Short-term Effects of Supplemental Oxygen on 6-Min Walk Test Outcomes in Patients With COPD A Randomized, Placebo-Controlled, Single-blind, Crossover Trial

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Short-term effects of supplemental oxygen on 6-minute walk test outcomes in COPD patients - a randomized, placebo-controlled, single-blind, cross-over trial

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Short-term effects of supplemental oxygen on 6-minute walk test outcomes in COPD patients - a randomized, placebo-controlled, single-blind, cross-over trial

Short title:

Acute effects of supplemental oxygen in COPD

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ABBREVIATIONS

6MWD	6-minute walk distance
$6MWD_{O2}$	6-minute walk distance by using supplemental oxygen
$6MWD_{RA}$	6-minute walk distance by using room air
6MWT	6-minute walk test
$6MWT_{O2}$	6-minute walk test on supplemental oxygen
$6MWT_{RA}$	6-minute walk test on room air
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusion capacity of the lung for carbon monoxide
EIH	Exercise-induced hypoxemia
FEV_1	Forced expiratory volume in 1 second
FEV_1/FVC	Ratio of FEV_1 and Forced vital capacity (Tiffeneau Index)
HYX	Resting hypoxemia
LTOT	Long-term oxygen therapy
MID	Minimal important difference
NOX	Normoxemia
$O_{2\_suppl.}$	Supplemental oxygen
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
RA	Compressed room air
RV	Residual volume
TLC	Total lung capacity

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ABSTRACT

Background: The acute effect of supplemental oxygen during exercise has been shown to differ largely among patients with COPD. It is unknown what the oxygen response is influenced by.

Methods: In a randomized and single-blinded fashion, 124 COPD patients underwent one 6-minute walk test on supplemental oxygen ($6MWT_{O2}$) and one on compressed room air ($6MWT_{RA}$) after a practice 6MWT. Both gases were delivered *via* standard nasal prongs (2 liters/min). For analyses, patients were stratified based on PaO_2 values: (a) 34 patients with resting hypoxemia (HYX), (b) 43 patients with exercise-induced hypoxemia (EIH) and (c) 31 normoxemic patients (NOX) were compared.

Results: Oxygen supplementation resulted in an increase of 6-minute walk distance (6MWD) in the total cohort (+27±42m, $p<0.001$) and in the subgroups of HYX (+37±40m, $p<0.001$) and EIH (+28±44m, $p<0.001$), but not in NOX patients (+15±43m, $p=0.065$). 42% of HYX and 47% of EIH patients improved 6MWD to a clinical relevant extent (≥30m) by using oxygen. These oxygen responders were characterized by significantly lower $6MWD_{RA}$ compared to patients without a relevant response (306±106m vs. 358±113m, $p<0.05$). Although SpO_2 was significantly higher during $6MWT_{O2}$ compared to $6MWT_{RA}$ in all 3 subgroups, it dropped below 88% during $6MWT_{O2}$ in 73.5% of HYX patients.

Conclusions: In contrast to NOX patients, HYX and EIH generally benefit from supplemental oxygen by increasing exercise capacity. However, less than half of them reached the threshold of clinical relevant improvements. These oxygen responders were characterized by significantly lower exercise capacity levels.

Trial registry: ClinicalTrials.gov; No.: NCT00886639; URL: www.clinicaltrials.gov.

INTRODUCTION

Supplemental oxygen ($O_{2\_suppl.}$) used during exercise testing has shown a direct positive effect in patients with moderate to severe COPD, as summarized in the British Thoracic Society guidelines for home oxygen use in adults.[1] These benefits are attributed to several mechanisms such as a delayed lactic acidosis, a decreased dynamic hyperinflation due to a slower breathing pattern and decreased pulmonary artery pressures.[2-4] Furthermore, improved oxygen delivery and uptake in respiratory and peripheral muscles were observed in COPD patients by using $O_{2\_suppl.}$.[5]

These effects were discussed to result in increased blood oxygenation, decreased symptoms of dyspnea and higher exercise capacities.[1] A Cochrane Review focused on the impact of $O_{2\_suppl.}$ during a single exercise intervention on exercise performance in moderate to severe COPD patients with variable resting levels of hypoxemia (PaO_2: 52 to 85mmHg).[6] $O_{2\_suppl.}$ improved 6-minute walk distance (6MWD) by only 19m compared to compressed room air (RA). Noticeably, the sample sizes of these 31 studies were rather limited (range: n=5 to 41), and the mean change in 6MWD showed a wide range from 6m to 52m. As the minimal important difference (MID) is assumed to be ≥30m[7], the clinical relevance of the direct effect of $O_{2\_suppl.}$ on 6MWD is difficult to interpret. Data about different individual responses to $O_{2\_suppl.}$ in COPD patients with different resting levels of hypoxemia were not available, as this was also discussed as a limitation by the authors.

Although COPD patients with normoxemia at rest as well as during exercise are not eligible for LTOT or ambulatory oxygen, $O_{2\_suppl.}$ has been found to decrease dynamic hyperinflation and to prevent exercise-induced oxidative stress in these patients.[4,8] However, in a small group of 9 normoxemic COPD patients, $O_{2\_suppl.}$ did not improve 6MWD.[9]

In order to provide $O_{2\_suppl.}$ to COPD patients who would benefit from this intervention, it is of clinical importance to detect patients with a high “oxygen response” and to gain more

knowledge about the direct oxygen-related effects, especially in subgroups with different levels of oxygenation.

Therefore, the primary aim of this randomized controlled cross-over trial was to investigate the direct effects of $O_{2\_suppl.}$ vs. compressed RA on the 6MWD and 6-minute walk test (6MWT) variables in a cohort of patients with severe to very severe COPD. Furthermore, oxygen-related effects were compared between three subgroups of patients with various resting levels of oxygenation.

METHODS

This prospective, randomized, placebo-controlled, single-blind, cross-over study was conducted in accordance with the Bavarian Ethics Committee (ID 08079). It was registered on clinicaltrials.gov (NCT 00886639) on 21st April 2009 after enrolling 20 pilot patients (starting in December 2008) who were not included in the current analyses. All subjects provided informed written consent.

Patients

Patients with severe to very severe COPD (GOLD stage III/ IV) entering an inpatient pulmonary rehabilitation program at the Schoen Klinik Berchtesgadener Land (Schoenau am Koenigssee, Germany) were asked to participate. Exclusion criteria were a COPD exacerbation within the last 4 weeks prior to enrollment, acute coronary syndrome, and/or any disability that inhibited patients to perform a 6MWT.

According to the recent GOLD guidelines[10], patients were divided into three groups retrospectively, depending on the level of oxygenation: [1] Hypoxemia at rest and following exercise (HYX): PaO_2 ≤55.0 mmHg at rest and during exercise; [2] exercise-induced hypoxemia (EIH): PaO_2 >55.0 mmHg at rest and ≤55.0 mmHg during 6MWT; and [3] normoxemia (NOX): PaO_2 >55.0 mmHg at rest and during exercise.

Assessment

On day 1, all patients performed post-bronchodilator body plethysmography and measurement of single-breath diffusion capacity of the lung for carbon monoxide (DLCO) in accordance to the ATS guidelines.[11,12]

On day 2, patients underwent a practice 6MWT under real-life conditions (RA or O_2 supplementation as prescribed by their physician) to minimize the influence of a potential learning effect.[13] Patients underwent two additional 6MWTs on day 3 and 4 in random order: one on supplO$_2$ ($6MWT_{O2}$) and one on compressed RA ($6MWT_{RA}$). Liquid oxygen (Linde AG, Pullach, Germany) and compressed RA (AGA Gas, Sollentuna, Sweden) were applied by using identical cylinders and a constant flow of 2 liters/min *via* common nasal prongs. The cylinder was carried in a backpack by the investigator in order to blind the patients to the provided gas mixture. The interval between the second and third 6MWT was 24±1 hours. All tests were conducted by the same investigator (IJ) and were performed according to the ATS guidelines[14] with additional continuous monitoring of oxygen saturation (SpO_2) and heart rate. Data were analysed at rest, at 1, 3:30 and 6 minutes of the 6MWT (Konica Minolta, Pulsox 300i, Osaka, Japan). To prevent patients from detecting the type of applied gas, heart rate and SpO_2 were recorded by a pulse oxymeter not visible for the patients during the test. Additionally, before and after each test, patients were asked to rate the level of perceived dyspnea on a modified Borg scale (0-10 points).[15] PaO_2 and $PaCO_2$ were measured in capillary blood from the earlobe, which is a common and well validated method in stable COPD patients.[16,17] Values were assessed before and directly following the 6MWTs.

Statistics

Patients were randomly assigned to start either with $6MWT_{O2}$ or $6MWT_{RA}$. Randomization was performed with a 1:1 ratio, on the basis of 4 permuted blocks with constant length (n=31).

Assuming a two-sided alpha level of 0.05 and a power of 95%, a sample size of n=124 including a drop-out rate of 15% was necessary to detect a clinically relevant difference of 6MWD of at least 30m between the two conditions (effect size: 0.35).

The “oxygen response”, defined as $6MWD_{O2}$ minus $6MWD_{RA,}$ was determined as the primary outcome parameter. Patients who increased their 6MWD by at least 30m due to $O_{2\_suppl.}$ were defined as "oxygen responders". As secondary outcomes, transcutaneous SpO_2, heart rate, PaO_2, $PaCO_2$ as well as dyspnea and fatigue levels rated on a modified Borg scale were used.

After checking data for normal distribution, comparisons of 6MWT outcomes between $6MWD_{O2}$ and $6MWD_{RA}$ were made by paired t tests. An ANOVA was used to determine differences between HYX, EIH and NOX COPD patients regarding the effects of $O_{2\_suppl.}$. To detect differences in the characteristic of oxygen responders and non-responders, an independent groups t-test was used. Due to the fact that NOX patients were not expected to improve 6MWD to a clinical relevant extent by using $O_{2\_suppl.}$, this subgroup analysis only included HYX and EIH patients.

All data was processed in PASW Statistics 18.0 (Chicago, IL, USA). Statistical significance was assumed if two-tailed p-value was less than 0.05.

RESULTS

Patient characteristics

124 patients were randomized and 108 completed the study (**Figure 1**). Baseline characteristics of 31 NOX (29%), 43 EIH (40%) and 34 HYX patients (32%) are summarized in **Table 1**.

Total COPD group

In the total cohort of 108 patients, 6MWD increased from 349m to 376m by using $O_{2\_suppl.}$ (+27m [95%CI: 19 to 35m] p<0.001). Moreover, 45 patients (41%) reached the threshold for clinical relevance (≥30m), while 8 patients (7%) walked further on compressed RA.

SpO_2 and PaO_2 values at the end of $6MWT_{O2}$ were significantly higher compared to $6MWT_{RA}$ (+5.9%, p<0.001 and +9.8mmHg, p<0.001). Heart rate was comparable after both 6MWT conditions. Symptoms of dyspnea were significantly lower after $6MWT_{O2}$ compared to $6MWT_{RA}$ (-0.9 pts., p<0.001), whereas leg fatigue did not differ (-0.1 pts, p=0.495).

Subgroups with different PaO_2 levels

Primary and secondary outcomes of the 3 subgroups are presented in **table 2**. $6MWD_{RA}$ was significantly lower in HYX compared to EIH and NOX patients. HYX patients needed longer stops during $6MWT_{RA}$ compared to EIH and NOX patients and showed a lower walking speed (2.5±1.8 km/h vs. 3.6±1.1 km/h and 3.6±1.1 km/h) with significant group differences between HYX vs. EIH and NOX patients.

By using O_2, 6MWD increased in HYX and EIH, but not in NOX patients (**Figure 2**). A clinically relevant improvement of ≥30m was observed in 47% of HYX, 42% of EIH and 26% of NOX patients (**Figure 3**). These oxygen responders had a significantly lower $6MWD_{RA}$ compared to non-responders (306±106m vs. 358±113m, p<0.05). All other clinical and $6MWT_{RA}$ data did not show any significant between-group difference (**Table 3**).

$O_{2\_suppl.}$ improved SpO_2 by 8.5% (HYX), 5.4% (EIH) and 3.5% (NOX) directly following the 6MWT in comparison to RA (**Figure 4**). Nevertheless, in 73.5% of HYX, 76.2% of EIH and 16.1% of NOX patients SpO_2 dropped below 88% or declined by ≥4% in the $6MWT_{O2}$. Also the PaO_2 values at the end of $6MWT_{O2}$ were significantly higher compared to $6MWT_{RA}$ in all

3 groups. $PaCO_2$ levels were significantly higher at the end of $6MWT_{O2}$ compared to $6MWT_{RA}$ in HYX and EIH but not in NOX patients.

Dyspnea scores at the end of $6MWT_{O2}$ were significantly lower compared to $6MWT_{RA}$ in EIH and NOX patients. The reduction, however, did not reach significance in HYX patients. 24% of HYX, 19% of EIH and 19% of NOX patients had a reduction in end-exercise dyspnea scores of ≥1 Borg point by breathing $O_{2\_suppl.}$. No significant between-group differences were observed.

DISCUSSION

Our findings reveal that COPD patients with resting or exercise-induced hypoxemia but not with normoxemia generally benefit in a clinically relevant magnitude from $O_{2\_suppl.}$ regarding 6MWD and SpO_2. Noticeably, less than half of HYX and EIH patients reached the threshold for clinically relevant 6MWD improvements by breathing $O_{2\_suppl.}$. These oxygen responders were characterized by significantly lower exercise capacity levels during $6MWT_{RA}$.

Oxygen-related effects on exercise capacity

For hypoxemic COPD patients, $O_{2\_suppl.}$ has been shown to improve exercise capacity, dyspnea and oxygenation.[18] In accordance, our results in the total group (+27m), in HYX (+37m) and in EIH patients (+28m) confirmed this by reaching a significant improvement in $6MWDO_2$ compared to $6MWD_{RA}$. As a clinical implication, it seems to be crucial to standardize 6MWTs by using or not $O_{2\_suppl.}$ in order to evaluate interventional treatments, e.g. pulmonary rehabilitation and to avoid bias caused by oxygen-related effects.

The recent ATS/ERS statement on field tests discussed an increase of ≥30m in 6MWD with a variability of 25 to 33m as clinically relevant.[7,19] However, only 47% of HYX and 42% of EIH patients who have a general indication for long-term or ambulatory oxygen therapy were

able to reach this level of clinical relevance by using $O_{2\_suppl.}$. In order to evaluate the characteristic of these oxygen responders, patients were divided into two subgroups of oxygen responders and non-responders. As a result, patients with lower exercise capacity level were detected to respond the most to $O_{2\_suppl.}$. We assume that O_2 increases oxygen delivery to peripheral muscles and may reduce glycolytic metabolism during exercise in oxygen responders. Thus, metabolic acidosis which is a strong stimulus for ventilation as well as a limitation for exercise tolerance is delayed.[20] As we did not detect lung function parameters differing between responders and non-responders, oxygen-processing systems such as oxidative enzymes in skeletal muscles might play a key role in explaining the oxygen response.

In normoxemic COPD patients, O_2-related effects are contradictory. Emtner et al. demonstrated that $O_{2\_suppl.}$ used during a 7-week exercise training program enables patients to keep training intensity at a higher level and therefore to improve endurance capacity significantly more compared to compressed air.[21] However, no significant increase of 6MWD was observed in NOX patients included in our study which is in line with the finding of Jolly et al..[9] This discrepancy might rely on the different methodology of applying oxygen as an adjunct to a several week exercise training program or just during a single assessment.

O_2-induced improvements in 6MWD we observed in our study were higher compared to results reported in a systematic review .[22] They found that $O_{2\_suppl.}$ improved 6MWD by 19m in hypoxemic patients, with a wide heterogeneity between the 8 included studies (from 6m to 52m; heterogeneity was defined as $I^2 \geq 20\%$ in a fixed-effect model). Most of these studies used a very short time interval between the two 6MWTs (10 to 60min) compared to ours (24h). This may partly explain the diverging results because muscle regeneration is further progressed after 24h and may facilitate performing the following 6MWT. Furthermore, in the studies included in the review patients could not be differentiated by the level of oxygenation

which was speculated to be a potential reason for the wide range of oxygen response in 6MWD. Also low vs. high doses of O_2 were used in these studies that might have influenced outcome parameters.[4]

Other oxygen-related effects

SpO_2 increased in the total group and in the 3 subgroups by using $O_{2\_suppl.}$, which is in line with the current literature.[6,9] However, there is not enough evidence to show that the SpO_2 increase of ≤4% observed in NOX patients is of any clinical relevance. Although 39% of NOX patients declined in SpO_2 by ≥4% during $6MWT_{RA}$, values of SpO_2 and PaO_2 did not drop below the protective threshold of 88% and 55.0mmHg, respectively. Nevertheless, in 73.5% of HYX and 76.2% of EIH patients SpO_2 values dropped below 88% during the 6MWT, although using $O_{2\_suppl.}$. In most of HYX and EIH patients, $O_{2_suppl.}$of 2l/min was not sufficient to enhance SpO_2 above 88%.

Symptoms of dyspnea were reduced by more than the MID of 1 point on the Borg scale [23] by using $O_{2\_suppl.}$ in EIH and NOX patients. Jolly et al. observed a reduction of dyspnea by using $O_{2\_suppl.}$ during 6MWT in COPD patients who desaturated during exercise (-2.1 Borg points) and in those who did not (-2.2 Borg points).[9] In our study, HYX patients did not show a clinically relevant reduction of dyspnea. This could be explained by the longer 6MWD that HYX patients were able to walk during $6MWT_{O2}$.

We observed a moderate increase in CO_2 levels during $6MWT_{O2}$. Although, HYX and EIH patients reached the threshold for hypercapnia, the recent guidelines for diagnosis and therapy of COPD stated that a $PaCO_2$ increase attributable to $O_{2\_suppl.}$ up to ≤60-70mmHg is no contraindication for the use of O_2.[17] In addition, we also observed an increase of CO_2 retention during 6MWT without $O_{2\_suppl.}$ that might indicate an exercise-induced increase which is independent on $O_{2\_suppl.}$.

In our study, some limitations have to be considered. First, we performed $6MWT_{O2}$ on 2 liters/min of oxygen. Although some patients would have needed more than 2l/min of O_2 during exercise to prevent from hypoxemia, we decided to standardize the procedure to this flow rate. With regard to the dose-dependent effect of oxygen,[4] patients might have reached higher O_2 benefits with higher flow rates. Additionally, in our study the investigator has carried the oxygen cylinder in order to determine the pure oxygen-related effects. Carrying the device is an additional burden for the patients that might affect physiological parameters in daily life.[24] Furthermore, the results of the three subgroups must be interpreted with caution, since the sample size calculation resulted in n=124 patients (minus 15% drop-out rate), while the subgroups are clearly smaller.

In conclusion, $O_{2\_suppl.}$ generally improved exercise capacity and oxygenation in COPD patients with resting as well as exercise-induced hypoxemia. However, these short-term benefits differed highly among patients who fulfilled the official criteria for ambulatory oxygen therapy.[1] Further studies have to evaluate the long-term benefits of $O_{2\_suppl.}$ during exercise in EIH patients.

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Authors contributions: IJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including adverse effects. RG, ED, AS and DB had substantial contributions to acquisition of data, revised the manuscript critically for important intellectual content, provided final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Additionally, RG and KK made substantial contributions to the

study design, analysis and interpretation of data and drafted (RG) and revised (KK) the manuscript. MS made substantial contributions to analysis and interpretation of data, revised the manuscript critically for important intellectual content, provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial/ nonfinancial disclosures: IJ and KK report grants for the clinic from ROX medical, California, USA, and study material (gases) from Linde Gas Therapeutics GmbH, Germany, during the conduct of the study. Outside the submitted work, MAS discloses receiving personal remuneration in the last two years for consultancy from Boehringer Ingelheim and GSK. RG, ED, AS, DB, and AJ have nothing to disclose.

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Other contributions: Inga Jarosch and Rainer Gloeckl contributed equally to the preparation of this manuscript.

REFERENCES

1 Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015; 70 Suppl 1:i1-43

2 Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. Chest 1982; 81:6-10

3 Porszasz J, Emtner M, Goto S, et al. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 2005; 128:2025-2034

4 Somfay A, Porszasz J, Lee SM, et al. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. Eur Respir J 2001; 18:77-84

5 Mannix ET, Boska MD, Galassetti P, et al. Modulation of ATP production by oxygen in obstructive lung disease as assessed by 31P-MRS. J Appl Physiol 1995; 78:2218-2227

6 Bradley JM, O'Neill B. Short-term ambulatory oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005:CD004356

7 Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44:1428-1446

8 van Helvoort HA, Heijdra YF, Heunks LM, et al. Supplemental oxygen prevents exercise-induced oxidative stress in muscle-wasted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173:1122-1129

9 Jolly EC, Di Boscio V, Aguirre L, et al. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. Chest 2001; 120:437-443

10 GOLD. Global Strategy of the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated February 2013; downloaded from www.goldcopd.org on 03.05.2013

11 Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26:720-735

12 Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176:532-555

13 Hernandes NA, Wouters EF, Meijer K, et al. Reproducibility of 6-minute walking test in patients with COPD. Eur Respir J 2011; 38:261-267

14 ATS statement: guidelines for the six-minute walk test. American journal of respiratory and critical care medicine 2002; 166:111-117

15 Kendrick KR, Baxi SC, Smith RM. Usefulness of the modified 0-10 Borg scale in assessing the degree of dyspnea in patients with COPD and asthma. J Emerg Nurs 2000; 26:216-222

16 Pitkin AD, Roberts CM, Wedzicha JA. Arterialised earlobe blood gas analysis: an underused technique. Thorax 1994; 49:364-366

17 Vogelmeier C, Buhl R, Criee CP, et al. [Guidelines for the diagnosis and therapy of COPD issued by Deutsche Atemwegsliga and Deutsche Gesellschaft fur Pneumologie und Beatmungsmedizin]. Pneumologie 2007; 61:e1-40

18 Bradley JM, O'Neill B. Short term ambulatory oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005:CD004356

19 Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J 2014; 44:1447-1478

20 Voduc N, Tessier C, Sabri E, et al. Effects of oxygen on exercise duration in chronic obstructive pulmonary disease patients before and after pulmonary rehabilitation. Can Respir J 2010; 17:e14-19

21 Emtner M, Porszasz J, Burns M, et al. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 2003; 168:1034-1042

22 Bradley JM, Lasserson T, Elborn S, et al. A systematic review of randomized controlled trials examining the short-term benefit of ambulatory oxygen in COPD. Chest 2007; 131:278-285

23 Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. Copd 2005; 2:105-110

24 Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". Lancet 1981; 1:907-909

TABLES

Table 1. Baseline characteristics

	Total (n=108)	HYX (n=34)	EIH (n=43)	NOX (n=31)
Male, %	67 (54)	27 (79)*	24 (56)**	13 (42)
Age, y	63 (9)	65 (8)	63 (8)	63 (11)
BMI, kg/m^2	24.8 (5.0)	26.1 (5.7)	24.3 (4.8)	24.7 (4.4)
FEV_1, % predicted	35.3 (11.5)	29.8 (8.4)***,#	35.8 (12.7)	40.8 (9.9)
FEV_1/FVC, %	45 (12)	45 (13)	41 (10)**	49 (13)
TLC, % predicted	126 (19)	120 (20)*	130 (19)	124 (16)
RV, % predicted	224 (55)	225 (59)	230 (52)	208 (48)
DLCO, mmol/min/kPa	35.8 (17.3)	29.7 (15.3)***	32.7 (12.4)***	46.1 (20.6)
PaO_2 at rest with room air, mmHg	58.9 (9.9)	49.4 (3.7)***,###	60.7 (4.2)***	68.2 (11.3)
$PaCO_2$ at rest with room air, mmHg	39.7 (6.8)	44.0 (6.4)***,###	38.9 (6.1)*	35.6 (5.0)

Values are mean (SD) unless otherwise noted. BMI=Body mass index; FEV_1=Forced expiratory volume in 1 second; FEV_1/FVC= ratio of FEV_1 and Forced vital capacity (Tiffeneau Index); TLC=total lung capacity; RV=residual volume; DLCO=diffusion capacity of the lung for carbon monoxide.

#p<0.05, ##p<0.01, ###p<0.001 (compared to EIH)

*p<0.05, **p<0.01, ***p<0.001 (compared to NOX)

Table 2 – End-exercise values of 6MWT outcomes in COPD patients with hypoxemia (HYX), exercise-induced hypoxemia (EIH) and normoxemia (NOX)

	HYX (n=34)			EIH (n=43)			NOX (n=31)		
	$6MWT_{RA}$	$6MWT_{O2}$	mean difference (95%CI)	$6MWT_{RA}$	$6MWT_{O2}$	mean difference (95%CI)	$6MWD_{RA}$	$6MWD_{O2}$	mean difference (95%CI)
Distance, m	283 (110)	320 (105)	37 (23 to 51)***	377 (96)	404 (94)	28 (14 to 41)***	380 (103)	395 (97)	15 (-1 to 30)
Stop length, sec	33 (69)	14 (30)	-19 (-2 to -37)*	8 (24)	4 (13)	-5 (0 to -9)*	6 (16)	1(5)	-5 (-11 to 2)
SpO_2, %	75 (9)	84 (8)	8.5 (6.4 to 10.6)***	79 (6)	84 (5)	5.4 (4.1 to 6.7)***	88 (5)	92(5)	3.5 (1.8 to 0.8)***
decline of ≥4% or end-SpO_2 ≤ 88%,% of patients	94	74	-20	100	76	-24	39	16	-23
Heart rate, beats/min	112 (19)	109 (18)	-2.9 (-6.5 to 0.6)	115 (16)	114 (15)	-1.0 (-5.0 to 3.0)	109 (16)	108 (16)	-1.8 (-6.1 to 2.5)
PaO_2, mmHg	42 (7)	51 (8)	9 (6 to 12)***	47 (5)	57 (9)	10 (8 to 12)***	64 (15)	75 (15)	11 (7 to 14)***
$PaCO_2$, mmHg	46 (8)	48 (7)	3 (1 to 5)**	43 (8)	45 (8)	2 (1 to 3)**	38 (6)	39 (6)	1 (-1 to 2)
Dyspnea, Borg	7.1 (1.9)	6.5 (1.6)	-0.6 (-1.3 to 0.1)	6.9 (1.8)	5.8 (1.9)	-1.1 (-1.6 to -0.5)***	6.1 (1.8)	5.0 (1.7)	-1.1 (-1.7 to -0.5)**
Leg fatigue, Borg	4.3 (2.8)	4.2 (2.3)	-0.1 (-0.7 to 0.5)	3.0 (2.5)	2.7 (2.0)	-0.2 (-0.8 to 0.4)	3.6 (2.2)	3.5 (2.1)	0.0 (-0.9 to 0.8)

Values are mean (SD) and deltas as mean. $6MWT_{RA}$= 6-minute-walk test on room air; $6MWT_{O2}$=6-minute-walk test on oxygen. Dyspnea and Fatigue were rated on a modified Borg scale (0-10), with higher scores denoting more severe symptoms. *p<0.05, **p<0.01, ***p<0.001

Table 3: Characteristics of oxygen responders compared to non-responders.

	Oxygen responder (n=34)	Non-responder (n=43)	Between-group differences (p value)
Male, %	55.8	61.5	n.s.
Age, y	63 (7)	65 (9)	n.s.
BMI, kg/m^2	24.1 (4.6)	25.9 (5.6)	n.s.
FEV_1, % predicted	30.8 (9.6)	35.0 (12.4)	n.s.
FEV_1/FVC, %	43 (10)	43 (13)	n.s.
TLC, % predicted	126 (22)	126 (19)	n.s.
RV, % predicted	232 (61)	224 (50)	n.s.
DLCO, mmol/min/kPa	29.7 (14.4)	32.9 (13.0)	n.s.
PaO_2 at rest with room air, mmHg	55.5 (7.0)	55.8 (6.9)	n.s.
$PaCO_2$ at rest with room air, mmHg	42.0 (7.1)	40.5 (6.3)	n.s.
End-exercise PaO_2, mmHg	45.1 (6.7)	44.6 (6.1)	n.s.
End-exercise $PaCO_2$, mmHg	45.5 (7.6)	42.9 (8.2)	n.s.
End-exercise dyspnea, Borg score	7.3 (1.7)	6.7 (1.9)	n.s.
End-exercise SpO_2, %	77 (9)	77 (7)	n.s.
End-exercise heart rate, bpm	114 (20)	113 (15)	n.s.
Stop length during $6MWT_{RA}$, sec	31 (65)	10 (33)	n.s.
$6MWD_{RA}$, m	306 (106)	358 (113)	<0.05

All end-exercise data were measured under room air condition ($6MWT_{RA}$). Values are mean (SD) unless otherwise noted. Oxygen responder=patients with 6MWD improvements ≥30m due to supplemental oxygen. BMI=Body mass index; FEV_1=Forced expiratory volume in 1 second; FEV_1/FVC= ratio of FEV_1 and Forced vital capacity (Tiffeneau Index); TLC=total lung capacity; RV=residual volume; DLCO=diffusion capacity of the lung for carbon monoxide; $6MWD_{RA}$=6-minute-walking distance on room air conditions.

FIGURE LEGEND

Figure 1: Flow diagram

Figure 2: Direct effect of supplemental oxygen compared to compressed room air on the 6-minute walk distance (6MWD) in hypoxemic patients (HYX), patients with exercise-induced hypoxemia (EIH) and normoxemic patients (NOX). Band marks the minimal important difference for the 6MWD (range: 25-33m)[19].

***p<0.001

Figure 3: Three groups were created according to the oxygen-related effect on the 6-minute walk distance: (a) no benefit (≤0m), (b) increase < 30m and (c) a clinically relevant benefit of ≥30m [19]. Data are presented in hypoxemic patients (HYX), patients with exercise-induced hypoxemia (EIH) and normoxemic patients (NOX).

Figure 4: Oxygen saturation (SpO_2) during 6-minute walk test with oxygen (O_2) versus room air (RA), measured pre, 1 minute and 3:30 minutes after starting and directly following the test in hypoxemic patients (A), patients with exercise-induced hypoxemia (B) and normoxemic patients (C). Dashed line marks the protective 88% threshold.

CONSORT 2010 Flow Diagram