Adjuncts to Physical Training of Patients With Severe COPD: Oxygen or Noninvasive Ventilation?

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BACKGROUND: Previous studies have shown positive effects from noninvasive ventilation (NIV) or supplemental oxygen on exercise capacity in patients with COPD. However, the best adjunct for promoting physiologic adaptations to physical training in patients with severe COPD remains to be investigated. METHODS: Twenty-eight patients (mean ± SD age 68 ± 7 y) with stable COPD (FEV_1 34 ± 9% of predicted) undergoing an exercise training program were randomized to either NIV (*n* = 14) or supplemental oxygen (*n* = 14) during group training to maintain peripheral oxygen saturation (S_{pO_2}) ≥ 90%. Physical training consisted of treadmill walking (at 70% of maximal speed) 3 times a week, for 6 weeks. Patients were assessed at baseline and after 6 weeks. Assessments included physiological adaptations during incremental exercise testing (ratio of lactate concentration to walk speed, oxygen uptake [$\dot{V}_{O_2}$], and dyspnea), exercise tolerance during 6-min walk test, leg fatigue, maximum inspiratory pressure, and health-related quality of life. RESULTS: Two patients in each group dropped out due to COPD exacerbations and lack of exercise program adherence, and 24 completed the training program. Both groups improved 6-min walk distance, symptoms, and health-related quality of life. However, there were significant differences between the NIV and supplemental-oxygen groups in lactate/speed ratio (33% vs −4%), maximum inspiratory pressure (80% vs 23%), 6-min walk distance (122 m vs 47 m), and leg fatigue (25% vs 11%). In addition, changes in S_{pO_2}/speed, $\dot{V}_{O_2}$, and dyspnea were greater with NIV than with supplemental-oxygen. CONCLUSIONS: NIV alone is better than supplemental oxygen alone in promoting beneficial physiologic adaptations to physical exercise in patients with severe COPD. *Key words: bi-level positive airway pressure; chronic respiratory disease; exercise training; exercise tolerance; non invasive ventilation; oxygen supplementation*. [Respir Care 2010;55(7):885–894. © 2010 Daedalus Enterprises]

Introduction

COPD is a highly prevalent disease and causes substantial morbidity and mortality in the adult population. COPD is characterized by chronic limitation of expiratory air flow, which leads to considerable disability, especially with an increasing severity of COPD.[1] Exercise intolerance in patients with COPD has been ascribed to respiratory mechanical abnormalities, pulmonary gas-exchange disturbances, and deconditioning of skeletal muscle.[2] In this context, a pulmonary rehabilitation program that incorporates physical training is the best way to improve exercise tolerance and quality of life in these patients.[3]

However, patients with more severe COPD may not be able to exercise[4] at a level that produces physiological

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adaptations, due to extreme dyspnea,[5] reduced muscle strength, and pronounced fatigue.[3,6,7] Additionally, patients with severe COPD present arterial hypoxemia during exercise and daily activities.[6] Thus, oxygen therapy and noninvasive ventilation (NIV) have been used as adjuncts to exercise in COPD patients, to enhance the effectiveness of exercise training.[8-12]

Some investigators have found that oxygen therapy during physical exercise significantly increases exercise tolerance and reduces dyspnea,[12-15] in hypoxemic[12] and normoxemic COPD patients.[15] Conversely, other studies found that supplemental oxygen during the physical training program did not affect exercise performance, compared to room air,[14,16] and a recent systematic review found inconclusive results about the effects on exercise tolerance in COPD patients.[17]

Recently, another approach to increasing exercise tolerance has been NIV. Some studies have found that NIV promotes control of the deleterious effects of dynamic hyperinflation on exercise capacity[8-11] and increases minute ventilation,[18] unloads respiratory muscles,[19] prolongs exercise-induced lactataemia,[20] decreases dyspnea, and increases exercise capacity.[8-11,19-21] In addition, Dreher et al[22] found that NIV plus supplemental oxygen, but not oxygen alone, prevented oxygen desaturation during walking in patients with severe COPD.

Although previous studies have shown the positive effects of NIV or supplemental oxygen as physical exercise adjuncts, no previous study has looked at the potential for the most effective adjunct during exercise training programs in COPD patients. Therefore, we evaluated the effects of 2 different adjuncts, NIV (via bilevel positive airway pressure) versus supplemental oxygen, that could promote better physiologic adaptations to physical training in patients with severe COPD. We hypothesized that NIV alone could promote a true physiological training effect after training that is greater than that of oxygen supplementation. An additional hypothesis was that the physiological mechanisms of improvement could be associated with better exercise performance.

Methods

This study was performed in the Physiotherapy Department of the Federal University of São Carlos, São Carlos, São Paulo, Brazil.

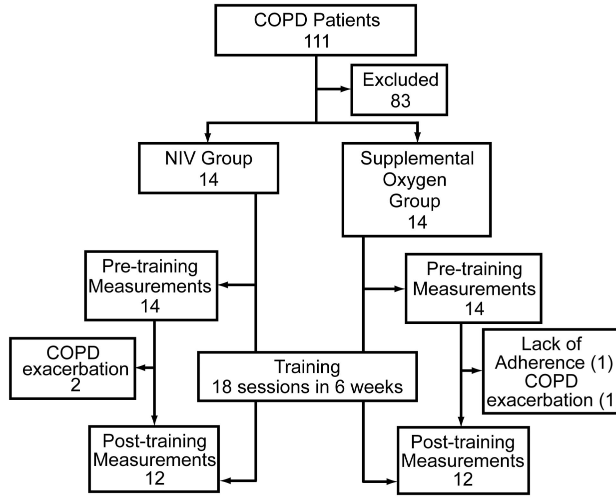

Fig. 1. Flowchart of patient participation and study protocol.

A prospective randomized trial was undertaken. One-hundred eleven patients were screened and 28 patients were included. We excluded patients with orthopedic or neurological conditions that would preclude participation in an exercise program; a history of cardiac arrhythmias or potential electrocardiographic alterations; a history consistent with heart disease, uncontrolled hypertension, diabetes mellitus, other respiratory diseases; or failure to comply with the research protocol. Eighty-three patients were excluded, due to concomitant cardiopathy ($n = 14$), other respiratory disease ($n = 5$), neurological deficit ($n = 2$), oxygen desaturation to $< 85\%$ ($n = 8$), and $FEV_1 > 50\%$ of predicted ($n = 39$). In addition, 8 patients declined participation without citing a reason, and 7 patients cited transportation issues as a primary reason for declining study participation.

Patients who were included presented stable, physician-diagnosed COPD, $FEV_1 < 50\%$ (corresponding to a Global Initiative for Chronic Obstructive Lung Disease [GOLD][1] stages III and IV), and a history of smoking. In addition, patients could not have been engaged in regular physical activity for at least 6 months. All patients were receiving regular treatment, consisting of inhaled bronchodilators and steroids, but were not using oral steroids or antibiotics. The study protocol was approved by our institutional ethics committee, and all participants signed a consent form before the initial testing session.

All the patients participated in a physical training program and were randomized to either NIV ($n = 14$) or supplemental oxygen ($n = 14$) by drawing of shuffled, opaque, coded envelopes that were opened immediately before starting each case. The flowchart of the patient's participation and protocol of the study is shown in Figure 1.

The authors have disclosed no conflicts of interest.

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Outcome Measurements

Patients underwent the study assessments on an outpatient basis, before and after a 6-week physical training program. The primary outcome measurement was the lactate concentration related to speed (lactate/speed ratio) as a main physiological adaptation after training. Secondary outcome measures included 6-min walk distance, peak $\dot{V}_{O_2}$, and Borg dyspnea index on cardiopulmonary exercise testing.

Procedures

Lung and Respiratory Muscle Function. Vital capacity and forced vital capacity maneuvers were performed with a spirometer (Hand-Held 2021, Vitalograph, Buckingham, England), according to recommendations for pulmonary function testing. At least 3 measurements of each maneuver were considered acceptable, and we determined the FEV_1, vital capacity, and forced vital capacity values according to the standardization of lung function testing.[23] Respiratory muscle strength was assessed by measuring maximum inspiratory and expiratory pressure, according to the method of Neder et al.[24] Maximum inspiratory and expiratory pressure were assessed with the maneuver starting at residual volume and total lung capacity, respectively, using a manovacuometer (Ger-Ar Med, São Paulo, Brazil) with scale of $\pm$ 300 cm H_2O. The subjects were verbally encouraged to give maximum effort. The determinations were repeated until 3 measurements differed by $< 5\%$.

6-Minute Walk Test. The 6-Min Walk Test was performed as described by the American Thoracic Society guidelines.[25] Two 6-min walk tests were performed on different days. The result of the second test was considered for analysis, because the first test tends to underestimate exercise capacity due to the subject's lack of familiarity with the test.[25] Each patient was instructed to walk as far as possible during the allotted time, and all patients were given standardized encouragement during the test.

St George's Respiratory Questionnaire (SGRQ). The SGRQ is a valid and reliable measure of health-related quality of life (HRQOL) in patients with COPD.[26] The SGRQ consists of 50 items with 76 responses and 3 component scores: symptoms, activities, and impacts (psychosocial dysfunction). A total score is calculated from all 3 components. A score of zero indicates no health impairment, and 100 represents maximum impairment. The SGRQ has been validated for the Brazilian population.[26]

Cardiopulmonary Exercise Testing. Using the protocol of Borghi-Silva et al,[27] an incremental symptom-limited exercise test was performed on a treadmill (ATL, Inbrasport, RS [Rio Grande do Sul], Brazil). The tests were terminated when, after standardized encouragement (ie, "keep up the good work" or "keep on a bit more"), the patient was unable to continue because of dyspnea. Simultaneously, S_{pO_2}, heart rate, systolic blood pressure, and speed were continuously monitored.[27] Blood samples were collected from the ear lobe to measure lactate, and analyzed on a lactimeter (YSI 1500 Sport, YSI Life Sciences, Yellow Springs, Ohio) as previously described.[27] Blood lactate at the peak and corrected for peak speed (lactate/speed]) were considered an index of aerobic performance. We measured respiratory rate, tidal volume, $\dot{V}_{O_2}$, carbon dioxide output ($\dot{V}_{CO_2}$), and minute ventilation throughout the test (VO_{2000}, Medical Graphics, St Paul, Minnesota), and we analyzed the highest values reached during the incremental protocol.[28]

Peripheral Muscle Strength and Fatigue Test. Maximum concentric isokinetic knee extensor strength on the dominant side was measured with an isokinetic dynamometer (System 3, Biodex Medical Systems, Shirley, New York, New York). All subjects performed (1) a maximum isokinetic strength test at an angular velocity of 60°/s to measure peak torque, and (2) a leg-fatigue test for 1 min at an angular velocity of 60°/s, to measure the total work, total power, and leg-fatigue index.[29] The subjects were verbally encouraged using high-demand instructions during all tests. Total power is expressed in watts, and a fatigue index is expressed as the percentage ratio between the work performed in the 3 last and 3 initial contractions during dynamometer isokinetic tests.[29]

Physical Training Protocol

The patients underwent a physical training program of 1-hour treadmill sessions 3 times per week, on alternate days, for 6 weeks. In the NIV group, NIV was delivered with a bi-level ventilator (BiPAP-S, Respironics, Murrysville, Pennsylvania) applied via a tight-fitting nasal or face mask. The airway pressure was titrated according to the method of Diaz et al.[30] The inspiratory level was initially set at 6 cm H_2O, then gradually increased, by increments of 2 cm H_2O every minute, to the maximum tolerated pressure. Expiratory pressure was started at 3 cm H_2O, then gradually increased by 1 cm H_2O every minute, to the maximum tolerated pressure. The gradual increase in inspiratory and expiratory pressures was aimed at increasing comfort and exercise capacity and maintaining $S_{pO_2} > 90\%$ during exercise training. These values were set in a rather arbitrary manner; the goal was to provide what would be considered by most clinicians as a relatively low expiratory pressure and a moderate inspiratory pressure support.[30]

The supplemental-oxygen group received oxygen via dual-prong nasal cannulae, at 1–3 L/min, which we stipulated as the minimum flow sufficient to keep the fingertip oxygen saturation > 90% during the physical training.

Each session consisted of a 5-min walking warm-up at 2 km/h, then 30 min with an initial intensity target of 70% of the patient's peak speed determined in the pre-training incremental exercise test.[28] After that 30-min period the patient did a cool-down period of stretching lower and upper limbs, in seated and supine positions, then vital signs final measurements were taken. Each session was supervised by a physiotherapist, who vigorously encouraged the patients to reach the intensity and duration targets. The intensity of training increased progressively in both groups in the successive sessions. The increase was 0.5 km/h when the patient's dyspnea was less than 4 on the Borg dyspnea scale.

Statistical Analysis

The target number of patients was calculated to be 28, based on a 5% type 1 error, a 2-sided test, and an 80% power to detect a 33% change of lactate/speed ratio between the groups. These calculations were based on the clinically important lactate difference.[31] Analyses were performed according to the intention-to-treat principle, assuming that patients who dropped out had the same chance for the average improvement in both groups.

Results are expressed as mean ± SD. We used the paired *t* test and Wilcoxon test for intra-group analysis, and the unpaired *t* test or Mann-Whitney test to compare inter-group responses, as appropriate. The gains obtained by the groups were derived from absolute delta comparisons (post-treatment minus pre-treatment). P values < .05 were considered significant. In addition, we considered clinically relevant a distance increase of > 50 m, a Borg dyspnea index reduction of 1 point, and an HRQOL score reduction of 4 points, according the methods of Make et al.[32] We used these criteria to classify patients as responders and non-responders. We used Pearson's correlation analysis to evaluate the relationship between the changes in 6-min walk distance and peak S_{pO_2}. The analysis was carried out with statistics software (Statistica 5.1, StatSoft, Tulsa, Oklahoma, and StatMate 1.01, GraphPad Software, San Diego, California).

Results

Twenty-eight patients were included in the study: 14 were assigned to NIV and 14 to supplemental oxygen. Two patients in the supplemental-oxygen group and 2 in the NIV group discontinued the study because of adverse events. Among these 4 patients, 3 (2 from the NIV group and 1 from the supplemental-oxygen group) had COPD exacerbations that disallowed continuing with the physical training and that required antibiotics and systemic steroids. One of the patients who had a COPD exacerbation required intensive-care admission. One patient dropped out after 2 weeks of training, complaining of a pain in the knee and difficulty in continuing the treadmill training.

Table 1. Patient Characteristics and Resting Pulmonary Function

	Group*	
	NIV (n = 14)	Supplemental Oxygen (n = 14)
Female (n)	5	5
Age (mean ± SD y)	68 ± 9	67 ± 7
Weight (mean ± SD kg)	61 ± 8	68 ± 11
Height (mean ± SD cm)	161 ± 1	163 ± 1
BMI (mean ± SD kg/m^2)	24 ± 4	25 ± 3
FEV_1 (mean ± SD L)	0.8 ± 0.3	0.8 ± 0.2
FEV_1 (mean ± SD % predicted)	34 ± 10	33 ± 7
FVC (mean ± SD L)	1.9 ± 0.7	2.0 ± 0.6
FVC (mean ± SD % predicted)	64 ± 17	66 ± 15
P_{aO_2} (mean ± SD mm Hg)	65 ± 8	63 ± 8
P_{aCO_2} (mean ± SD mm Hg)	42 ± 6	44 ± 6
S_{aO_2} (mean ± SD %)	92 ± 4	91 ± 3
Required domiciliary supplemental oxygen (n)	6	6
BODE index† (mean ± SD)	6.2 ± 2.0	6.0 ± 1.5

* There were no significant differences between the groups.
† The BODE index uses a 10-point scale based on body mass index, airflow obstruction, dyspnea, exercise capacity.
NIV = noninvasive ventilation
BMI = body mass index
FVC = forced vital capacity
S_{aO_2} = arterial oxygen saturation at rest

All the patients who remained in the study completed 18 exercise training sessions. Randomization resulted in well-balanced groups with respect to possible prognostic factors for outcomes of exercise training, patient characteristics, resting pulmonary function, and BODE index, which uses a 10-point scale based on body mass index, airflow obstruction, dyspnea, exercise capacity (Table 1).[33] All the patients had moderate to severe air-flow obstruction. Six patients in the NIV group and 5 in the supplemental-oxygen group had GOLD stage II COPD, and the remaining patients had GOLD stage III or IV COPD.

The mean ± SD inspiratory and expiratory pressures were 12 ± 1 cm H_2O and 4 ± 2 cm H_2O, respectively. The supplemental-oxygen group's mean ± SD oxygen flow was 1.5 ± 0.8 L/min during the training sessions. Two patients in the NIV group used a face mask and 12 opted for the nasal mask.

The intensity of training increased progressively in both groups, and there was no significant difference in the max-

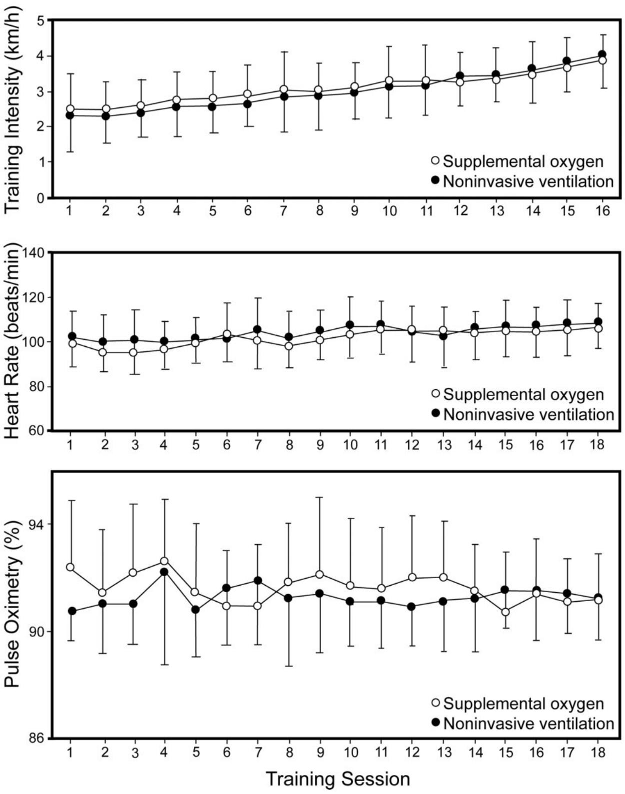

Fig. 2. Evolution of training intensity, heart rate, and pulse oximetry readings during the exercise training sessions. The values are as mean ± SD. There were no significant differences between the groups.

imum training intensity between the groups (Fig. 2). Heart rate similarly increased across the sessions in both groups (see Fig. 2). Mean S_{pO_2} remained ≥ 90% in both groups during physical training (see Fig. 2).

Table 2 shows the differences in the outcomes after the training program. In the NIV group 10 patients walked more than 50 m, in contrast to 6 patients in the supplemental-oxygen group. There was a significant increase in 6-min walk distance in both groups, but this improvement was significantly higher in the NIV group ($P < .01$). Only the NIV group had significant improvements in respiratory muscle strength (maximum inspiratory and expiratory pressure), peripheral muscle strength (peak torque, total work, total power), and fatigue index after the training program (see Table 2). The NIV group had significantly higher maximum inspiratory pressure and significantly lower leg fatigue after training than did the supplemental-oxygen group. HRQOL, symptoms, and disease impact were significantly lowered in both groups, but the activity and total SGRQ scores were significantly reduced only in the NIV group after training.

Table 2 also shows the outcomes differences at peak exercise in the incremental exercise test. Speed, heart rate, minute ventilation, tidal volume, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ peak significantly increased, and respiratory rate and dyspnea significantly decreased only in the NIV group after training. In the supplemental-oxygen group, the lactate peak was significantly higher at peak exercise after training. There was significant reduction in lactate/speed ratio only in the NIV group. Furthermore, the lactate/speed ratio was significantly lower in the NIV group, compared to the supplemental-oxygen group.

Figure 3 shows the before-versus-after changes at peak exercise in the incremental exercise test. There was a significant difference in the change in lactate/speed ratio, $\dot{V}_{O_2}$, dyspnea, and S_{pO_2}/speed between the groups. $\dot{V}_{O_2}$ significantly increased, whereas lactate/speed ratio and dyspnea and S_{pO_2}/speed significantly decreased in the NIV group, compared to the supplemental-oxygen group.

Figure 4 shows the significant positive correlation between peak S_{pO_2} after training and change in 6-min walk distance after training in both groups ($r = 0.79$, $P < .01$).

When patients were classified as responders and non-responders, 64% in the NIV group and 43% in the supplemental-oxygen group were responders. Three non-responders in the NIV and four in the supplemental-oxygen group used domiciliary oxygen. The non-responders in the NIV group had lower body mass index and related greater impact from COPD in their SGRQ score, when compared to responders. In relation to the supplemental-oxygen group, the non-responders were older, had significant lower maximal performance (expressed by $\dot{V}_{O_2}$, lactate/speed ratio, and SGRQ activity score), had more desaturation during peak exercise and dyspnea, and impaired quality of life, when compared to the responders (Table 3).

Discussion

The main findings of this study are:

1. NIV improved physiological adaptations, as shown by reduced lactate/speed ratio.
2. NIV was associated with better physiological adaptations (significant and clinically meaningful changes) on submaximal performance, $\dot{V}_{O_2}$, dyspnea and S_{pO_2}, when contrasted with the supplemental-oxygen group.
3. The 6-week exercise training program with NIV or supplemental oxygen improved symptoms and the impact of disease on HRQOL.

Importance of This Study and Methodological Considerations

To our knowledge, this is the first study to contrast the effects of a physical training program in which several

Table 2. Effects of Noninvasive Ventilation Versus Supplemental Oxygen

	Noninvasive Ventilation (n = 12)		Supplemental Oxygen (n = 12)	
	Before Training (mean ± SD)	After Training (mean ± SD)	Before Training (mean ± SD)	After Training (mean ± SD)
Maximum inspiratory pressure (cm H_2O)	41 ± 29	74 ± 28*	43 ± 21	50 ± 23†
Maximum expiratory pressure (H_2O)	67 ± 25	88 ± 40*	67 ± 38	69 ± 40
6-min walk distance (m)	372 ± 115	494 ± 103*	373 ± 103	420 ± 104*†
Dynamometry				
Peak torque (Newton-meters)	97 ± 33	115 ± 40*	94 ± 24	99 ± 26
Total work (J)	1,315 ± 444	1,481 ± 445*	1,367 ± 366	1,397 ± 379
Total power (W)	46 ± 14	57 ± 21*	46 ± 12	47 ± 12
Fatigue index (SD %)	44 ± 13	32 ± 12*	44 ± 18	49 ± 20†
SGRQ Scores				
Symptoms	54 ± 16	40 ± 19*	59 ± 21	41 ± 20*
Activity	51 ± 13	25 ± 19*	47 ± 19	34 ± 23
Impacts	52 ± 25	32 ± 21*	52 ± 17	41 ± 17*
Total	50 ± 20	29 ± 19*	52 ± 17	37 ± 15
Incremental Exercise Testing				
Walk speed (km/h)	2.9 ± 1.0	4.4 ± 1.0*	3.2 ± 0.9	3.7 ± 1.3
Heart rate (beats/min)	107 ± 12	116 ± 11*	110 ± 13	110 ± 12
$\dot{V}_{O_2}$/heart rate (mL · beats/min)	8.3 ± 1.6	9.4 ± 1.7	8.4 ± 1.6	8.6 ± 2.1
Minute ventilation (L/min)	29.9 ± 6.9	33.8 ± 7.6*	29.5 ± 4.3	30.7 ± 7.3
Respiratory rate (breaths/min)	31 ± 4	29 ± 3*	30 ± 5	31 ± 4
Tidal volume (L)	0.96 ± 0.17	1.17 ± 0.21*	1.0 ± 0.20	1.0 ± 0.18
$\dot{V}_{CO_2}$ (mL/min)	0.89 ± 0.17	1.03 ± 0.25*	0.93 ± 0.24	0.96 ± 0.17
$\dot{V}_{O_2}$ (mL/min)	0.88 ± 0.16	1.07 ± 0.22*	0.92 ± 0.17	0.95 ± 0.18
Lactate (mmol/L)	1.8 ± 0.7	1.8 ± 0.5	1.9 ± 0.8	2.2 ± 0.7*
Lactate/speed (mmol/L/km/h)	0.7 ± 0.3	0.4 ± 0.2*	0.6 ± 0.2	0.6 ± 0.3†
S_{pO_2} (%)	88 ± 2	88 ± 3	87 ± 2	87 ± 2
Systolic blood pressure (mm Hg)	178 ± 13	181 ± 17	180 ± 20	177 ± 21
Dyspnea (Borg score [0–10 scale])	5.5 ± 2.1	3.5 ± 1.8*	4.6 ± 1.7	4.2 ± 2.2

* Significant difference for before vs after training ($P < .05$).
† Significant difference between groups after training ($P < .01$).
SGRQ = St George's respiratory questionnaire
$\dot{V}_{O_2}$ = oxygen uptake
$\dot{V}_{CO_2}$ = carbon dioxide output

outcomes of training with NIV (bi-level positive airway pressure) or supplemental oxygen were compared in patients with severe COPD. Previous studies have reported the effects of each adjunct to physical training compared to a control group.[8,31,33] Furthermore, those authors also demonstrated that NIV can increase performance, reduce dyspnea, and prevent oxygen desaturation during exercise; nevertheless, different from the present study, most of them used oxygen plus NIV in a substantial number of patients.[8,33] We also investigated whether this potential effect of NIV or supplemental oxygen could be sustained after a 6-week physical training program, through the assessments of the patients without any influence of adjuncts. Another aspect was the intensity of training, which could be increased similarly between groups, independently of the adjunct tested.

Effects of NIV and Supplemental Oxygen on Inspiratory Muscle Strength and 6-Minute Walk Distance

Respiratory muscle weakness was observed in both groups before training, which possibly contributed to the initial reduced exercise capacity, arising from a mechanical disadvantage of the ventilatory muscles and early fatigue.[1,2] During maximal exercise, fatigability would cause ischemia of the diaphragm, thus evoking respiratory muscle metaboreflex and a consequent sympathetic mediated vasoconstriction in the exercising muscles.[34] The improvement of inspiratory muscle strength in the NIV group could be explained by the reduction of mechanical load and a delay in the onset of respiratory muscle fatigue,[35,36] with

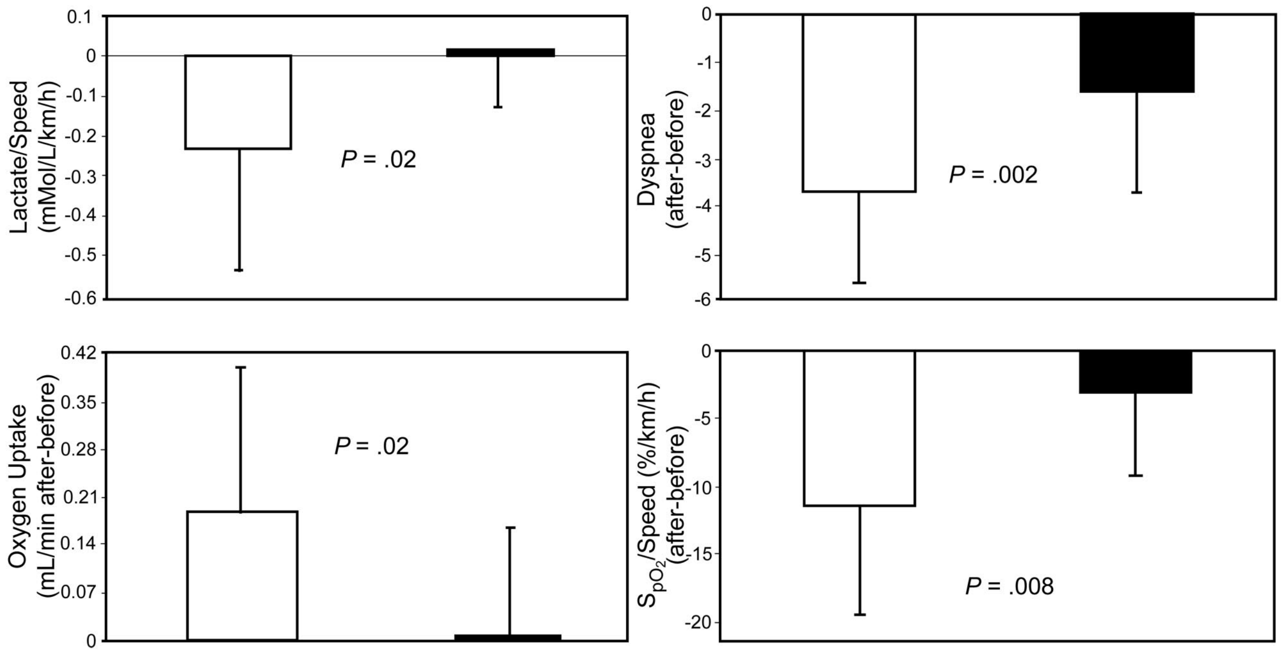

Fig. 3. Changes (before versus after exercise training program) in lactate/speed ratio, dyspnea, $\dot{V}_{O_2}$, and S_{pO_2}/speed at peak exercise in the incremental exercise test. White bars = noninvasive ventilation. Black bars = supplemental oxygen. The error bars show the standard error.

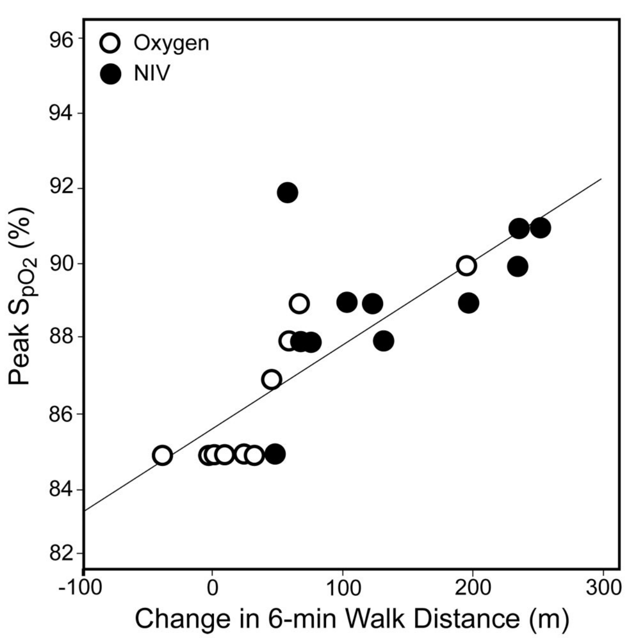

Fig. 4. Correlation between peak S_{pO_2} after training and change in 6-min walk distance (before vs after exercise training program with either noninvasive ventilation [NIV] or supplemental oxygen) (r = 0.79, $P < .01$).

reduction of inspiratory muscle metaboreflex activity. In this way, we speculated that the clinically meaningful improvement in 6-min walk distance in the NIV group may be explained by a respiratory muscle strength improvement that contributed to leg-fatigue reduction.

Effects of NIV on Physiological Responses in the Cardiopulmonary Exercise Testing and Peripheral Muscle Strength and HRQOL

Only the NIV group had significant increases in $\dot{V}_E$, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ peak in the incremental test, as they did for peripheral muscular strength and reduced leg fatigue. Moreover, a significant reduction in the dyspnea and lactate/speed ratio was seen only in the NIV group (see Table 2 and Fig. 3). In a previous study we demonstrated the beneficial effect of NIV on $\dot{V}_{O_2}$ after physical training.[37] The decrease in lactate/speed ratio also suggests a better oxidative capacity of the exercising muscles, and, thus, true beneficial physiologic adaptations. Some authors[33] have shown increased capillary density, mitochondria, and oxidative enzymes in the quadriceps of COPD patients following cycle training, which suggests greater muscular efficiency between the production and the removal of lactate.

We have previously demonstrated that respiratory muscle unloading with NIV improved leg oxygenation in patients with COPD.[19] In well trained, healthy subjects, NIV during high-intensity exercise improved respiratory muscle effort by redistributing blood flow away from the exercising leg muscles and to the respiratory muscles.[38] NIV during training in our current study may have likewise unloaded the respiratory muscles, thereby minimizing the impact of diminished respiratory muscle blood flow, enabling most effective physiologic adaptations to peripheral muscles.

Table 3. Characteristics of Responders and Non-Responders

	Noninvasive Ventilation			Supplemental Oxygen		
	Responders ($n = 9$) (mean ± SD)	Non-Responders ($n = 5$) (mean ± SD)	P	Responders ($n = 6$) (mean ± SD)	Non-Responders ($n = 8$) (mean ± SD)	P
Age (y)	65 ± 10	72 ± 4	.13	63 ± 6	71 ± 4	.01
Body mass index (kg/m^2)	25 ± 4	21 ± 2	.04	24 ± 3	26 ± 4	.24
FEV_1 (% predicted)	34 ± 10	33 ± 10	.80	34 ± 5	33 ± 8	.57
P_{aO_2} at rest (mm Hg)	66 ± 6	64 ± 7	.60	67 ± 6	61 ± 8	.14
Maximum inspiratory pressure (cm H_2O)	41 ± 32	39 ± 20	.64	39 ± 22	41 ± 19	.84
Peak torque (Newton-meters)	100 ± 38	91 ± 5	.46	90 ± 25	85 ± 31	.14
6-min walk distance (m)	356 ± 129	353 ± 99	.45	392 ± 95	332 ± 105	.28
Maximum speed (km/h)	3.5 ± 1.4	3.0 ± 1.0	.48	3.2 ± 1.0	2.9 ± 1.0	.60
$\dot{V}_{CO_2}$ (% predicted)	60 ± 20	50 ± 14	.30	62 ± 14	43 ± 11	.02
Heart rate (% predicted)	71 ± 10	69 ± 9	.59	73 ± 10	73 ± 12	.95
$\dot{V}_{O_2}$/heart rate (% predicted)	85 ± 34	74 ± 24	.45	86 ± 20	64 ± 21	.04
Lactate/speed (mmol/L/km/h)	0.65 ± 0.4	0.47 ± 0.3	.23	0.52 ± 0.2	1.0 ± 0.5	.03
Dyspnea (Borg score [0–10 scale])	6 ± 2	5 ± 1	.39	4 ± 2	6 ± 1	.01
Peak S_{pO_2} (%)	88 ± 2	87 ± 3	.65	88 ± 2	85 ± 1	.01
SGRQ Scores						
Activity	54 ± 28	45 ± 21	.55	38 ± 8	48 ± 20	.01
Impacts	53 ± 15	46 ± 21	.05	35 ± 8	56 ± 23	.01
Total	51 ± 21	58 ± 14	.45	35 ± 20	52 ± 19	.001

$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_{O_2}$ = oxygen consumption
SGRQ = St George's Respiratory Questionnaire

The reduction in lactate/speed ratio and leg fatigue, and the increase in submaximal exercise in the NIV group following training demonstrate it was possible to achieve a greater level of effort during the proposed reassessment. Although lactate remained unchanged at peak exercise in the incremental exercise test after training, the significant increase in the speed and reduced dyspnea indicate that aerobic physical capacity had increased. Some studies also have demonstrated that exercise can improve muscle aerobic metabolism and functional capacity, which decreases dyspnea for a given metabolic demand.[33] We found no evidence of a similar effect in the supplemental-oxygen group.

The S_{pO_2} improvement in the NIV group could be explained by 4 mechanisms: improved ventilation, reduced dynamic hyperinflation, better ventilation-perfusion matching, or improved pulmonary hemodynamics. However, the roles of the 3 latter mechanisms were not specifically addressed in this study and therefore remain speculative. Desaturation during exercise has been observed in some COPD patients, and NIV might preserve hypoxic ventilatory drive, which might prevent hypoxia-induced complications associated with physical exercise.[21] In fact, exercise performance was expressly related to oxygen desaturation in both groups (see Fig. 4).

Additionally, previous studies observed that supplemental oxygen also substantially improves exercise tolerance in normoxemic and slightly hypoxemic patients.[12] The mechanism of this benefit is related to increased P_{aO_2} and carotid-body inhibition, better muscle oxygenation, and reduced lactic acid.[12,39] The inconsistency of similar findings in the supplemental-oxygen group can be explained by the absence of supplemental oxygen over the tests, and the maintenance of exercise training level in both groups. Emtner et al[12] showed that supplemental oxygen permitted higher exercise training intensity, but the time of tolerance, maximal exercise performance, and true physiological benefits were not better after training when these patients were tested on room air.

In the present study, although supplemental oxygen in COPD patients improved maximal exercise capacity and HRQOL, there was superiority in the physiologic adaptations in the NIV group. Another plausible explanation for the poor results in the supplemental-oxygen group may be related to the supplemental oxygen dose offered in this study ($S_{pO_2} > 90\%$, mean flow 1.5 ± 0.8 L/min, which corresponded to an F_{IO_2} of 0.24–0.28%). As in our study, Somfay et al[40] suggested that improvements of exercise tolerance were observed when patients were supplemented in low doses, and, in contrast, other studies[12,39] reported positive effects of oxygen in high doses.

HRQOL has become an established outcome measure for evaluating the efficacy of therapies. Thus, the improvement of exercise tolerance in the 6-min walk test and the reduction of dyspnea could be reflected in improvement of HRQOL as evaluated by the SGRQ. This study demonstrated improvement in the SGRQ impacts and symptoms domains in both groups after training, and this is in accordance with previous studies that reported improved quality of life following rehabilitation programs, independent of any training adjunct.[8,41] In addition, a change of at least 4 points in the total SGRQ score is the established clinically important minimum,[32] and, in this context, we observed that this improvement was achieved by groups trained.

Responders and Non-Responders to NIV and Supplemental Oxygen

The results from the non-responders should be read with caution, because we analyzed only a few patients in each subgroup. Despite the fact that the non-responders in the NIV group had lower body mass index, that was not associated with lower exercise performance or skeletal muscle weakness. In the NIV group the responders and non-responders had, on average, a similar rise of physiological responses and ventilatory limitation. However, a previous study showed that patients who presented a combination of decreased skeletal muscle force and some preserved ventilatory reserve at the end of maximal exercise were prone to improvement.[42] However, the non-responders in the supplemental-oxygen group were older and presented significantly reduced functional capacity, as shown by reduced $\dot{V}_{O_2}$ and lactate/speed ratio, more dyspnea, and desaturation during peak exercise. These findings were accompanied by lower SGRQ scores. In this study, desaturation in the supplemental-oxygen group was accompanied by a higher lactate/speed ratio, lower $\dot{V}_{O_2}$, and lower S_{pO_2}, suggesting a worsening in muscle oxygenation. In accordance with our results, previous studies showed that desaturation could negatively impact exercise performance during exercise in these patients.[12,17]

Limitations

We did not assess if the groups had similar static or dynamic lung volumes or diffusion capacity. However, the groups' ventilatory limitation, ventilatory pattern, and dyspnea were similar. In addition, we did not measure for consistent changes in hemodynamic variables between the groups, which could explain our results. However, S_{pO_2} could indirectly reflect cardiopulmonary oxygen transport. Furthermore, considering the small sample size, it was not possible to determine with certainty which patient characteristics would predict the effectiveness of NIV or supplemental oxygen before training. However, we did find a consistent association between desaturation and submaximal performance ($r = 0.79$, $P < .001$)

Conclusions

In patients with severe COPD in a 6-week exercise training program, NIV alone was more beneficial than supplemental oxygen alone in improving submaximal exercise tolerance and HRQOL. These data suggest that NIV was more effective than supplemental oxygen as adjunct to physical exercise to promote beneficial physiologic adaptations to physical training in patients with severe COPD. However, studies with large samples must be conducted on this topic.

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