

Acute effect of oxygen therapy on exercise tolerance and dyspnea perception in ILD patients

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Abstract

Ambulatory oxygen therapy (AOT) is commonly prescribed in interstitial lung disease (ILD) patients, with the aim of reducing dys-

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pnea 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 O₂ 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_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_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 exercise induced hypoxia (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 min 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, USA) 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: i) overall dyspnea discomfort, ii) unsatisfied inspiration, iii) unsatisfied expiration, iv) anxiety, fear of breathing, v) 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 \pm SD 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-

Table 1. Subjects' characteristics.

	Population (n=47)*
Male, n (%)	26, 55%
Age, yrs	69 \pm 8.4
Height, cm	160 \pm 9.4
Weight, kg	76 \pm 12
FEV ₁ , L (%pr)	1.67 \pm 0.64 (76 \pm 22)
FVC, L (%pr)	2.09 \pm 0.83 (75 \pm 21)
FEV ₁ /FVC, %	81 \pm 12
TLC, L (%pr)	3.81 \pm 1.31 (72 \pm 20)
FRC, L (%pr)	2.32 \pm 1.02 (77 \pm 33)
RV, L (%pr)	1.67 \pm 0.86 (77 \pm 44)
DL'co-sb ml/min/mmHg (%pr)	2.50 \pm 1.20 (35 \pm 17)
mMRC	2.4 \pm 1.2
VAS, %	55.4 \pm 18.4
OCD, %	44.1 \pm 19.2
BDI	5.1 \pm 2.4

*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); hypersensitivity 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 \pm SD.

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±106 m vs 242±43 m, 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 (0.4±0.9BU vs 1.1±1.4BU, Ox vs RA, respectively, p<0.01) and at the end of exercise (3.7±2.5BU vs 5.1±2.6 BU,

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±1.6 BU vs 0.5±1.3BU, p<0.05) and at the end of exercise (3.4±2.9BU vs 2.5±2.8BU, 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: i) oxygen supplementation increases exercise tolerance and decreases dyspnea perception both at rest and at the end of exercise in ILD subjects

Table 2. Six-minute walk test before and after oxygen supplementation.

	Room air	Oxygen supplementation
6MWD, m	242±143	345±106***
SpO ₂ nadir, %pr	80±5	91±3***
Dyspnea overall rest, BU	1.1±1.4	0.4±0.9**
Dyspnea overall peak, BU	5.1±2.6	3.7±2.5***
Leg fatigue rest, BU	1.1±1.7	0.9±1.7
Leg fatigue peak, BU	2.7±2.9	2.9±2.8
Unsatisfied inspiration rest, BU	1.1±1.6	0.6±1.1
Unsatisfied inspiration peak, BU	2.9±2.7	2.3±2.6
Difficult expiration rest, BU	1.1±1.6	0.5±1.3
Difficult expiration peak, BU	2.6±2.7	2.2±2.5
Anxiety/fear of breathing rest, BU	1.1±1.6	0.5±1.3*
Anxiety/fear of breathing peak, BU	1.5±2.4	0.8±1.9

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.

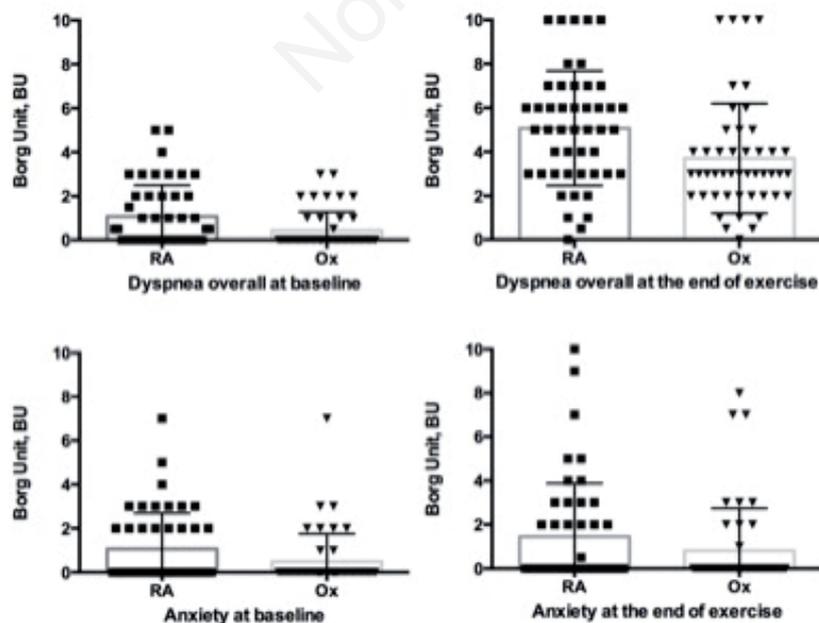


Figure 1. Dyspnea perception overall at baseline and at the end of exercise; anxiety perception at baseline and at the end of exercise on room air (RA) and with oxygen supplementation (Ox). All the differences are significant (p<0.05). The columns represent the average, and the bars the standard deviation.

with EIH; ii) the main dyspnea component influenced by oxygen supplementation is anxiety; iii) 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 [10]. 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 $\geq 88\%$, 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 [10]. 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.

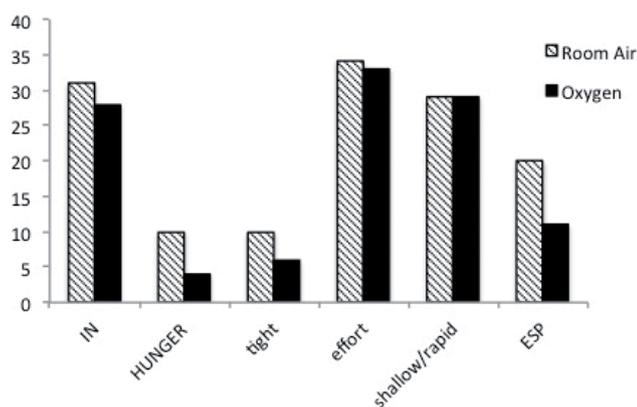


Figure 2. Frequency of dyspnea descriptors at the end of exercise, clustered according to the most representative descriptors of dyspnea sensation [9]. IN, difficult inspiration; ESP, difficult expiration.

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. Parshall *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 in 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.

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