Effect of a Ventilatory Assist Device in Addition to Supplemental Oxygen on Exercise Endurance in Subjects With COPD

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BACKGROUND: This study assessed the clinical effects of a ventilatory assist (VA) device in addition to supplemental O_2 ($VA+O_2$) on exercise endurance in subjects with severe to very severe COPD managed with long-term oxygen therapy (LTOT). METHODS: This was a crossover clinical feasibility study of the effects of $VA+O_2$ in subjects with severe to very severe COPD managed with LTOT ($N = 15$). At visit 1, physiologic measures were obtained, and subjects were tested on the cycle ergometer with VA. Peak work rate and flow for continuous supplemental O_2/$VA+O_2$ were established. At visit 2, subjects exercised at a constant work rate of 80% peak work rate to maximum endurance after allocation to $VA+O_2$ or O_2. Cardiorespiratory variables, work rate, and dyspnea were included to define potential clinical benefits of $VA+O_2$. Data were analyzed using a linear mixed model. RESULTS: Fifteen subjects with COPD (mean ± SD, age 67.9 ± 9.0 y, FEV_1 0.89 ± 0.35 observed) completed the study. Exercise duration in minutes was significantly longer with $VA+O_2$ versus O_2 (least squares mean [standard error], 12.0 [2.0] vs 6.2 [2.0], $P = .01$). $VA+O_2$ versus O_2 was also associated with significantly greater isotime improvements in Borg dyspnea scores (3.6 [0.5] vs 5.7 [0.5], $P < .001$), S_{pO_2} (96.9 [0.9] vs 91.4 [0.9], $P < .001$), leg fatigue scores (3.8 [0.6] vs 5.2 [0.6], $P = .008$), and breathing frequency (22.8 [0.9] vs 25.8 [0.9] breaths/min, $P = .01$). There were no differences in heart rate. CONCLUSIONS: In symptomatic subjects with severe to very severe COPD, $VA+O_2$ significantly increased exercise time and improved dyspnea, S_{pO_2}, breathing frequency, and leg fatigue versus O_2 alone. *Key words: COPD; pulmonary ventilation; dyspnea; exercise endurance; leg fatigue; oxygen therapy.* [Respir Care 2024;69 (5):527–533. © 2024 Daedalus Enterprises]

Introduction

Limited exercise tolerance is a hallmark symptom of COPD and has a significant, negative effect on quality of life.[1] Improving exercise tolerance and endurance is an important treatment goal. Widely used strategies for improving exercise intolerance in patients with COPD include pharmacotherapies such as long-acting bronchodilators and pulmonary rehabilitation.[1] Supplemental O_2 has been studied as a way to ameliorate exercise intolerance, but results have been inconsistent.[2] Most studies on supplemental O_2 report improvements in exercise duration[3-5] and dyspnea,[3,4] but others show improvements in exercise duration but no effects on dyspnea, health status, or quality of life.[6,7] Bell et al[8] conducted a systematic review on studies evaluating short-term O_2 therapy in subjects with interstitial lung disease, demonstrating no significant effects on dyspnea[9,10] but improved peak work capacity[9] and exercise endurance time.[11,12]

A number of assist devices have been designed to address the limitations of standard O_2 therapy.[13-15] Most are bulky, complex to operate, cumbersome to wear, and have had limited adoption due to these shortcomings as well as cost. Newer noninvasive open ventilation (NIOV) systems (eg, Life2000 Ventilation System, Hillrom, Chicago, Illinois) are more portable than previous systems, allowing patients greater mobility. A previous study on subjects with severe COPD demonstrated improved stationary exercise duration using NIOV.[16] However, these devices can be expensive and can function only with O_2 cylinders that are heavy, bulky, and detract from portability. Thus, there is an unmet need for portable devices that further increase patient mobility and ability to perform daily activities.

The present study's intent was to evaluate the clinical benefits of ventilatory assist (VA) + supplemental O_2 ($VA+O_2$) in comparison to standard low-flow nasal O_2, investigating the effect on exercise endurance, dyspnea, oxygenation, and leg fatigue in subjects with severe to very severe COPD.

Methods

This was an open-label, crossover, clinical feasibility study (ClinicalTrials.gov registration, NCT02278107). The study was conducted at the John Muir Health Center Outpatient Center pulmonary rehabilitation facility in Concord, California. Subjects were recruited and alternatively assigned to the crossover sequence according to the protocol approved by the John Muir Health Concord Center's Institutional Review Committee (protocol number P-JM-001-2014) and in accordance with good clinical practice guidelines.

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VA+O_2 was delivered using a VA device (Tidal Assist Ventilator, Inogen, Goleta, California). This NIOV assist device weighs 3.8 ounces (about 108 g) and was designed to be powered by compressed O_2 delivered by a cylinder, wall source, or modified higher-pressure stationary O_2 concentrator. The device was designed to be worn on the patient's body and is breath activated. When activated, a bolus of delivered O_2 (1–5 L/min O_2) entrains additional room air at the nasal interface, delivering it under positive pressure during the patient's inhalation to assist breathing. The VA device has a control to adjust the flow of synchronized positive inspiratory pressure to one of 5 levels to meet the patient's perceived need and activity level. O_2 alone was delivered via a standard nasal cannula attached to either an E-size O_2 cylinder or an O_2 concentrator.

Clinically stable volunteer subjects (males and females age $\geq$ 18 y) with a diagnosis of severe to very severe COPD who required between 2–5 L/min of constant-flow O_2 to maintain $S_{pO_2} > 90\%$ during exercise were included in the study. Subjects had to be able to use the VA device and cycle ergometer and were willing and able to provide written, informed consent. Patients were excluded if they reported serious epistaxis $\leq$ 14 d of study start, were currently enrolled or had participated in another clinical trial $\leq$ 30 d of study start, or showed any condition or abnormality that in the opinion of the investigators may have compromised the participant's safety or the quality of the study data.

QUICK LOOK

Current knowledge

Severe COPD is associated with hypoxemia and reduced exercise tolerance, which impact patients' quality of life. Despite advances in the modern modalities of O_2 therapy, the limitations in the ability to augment activities of daily living present a significant unmet need, which might be addressed by combining O_2 therapy with ventilation. This warrants the use of delivery systems that are lightweight and noninvasive, providing patients with greater autonomy.

What this paper contributes to our knowledge

This study used a submaximal physical stress model on a stationary device, and a crossover design in subjects with severe to very severe COPD. When compared to continuous O_2 therapy alone, ventilatory assistance combined with O_2 significantly improved mean exercise endurance, S_{pO_2}, dyspnea, and leg fatigue. The magnitude of the observed effect was nearly a doubling, but there was variability between individual subjects. This exploratory study supports further investigation of the clinical benefits and utility of ventilatory assist + O_2 therapy.

Subjects who met all inclusion criteria were consented and allocated to a treatment sequence. The allocation process was based on a coin flip to determine the treatment order for participant number 1, after which every other subject started with the alternate therapy (1:1 ratio VA+O_2 or O_2). Neither the subjects nor the investigators were blinded to the therapy administered. No sham controls were utilized. Subjects were provided with scripted encouragement by the investigators.

The study design consisted of 2 visits and used a protocol modified from Porszasz et al.[16] During visit 1, baseline physiologic measures, including vital signs and ratings on the Borg dyspnea[17,18] and leg fatigue scales, were obtained. Subjects received training on the cycle ergometer (SO1000R Recumbent Bike, SCIFIT, Tulsa, Oklahoma) and the VA device. Peak work rate O_2 flow

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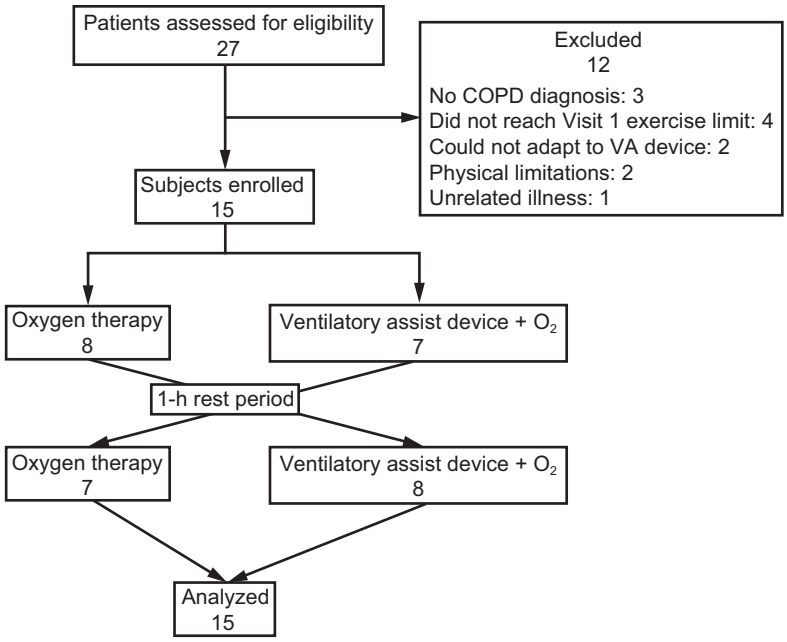

Fig. 1. Flow chart. VA = ventiltory assist

was established by incrementing the subject's work rate on the cycle ergometer in the range of 2–10 W and titrating the constant flow O_2 level to maintain an average S_{pO_2} level of 90–93%, as possible. The flow of the VA device could be adjusted by the subjects to their level of comfort while maintaining $S_{pO_2} > 90\%$; then the subjects exercised at a constant work rate of 80% of the peak work rate.

A week later, subjects returned for visit 2, when they were to first use the VA+O_2 or O_2 according to their initial allocation and at the respective flows as determined during the baseline study, while exercising for as long as they could at a constant work rate of 80% peak work rate. After a 1-h rest period, subjects switched (crossover phase) to the other mode of treatment and repeated the exercise protocol. No data were gathered during the recovery phase.

Cycling exercise time was determined by stopwatch from the start of cycling at 80% peak work rate until the subject could no longer sustain that work load. Additional measures collected were the Borg scale ratings of dyspnea,[17,18] leg fatigue ratings, S_{pO_2} (forehead and finger pulse oximeters, LNCS TF-I adult forehead sensor, Masimo, Irving, California), heart rate (pulse oximeters, RD SET Adt, Masimo), and breathing frequency/min (counted by the investigator). Except for endurance time, end point comparisons were taken at the point of exercise termination for the shorter constant work rate test (VA +O_2 or O_2) for each subject (referred to as isotime). In addition, heart rate and S_{pO_2} were monitored continuously, with values recorded every 30 s. Dyspnea and discomfort scores were collected every 60 s independently of the isotime measurements. Only the isotime data points were used as dependent measures. Safety and tolerability were assessed by recording all adverse events throughout the study. The study was conducted between October 2014–February 2016.

Statistical Analysis

Continuous data were summarized by means and SD, and categorical data were summarized by counts and percentages. The effect of the intervention on each of the end points was assessed using a linear mixed model fit with restricted maximum likelihood and including treatment, period, and sequence as fixed effects and a random intercept per subject. For all analyses a 2-sided 0.05 level of significance was used. The analyses were conducted using SAS Enterprise Guide software, version 8.3 update 3 (SAS Institute, Cary, North Carolina).

Results

Twenty-seven patients (16 males/11 females) with moderate to very severe COPD were screened and completed visit 1; 15 subjects (mean ± SD, age 67.9 ± 9.0 y) with COPD were enrolled. Twelve subjects were screen failures (Fig. 1). Baseline demographic and pulmonary function characteristics of subjects who completed the study are shown in Table 1. The individual subjects' baseline VA+O_2, O_2 flows, and baseline S_{pO_2} with O_2 alone and with VA+O_2 are presented in the online supplementary materials, Table SM1 (see related supplementary materials at http://www.rcjournal.com).

Table 1. Baseline Demographics and Pulmonary Function by Sequence

Characteristic	Standard O_2-VA+O_2 ($n = 8$)	VA+O_2-Standard O_2 ($n = 7$)	Total ($N = 15$)
Age, y	67.8 ± 6.9	68.0 ± 11.6	67.9 ± 9.0
Sex			
Female	5 (62.5)	3 (42.9)	8 (53.3)
Male	3 (37.5)	4 (57.1)	7 (46.7)
BMI, kg/m^2	27.0 ± 6.1	26.7 ± 5.0	26.8 ± 5.4
FEV_1, observed	0.84 ± 0.25	0.94 ± 0.47	0.89 ± 0.35
FVC, observed	1.88 ± 0.73	1.87 ± 0.78	1.88 ± 0.72
FEV_1/FVC, observed	0.47 ± 0.11	0.52 ± 0.11	0.49 ± 0.11
FEV_1/FVC, % predicted	0.60 ± 0.13	0.66 ± 0.15	0.63 ± 0.14
GOLD stage (2/3/4)	0/4/4	1/4/2	1/8/6
Flow setting (1–5) during exercise with VA+O_2, L/min	3.6 ± 0.5	3.1 ± 0.4	3.4 ± 0.5
Flow setting (1–5) during exercise with standard O_2, L/min	2.6 ± 1.1	2.6 ± 1.1	2.6 ± 1.1
Constant work rate, W	27.8 ± 14.3	28.4 ± 14.9	28.1 ± 14.0
Peak work rate, W	34.7 ± 17.8	35.5 ± 18.6	35.1 ± 17.5

Data are presented as *n* (%) or means ± SD.
VA = ventilatory assist
VA+O_2 = VA device in addition to supplemental O_2
BMI = body mass index
GOLD = Global Initiative for Chronic Obstructive Lung Disease

There were no significant effects of treatment order or period on exercise endurance, isotime dyspnea scores, S_{pO_2}, or leg fatigue scores (online supplementary materials, Table SM2, see related supplementary materials at http://www.rcjournal.com). Exercise endurance times for individual subjects are presented in Figure 2.

Mean exercise times (Table 2) almost doubled during use of VA+O_2 versus O_2 (least squares [LS] mean [standard error [SE]] 12.0 [2.0] vs 6.2 [2.0], $P = .01$). However, there was notable variability in individual results (Fig. 2). For treatment effects on blood O_2 saturation, the between–treatment-group LS mean (SE) difference in S_{pO_2} was 5.5 (0.9) ($P < .001$). Breathing frequency was significantly less with VA+O_2 versus O_2; the between–treatment-group LS mean (SE) difference was −2.9 (1.0) ($P = .01$). Between–treatment-group LS mean (SE) differences in Borg dyspnea ($P < .001$) and leg fatigue scores ($P = .008$) favored VA+O_2 over O_2. Heart rate values were similar in the 2 conditions ($P = .77$) (Table 2). VA+O_2 was well tolerated, and no adverse events occurred during either treatment period.

Discussion

In this open-label, crossover study, conducted on clinically stable subjects with severe to very severe COPD enrolled in an out-patient rehabilitation program, VA+O_2 improved cycling endurance, dyspnea, S_{pO_2}, breathing frequency, and leg fatigue versus O_2 alone. For the primary end point, subjects using the VA+O_2 increased their cycle endurance by 5.8 min (94%) over O_2; and Borg dyspnea scores dropped by 2.1 points, which is considered a clinically meaningful improvement.[19] Breathing frequency was significantly lower with VA+O_2 versus O_2, which is probably related to the higher S_{pO_2} levels observed in the VA+O_2 group. Heart rate response was similar during exercise, suggesting that the increased endurance was achieved despite a similar cardiovascular response. In addition, the VA+O_2 was well tolerated with no reported adverse events.

These findings are consistent with those previously reported by Porszasz et al[16] in a similar population of subjects with severe COPD treated with the similar NIOV device. In that study, there was a 214% increase in cycle endurance time with the NIOV versus standard O_2 (17.6 min vs 5.6 min). There also was a significant reduction in dyspnea at isotime but no change in transcutaneous P_{CO_2}. S_{pO_2} at isotime was 5.8% higher with the NIOV+O_2 (98.5%) compared to standard O_2 (92.7%), very close to the 5.5% higher forehead S_{pO_2} observed with the VA+O_2 compared to O_2. Intercostal, scalene, and diaphragm electromyography (EMG) activities were reduced during NIOV use compared with standard nasal O_2, suggesting respiratory muscle unloading. EMG was not measured in the current study, but the significantly lower breathing frequency in the VA+O_2 group compared with the standard nasal O_2 group is also consistent with reduced respiratory muscle work.

The mechanism for the improved exercise endurance with ambulatory ventilation systems has not been defined. Porszasz et al[16] speculated that reduced respiratory muscle activation (as evidenced by the reduced respiratory muscle EMG activity) and enhanced oxygenation were the main mechanisms, with the latter being related to the greater oxygenation efficiency of the NIOV versus standard continuous

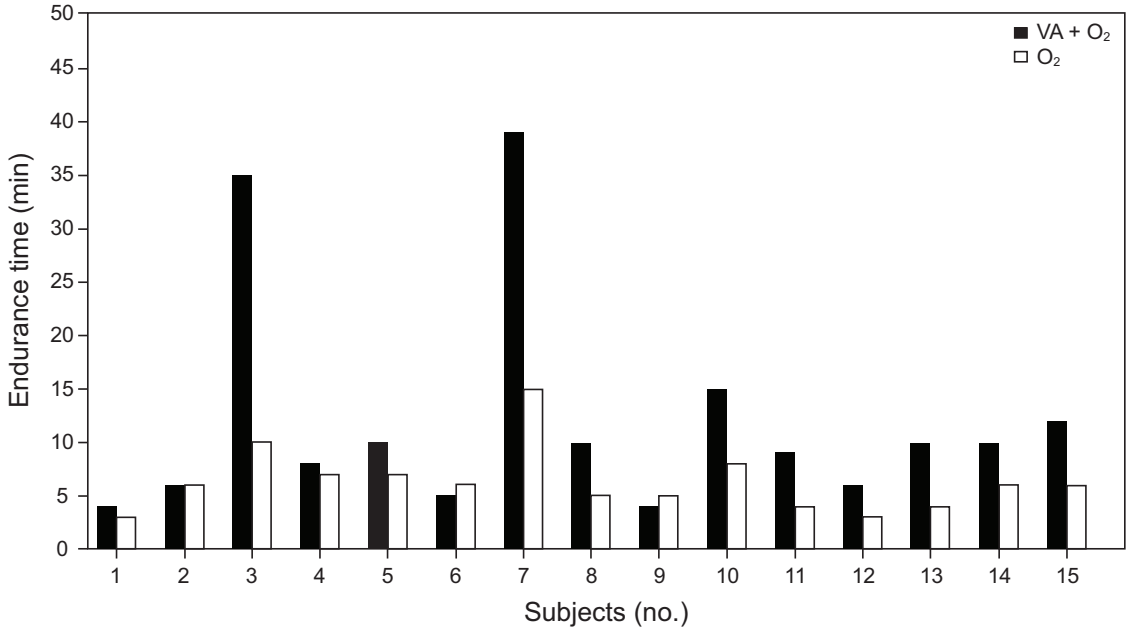

Fig. 2. Exercise endurance time (min) with VA+O_2 vs O_2 alone.

Table 2. Constant Work Rate Exercise Testing

Variable	VA+O_2	Standard O_2	Treatment Difference	*P*
Exercise time, min*				
LS mean (SE)	12.0 (2.0)	6.2 (2.0)	5.8 (2.0)	.01
95% CI	7.9–16.1	2.1–10.3	1.5–10.1	
Borg dyspnea score				
LS mean (SE)	3.6 (0.5)	5.7 (0.5)	−2.1 (0.4)	< .001
95% CI	2.5–4.7	4.6–6.7	−2.9 to −1.3	
S_{pO_2}, %				
LS mean (SE)	96.9 (0.9)	91.4 (0.9)	5.5 (0.9)	< .001
95% CI	94.9–98.9	89.4–93.3	3.7–7.4	
Leg fatigue score				
LS mean (SE)	3.8 (0.6)	5.2 (0.6)	−1.4 (0.5)	.008
95% CI	2.5–5.0	3.9–6.4	−2.4 to −0.4	
Heart rate, beats/min				
LS mean (SE)	111.3 (4.9)	110.9 (4.9)	0.5 (1.6)	.77
95% CI	100.8–121.9	100.3–121.4	−2.9 to 3.8	
Frequency, breaths/min				
LS mean (SE)	22.8 (0.9)	25.8 (0.9)	−2.9 (1.0)	.01
95% CI	20.9–24.8	23.8–27.7	−5.2 to −0.7	

*Assessed at the end of test.
Inferential statistical tests were evaluated using a linear mixed model where sequence, period, and treatment were included as fixed effects, and a random effect was included for each subject.
VA = ventilatory assist
VA+O_2 = VA device in addition to supplemental oxygen
LS = least squares
SE = standard error

or pulsed O_2 delivery systems. Both the NIOV and VA+O_2 devices inject a predetermined volume of O_2 timed during inspiration that enriches inspired gas, although the actual F_{IO_2} of the inspiratory gas mixture has not been measured. The substantially greater S_{pO_2} at isotime in the NIOV+O_2 group compared to the standard O_2 group supports this idea. The injected bolus of O_2 during inspiration with the NIOV and VA+O_2 devices increases inspiratory flow that could

assist inhalation, lowering work of breathing. However, Porszasz et al[16] found that when the NIOV injected the same volume of air (NIOV+air) there was less decrease in dyspnea than with NIOV+O_2 and no increase in exercise endurance compared to air without NIOV. This suggests that it is the O_2 in the bolus more than the augmented gas flow that is primarily responsible for benefit. Furthermore, the novel observation that leg fatigue is reduced with VA+O_2 as compared to standard O_2 suggests an additional mechanism for prolonged cycle duration, perhaps related to improved O_2 delivery.

A concern with these devices is that patients with very severe airway obstruction could develop dynamic hyperinflation during exertion that could delay triggering of a pulsed device, countering its benefit.[20] However, the lower breathing frequency (and longer expiratory phase) observed with VA+O_2 should mitigate this effect. Better understanding of the mechanisms of benefit as well as potential adverse effects of VA+O_2 will require further investigation.

Previous studies have shown favorable effects of noninvasive devices on stationary exercise endurance, including continuous and bi-level positive airway pressure devices, and proportional assist ventilation, all administered via noninvasive masks.[13-15] However, these devices are not well tolerated because of the need to use tight-fitting masks, and they are not sufficiently portable to provide benefit during ambulation.

The main limitations of our study are related to the overall small number of subjects, although the study was successful in detecting significant differences in multiple physiologic outcomes. The main advantage of the crossover design is that it permits powerful paired statistical analyses, requiring a much smaller sample size than a randomized parallel design. However, it also raises the concern about potential carry-over effects. In this study, a 1-h rest period before crossover was used to mitigate any carry-over effects. The randomization scheme was applied only to the first subject, with subsequent subjects alternating the order of conditions. However, there were no differences in results attributable to treatment order (see online supplementary materials, Table SM2). Although not a true randomization procedure, this assured control for the order of conditions. Furthermore, the investigators and subjects were not blinded to the condition, so possible bias cannot be excluded.

Conclusions

These findings support the idea that VA+O_2 therapy could offer an alternative to O_2 therapy alone that could address the unmet need for a portable VA device that improves oxygenation and enhances exercise endurance while decreasing dyspnea and leg fatigue. It is important to bear in mind that the current results are acute, short-term physiologic outcomes obtained using cycle ergometry and that O_2 supply necessitated an E-tank or modified stationary concentrator. Thus, the results cannot be extrapolated to performance of activities of daily living during the long term. Future larger and longer-term studies of VA+O_2 using more portable O_2 sources are needed to better understand the mechanisms of benefit, patient characteristics that predict a favorable response, patient acceptance and tolerability, and effects on activity levels in everyday settings.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2024. https://goldcopd.org/2024-gold-report.
2. Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B; Long-term Oxygen Treatment Trial Research Group. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. Chest 2010;138(1):179-187.
3. Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gene RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. Chest 2001;120 (2):437-443.
4. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in non-hypoxemic COPD patients. Eur Respir J 2001;18(1):77-84.
5. Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. Chest 1982;81(1):6-10.
6. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive-pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162(4 Pt 1):1335-1341.
7. McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. Am J Respir Crit Care Med 1995;152(5 Pt 1):1616-1619.
8. Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, et al. Oxygen therapy for interstitial lung disease: a systematic review. Eur Respir Rev 2017;26(143).
9. Harris-Eze AO, Sridhar G, Clemens RE, Gallagher CG, Marciniuk DD. Oxygen improves maximal exercise performance in interstitial lung disease. Am J Respir Crit Care Med 1994;150(6 Pt 1):1616-1622.
10. Nishiyama O, Miyajima H, Fukai Y, Yamazaki R, Satoh R, Yamagata T, et al. Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. Respir Med 2013;107(8):1241-1246.
11. Anderson SD, Bye PT. Exercise testing in the evaluation of diffuse interstitial lung disease. Aust N Z J Med 1984;14(5 Suppl 3): 762-768.
12. Bye PT, Anderson SD, Woolcock AJ, Young IH, Alison JA. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. Am Rev Respir Dis 1982;126(6):1005-1012.
13. Bianchi L, Foglio K, Pagani M, Vitacca M, Rossi A, Ambrosino N. Effects of proportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia. Eur Respir J 1998;11(2):422-427.
14. Bianchi L, Foglio K, Porta R, Baiardi R, Vitacca M, Ambrosino N. Lack of additional effect of adjunct assisted ventilation to pulmonary rehabilitation in mild COPD patients. Respir Med 2002;96(5):359-367.
15. Hawkins P, Johnson LC, Nikoletou D, Hamnegård C-H, Sherwood R, Polkey MI, et al. Proportional assist ventilation as an aid to exercise

training in severe chronic obstructive pulmonary disease. Thorax 2002;57(10):853-859.
16. Porszasz J, Cao R, Morishige R, van Eykern LA, Stenzler A, Casaburi R. Physiologic effects of an ambulatory ventilation system in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;188 (3):334-342.
17. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381.
18. Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. N Engl J Med 2009;360 (13):1329-1335.
19. Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg scale, and Visual Analog Scale. COPD 2005;2(1):105-110.
20. O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev 2006;15(100):61-67.