beneficial effect of oxygen supplementation on dyspnea perception, reducing dyspnea of 0.7BU at rest and 1.4BU at the end of exercise
compared to RA. The magnitude of effect of oxygen on dyspnea … might be considered even greater being dyspnea evaluated at the end of six minutes of walking, with a greater distance (103 m) walked in the test with oxygen supplementation. We believe that our study reinforces the evidence coming from the usual clinical practice by pointing out that if oxygen therapy is given in ILD patients with EIH to an oxygen flow appropriate to prevent EIH, there is an improvement in dyspnea and exercise tolerance.

Furthermore, our results demonstrate for the first time that in ILD patients oxygen supplementation decreases mostly the affective component of dyspnea reducing the anxiety/fear of breathing, but it does not affect the perception of breathing effort, or the feeling of difficult inspiration. Banzett et al have showed in healthy subjects that it is possible to varying the hunger of breathing and the unpleasantness related to dyspnea just manipulating some external conditions as hypoxemia and breathing pattern. In recent years, neuroimaging have demonstrated a cortical limbic structures activation during dyspnea (12), … oxygen supplementation may decrease the anxiety/fear of breathing giving a feeling of safety to the patient and a faster recovery. In our population anxiety/fear of breathing was reported in 21 subjects, and 9 patients experienced it only without oxygen supplementation.

This study has some limitations. The lack of a sham test with compressed room air does not allow ruling out a beneficial effect of flow on dyspnea perception (27). Physiological measurements, such as ventilation, inspiratory capacity, CO₂ production were not evaluated and it is not possible to correlate them with dyspnea perception to better understand the underpinning cause of dyspnea relief with oxygen supplementation.

Conclusions

This study demonstrates that oxygen supplementation increases the exercise tolerance and reduces overall dyspnea perception n ILD patients with EIH. This is the first study to demonstrate that oxygen supplementation reduces the anxiety component in ILD patients. These results can have important impacts on the ILD rehabilitation.

Abbreviations

Ambulatory oxygen therapy AOT
Baseline Dyspnea Index BDI
Borg Unit BU
cardiopulmonary exercise test CPET
Chronic Obstructive Pulmonary Disease COPD
Diffusion Lung Capacity for CO2  
exercise induced hypoxia  
Forced Vital Capacity  
Idiopathic Pulmonary Fibrosis  
Interstitial Lung Disease  
Medical Research Council Dyspnea Scale  
Meter  
Oxygen Cost Diagram  
Oxygen supplementation  
pulmonary function testing  
Room Air  
six minute walk distance  
six minute walk test  
Total Lung Capacity  
Visual Analogue scale

References
Table 1. Subjects’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Population (n= 47)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>26, 55%</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>69 ± 8,4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160 ± 9,4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 12</td>
</tr>
<tr>
<td>FEV1, L (%pr)</td>
<td>1,67 ± 0,64 (76 ± 22)</td>
</tr>
<tr>
<td>FVC, L (%pr)</td>
<td>2,09 ± 0,83 (75 ± 21)</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>81 ± 12</td>
</tr>
<tr>
<td>TLC, L (%pr)</td>
<td>3,81 ± 1,31 (72 ± 20)</td>
</tr>
<tr>
<td>FRC, L (%pr)</td>
<td>2,32 ± 1,02 (77 ± 33)</td>
</tr>
<tr>
<td>RV, L (%pr)</td>
<td>1,67 ± 0,86 (77 ± 44)</td>
</tr>
<tr>
<td>DL’co-sb ml/min/mmHg (%pr)</td>
<td>2,50 ± 1,20 (35 ± 17)</td>
</tr>
<tr>
<td>mMRC</td>
<td>2,4 ± 1,2</td>
</tr>
<tr>
<td>VAS, %</td>
<td>55,4 ± 18,4</td>
</tr>
<tr>
<td>OCD, %</td>
<td>44,1 ± 19,2</td>
</tr>
<tr>
<td>BDI</td>
<td>5,1 ± 2,4</td>
</tr>
</tbody>
</table>

* Specific diagnoses included idiopathic pulmonary fibrosis (n=18), combined pulmonary emphysema fibrosis (n=3), non specific interstitial pneumonia (n=9), sarcoidosis (n=3); connective tissue disease – interstitial lung pneumonia (n=5); cryptogenic organizing pneumonia (n=2); hypersensibility pneumonia (n=5) and pulmonary fibrosis result of toxic lung damage (n=2). FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; FRC: Functional Residual Capacity; RV: residual volume; DLco -SB: diffusing lung capacity for carbon monoxide – single breath; mMRC: modified Medical Research Council Dyspnea Scale; VAS: Visual Analogue Scale; OCD: Oxygen Cost Diagram; BDI: Baseline Dyspnea Index; %pr: %predicted value. Values are expressed as mean ± SD.
Table 2. Six minute walk test before and after oxygen supplementation

<table>
<thead>
<tr>
<th></th>
<th>Room air</th>
<th>Oxygen supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD, m</td>
<td>242 ± 143</td>
<td>345 ± 106 ***</td>
</tr>
<tr>
<td>SpO2 nadir, %pr</td>
<td>80 ± 5</td>
<td>91 ± 3 ***</td>
</tr>
<tr>
<td>Dyspnea overall rest, BU</td>
<td>1,1 ± 1,4</td>
<td>0,4 ± 0,9 **</td>
</tr>
<tr>
<td>Dyspnea overall peak, BU</td>
<td>5,1 ± 2,6</td>
<td>3,7 ± 2,5 ***</td>
</tr>
<tr>
<td>Leg Fatigue rest, BU</td>
<td>1,1 ± 1,7</td>
<td>0,9 ± 1,7</td>
</tr>
<tr>
<td>Leg Fatigue peak, BU</td>
<td>2,7 ± 2,9</td>
<td>2,9 ± 2,8</td>
</tr>
<tr>
<td>Unsatisfied Inspiration rest, BU</td>
<td>1,1 ± 1,6</td>
<td>0,6 ± 1,1</td>
</tr>
<tr>
<td>Unsatisfied Inspiration peak, BU</td>
<td>2,9 ± 2,7</td>
<td>2,3 ± 2,6</td>
</tr>
<tr>
<td>Difficult Expiration rest, BU</td>
<td>1,1 ± 1,6</td>
<td>0,5 ± 1,3</td>
</tr>
<tr>
<td>Difficult Expiration peak, BU</td>
<td>2,6 ± 2,7</td>
<td>2,2 ± 2,5</td>
</tr>
<tr>
<td>Anxiety/fear of breathing rest, BU</td>
<td>1,1 ± 1,6</td>
<td>0,5 ± 1,3 *</td>
</tr>
<tr>
<td>Anxiety/fear of breathing peak, BU</td>
<td>1,5 ± 2,4</td>
<td>0,8 ± 1,9</td>
</tr>
</tbody>
</table>

6MWT: six minute walk test; SpO2: oxygen saturation by pulse oximetry; BU: Borg Unit, %pr: %predicted value. Values are expressed as mean ± SD. (T test, *p.<0.05, **p.<0.01, ***p.<0.001 )
**Figure 1.** Dyspnea perception overall at baseline and at the end of exercise; anxiety perception at baseline and at the end of exercise on room air (RA) and with oxygen supplementation (Ox). All the differences are significant (p<0.05). The columns represent the average, and the bars the standard deviation.

**Figure 2.** Frequency of dyspnea descriptors at the end of exercise, clustered according the most representative descriptors of dyspnea sensation [9]. IN: difficult inspiration; ESP: difficult expiration.