

Ventilatory Support during Training Improves Training Benefit in Severe Chronic Airway Obstruction

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Abstract

Background: One mechanism that may limit training effect in chronic obstructive pulmonary disease is the ventilatory limitation and associated dyspnea.

Objectives: To minimize ventilatory limitation during training of patients with severe COPD by applying bi-level positive pressure ventilation during training in order to augment training intensity (and effect).

Methods: The study group comprised 19 patients (18 males, 1 female) with a mean age of 64 ± 9 years. Mean forced expiratory volume in 1 second was $32 \pm 4\%$ of predicted, and all were ventilatory-limited (exercise breathing reserve 3 ± 9 L/min, normal > 15 L/min). The patients were randomized: 9 were assigned to training with BiPAP and 10 to standard training. All were trained on a treadmill for 2 months, twice a week, 45 minutes each time, at maximal tolerated load. Incremental maximal unsupported exercise test was performed before and at the end of the training period.

Results: BiPAP resulted in an increment of $94 \pm 53\%$ in training speed during these 2 months, as compared to $41 \pm 19\%$ increment in the control group ($P < 0.005$). Training with BiPAP yielded an average increase in maximal oxygen uptake of $23 \pm 16\%$ ($P < 0.005$), anaerobic threshold of $11 \pm 12\%$ ($P < 0.05$) and peak O_2 pulse of $20 \pm 19\%$ ($P < 0.05$), while peak exercise lactate concentration was not higher after training. Interestingly, in the BiPAP group, peak exercise ventilation was also $17 \pm 20\%$ higher after training ($P < 0.05$). Furthermore, contrary to our expectation, at any given work rate, ventilation (and tidal volume) in the BiPAP group was higher in the post-training test as compared to the pre-training test, and the end tidal partial pressure of CO_2 at 55 watts was lower, 40 ± 4 and 38 ± 4 mmHg respectively ($P < 0.05$). No improvement in exercise capacity was observed after this short training period in the control group.

Conclusion: Pressure-supported ventilation during training is feasible in patients with severe COPD and it augments the training effect. The improved exercise tolerance was associated with higher ventilatory response and therefore lower $P_{ET}CO_2$ at equal work rates after training.

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Impaired exercise tolerance affects the quality of life of patients with chronic obstructive pulmonary disease. Pulmonary rehabilitation is an attempt to improve this disability. The physiologic response to training depends on its frequency, intensity and

duration [1]. Previous studies have shown that in moderate COPD, high intensity training ($>70\%$ of peak oxygen uptake or maximal work rate and/or above the anaerobic threshold) induces a significant training effect [2-7]. However, it is generally believed that in severe obstruction, high intensity training is not possible due to ventilatory limitation [5,6,8-11]. Recent studies have shown an 11-17% improvement in peak oxygen uptake after intense training in severe COPD [2,5,12,13]. However, the message from most rehabilitation programs is that in severe disease, improvement is limited and is achieved only after prolonged and intensive training [5,6,8-11]. To facilitate training efficiency, investigators have attempted to overcome ventilatory limitation and thereby augment training intensity. Most of the studies found that the use of oxygen during training, which reduces ventilation for a given task, has no benefit over room-air training [14,15]. Recently, a study demonstrated higher training intensity with supplemental oxygen in non-hypoxemic COPD patients, but the training effect on exercise capacity was not higher compared with room-air training. [16].

The use of bi-level positive pressure ventilation during exercise increased endurance by 48%, walking distance by 62% and exercise duration above the AT, and attenuated dyspnea [8,17]. In these studies, support was used only during exercise testing but not as an aid to augment training intensity. Three studies used ventilatory support during training, but in no subject was peak unsupported exercise $\dot{V}O_2$ max higher after supported training [18-20].

We hypothesized that attenuation of the ventilatory limitation during training by using pressure support will enhance training intensity and thereby increase training effect in more severe COPD. We further hypothesized that this improved effect will be carried over to unsupported exercise. In the present study, this approach was tested in severe COPD by measuring unsupported $\dot{V}O_2$ max and AT before and after training, while ventilation during training was augmented by BiPAP, as compared with standard unsupported training.

Patients and Methods

Patients

Twenty-four patients with severe, stable COPD participated in the training program of the Pulmonary Institute at Sheba Medical Center. The diagnosis of COPD was based on smoking history, classical clinical findings, and pulmonary function testing, which confirmed the presence of severe, mostly irreversible, bronchial

* Deceased

COPD = chronic obstructive pulmonary disease
BiPAP = bi-level positive pressure ventilation
 $P_{ET}CO_2$ = end tidal partial CO_2 pressure

AT = anaerobic threshold
 $\dot{V}O_2$ = peak oxygen uptake

obstruction (defined as forced expiratory volume in 1 second <40% of predicted and <12% reversibility). Only patients who were ventilatory limited during exercise (exercise breathing reserve of <5 L/min) were chosen. No other diseases that could limit exercise capacity (cardiovascular, orthopedic or neuromuscular) were present. The institutional ethics committee approved the study and participants signed an informed consent.

Evaluation

Subjects were evaluated within 1 week before and at the end of the 8 week training program. Pulmonary function tests included spirometry and body plethysmography (Jaeger ML/b- AT, Germany). Incremental cycle ergometry was performed using the CPX system (MedGraphics, MN, USA) while breathing through a full-face mask. Expiratory fraction of O₂ and expiratory fraction of CO₂ were measured by discrete analyzers and expired ventilation (V'_E) by a heated wire. $V'O_2$ and carbon dioxide production were calculated breath by breath, and plotted as a 10 second moving average. Electrocardiogram and percent saturation of hemoglobin O₂ were recorded throughout the test (BCI Autocore, USA). Peripheral venous blood was sampled for plasma lactic acid concentration 2 minutes after cessation of exercise [21].

After resting on the cycle for 3 minutes, exercise was started by unloaded pedaling for 3 minutes. Work rate was then increased incrementally at a rate of 15 watts/min to fatigue. After training, each subject repeated the same tests. No ventilatory assistance was given during the pre- and post-training exercise testing.

Measurements

Peak O₂ uptake was considered as $V'O_2$ max. The AT was determined by the V-slope method and confirmed by the traditional gas exchange method [22]. Maximal voluntary ventilation was estimated by multiplying FEV₁ by a factor of 35 [23]. Although it was not feasible to blind the patients or the trainers to the condition of their exercise training, the investigators conducting exercise testing and interpreting the exercise data did so without knowing to which group patients were assigned.

Training program

Subjects were randomly assigned (by choosing a sealed envelope) to be trained with or without BiPAP. Training sessions were held on a treadmill (the only component of the training program) twice a week for 8 weeks. The aim was to reach an intensity of 65–70% at each subject's own predetermined maximum and to maintain it for 45 minutes. This was achieved gradually by increasing the treadmill speed at increments of 0.2 km/hour each week and the length of time that the exercise continued. The slope was maintained at 0 throughout. The initial speed was not less than 2 km/hour and was based on what the patient was able to maintain for 15 minutes. When a patient was able to maintain that target intensity for 45 minutes, the speed was further increased by a constant increment of 0.2 km/hr each week unless severe dyspnea was observed.

Supplemental oxygen was delivered during training to achieve an Hb-O₂S% of >92%. The oxygen saturation was monitored during training by pulse oximeter (BCI Autocore). The pressure support was provided using a ventilator (BiPAP, Respironics, USA) via a silicon full-face mask. Subjects had a week to adjust to the BiPAP before training. During the first pre-training session the BiPAP apparatus was set according to the patients' comfort, at rest and during exercise. The expiratory pressure was maintained constant at 2 cm H₂O, and the inspiratory pressure was set at the minimum value of 4 cm H₂O. Later, the inspiratory pressure was titrated at 2 cm H₂O increments in each patient, as long as the patient felt comfortable, to achieve a tidal volume equal to that reached by each individual at his/her peak exercise. This pressure ranged from 7 to 10 cm H₂O. We expected that this V_T would enable maximal benefit.

Statistical analysis

Data are presented as mean and SD. Student's *t*-test was used to compare within-group changes before and after training. Analysis of variance (ANOVA) was utilized for between-group comparisons. Differences were considered significant when *P* was less than 0.05. To test whether a difference in the breathing pattern had occurred, the slopes of the linear regression by group of the pre- and post-training V_T , respiratory rate and minute ventilation against work rate were compared. End-tidal PCO₂ before and after training was also compared at the lowest of the peak intensities (55 and 53 watts for the BiPAP and control group, respectively) by paired *t*-test.

Results

Of the 24 patients 5 did not complete the study: 3 from the BiPAP group, who failed to adjust to the mask, and 2 from the control group – one due to lung transplant and one because of back pain. During the study, and for at least 2 months preceding it, no patient (except one) was on oral prednisone; all used inhaled broncho-dilators (as needed), and four from the BiPAP group and two from the control group used nocturnal oxygen. The number of oxygen-treated patients was well-matched between the groups. In the control group, oxygen was delivered through a nasal cannula to eight patients and in the ventilated group it was delivered by a hose connected to the BiPAP mask in nine patients.

Nineteen patients, 9 BiPAP and 10 controls, comprised the study group. Patient data are shown in Table 1. The two groups appeared well matched.

Physiologic changes following training

Lung function did not change significantly after training in either group. Mean body weight did not change significantly in either group.

Ventilated group. Exercise tolerance improved after training [Table 2]. $V'O_2$ max [Figure 1] increased by $23 \pm 16\%$ ($P < 0.005$), AT by $11 \pm 12\%$ ($P < 0.05$) and oxygen uptake per heart beat (O₂ pulse) by $20 \pm 19\%$ ($P < 0.05$). Post-exercise venous lactic acid concentration,

V'_E = minutes ventilation

FEV₁ = forced expiratory volume in 1 sec

Hb-O₂S% = percent saturation of O₂ hemoglobin

V_T = tidal volume

Table 1. Patient characteristics and resting pulmonary function

	Ventilated group (n=9)	Control group (n=10)
Age (yrs)	64 ± 9	63 ± 9
Weight	78 ± 9	70 ± 16
FEV ₁ (L)	0.93 ± 0.16	0.99 ± 0.83
FEV ₁ (% predicted)	32 ± 4	33 ± 9
FEV ₁ /FVC (%)	59 ± 16	58 ± 16
TLC (% predicted)	102 ± 11	111 ± 17
FRC (% predicted)	141 ± 25	164 ± 45
RV (% predicted)	194 ± 34	215 ± 56
RV/TLC (%)	164 ± 19	165 ± 17
BR (L)	3 ± 9	2 ± 7
DLCO (% predicted)*	57 ± 20	

None of the differences reached significance.

Values are pre-training means ± SD

* The DLCO (single breath diffusion capacity) was measured in only 9 patients (6 control, 3 BiPAP)

TLC = total lung capacity, RV = residual volume, FRC = functional residual capacity, BR = breathing reserve, DLCO = diffusion capacity.

Table 2. Effect of training on peak exercise response

	Ventilated group		Control group	
	Before	After	Before	After
Work rate (watts)	54 ± 11	67 ± 13	56 ± 13	59 ± 17
V _O ₂ (ml/min)	824 ± 219	1,011 ± 284**	893 ± 162	927 ± 223
AT (ml/min)	587 ± 138	654 ± 140**	610 ± 153	641 ± 145
O ₂ pulse (ml/beat)	7.4 ± 2	9 ± 2**	8 ± 1	8 ± 2
V _E (L/min)	30 ± 5	35 ± 9**	30 ± 9	32 ± 10
V _T (ml)	924 ± 245	1,074 ± 303***	1,050 ± 310	1,022 ± 275
Lactate (mmol/L)	3.12 ± 1.05	3.5 ± 0.92	3 ± 0.73	3.35 ± 0.84
Hb-O ₂ (% saturation)	92 ± 4	92 ± 6	94 ± 4	94 ± 5
P _{ET} CO ₂ * (mmHg)	40 ± 4	38 ± 4*	40 ± 7	40 ± 8

Values are means ± SD.

* Values compared at the lower peak work rate (average 55 and 53 watts for the BiPAP and control group, respectively).

** Significant difference from pre-training response at $P < 0.05$.

*** Significant difference from pre-training response at $P < 0.005$.

V_O₂ = O₂ uptake, AT = anaerobic threshold, V_E = minutes ventilation,

V_T = tidal volume, P_{ET}CO₂ = end-tidal PCO₂.

before and after training, was not different despite higher post-training exercise intensity. Maximal minute ventilation increased by $17 \pm 20\%$ and V_T max increased by $16 \pm 12\%$ ($P < 0.005$), however the peak respiratory rate did not change.

Control group. No physiologic improvement was found in any of the cardiorespiratory parameters after training in the controls.

Comparison between the two groups

Training intensity. The ventilated group began training at a lower speed (2.0 ± 0.64 km/hr) and was able to increase it by $94 \pm 53\%$ (up to 4.0 ± 0.11 km/hr). The control group began training at a higher speed (3.0 ± 0.72 km/hr) but could increase it by only $41 \pm 19\%$ (up to 4.0 ± 0.75 km/hr) ($P < 0.005$). The difference at baseline for the training intensity (speed) was not statistically significant.

Physiologic changes at peak exercise. V_O₂ max and AT increased only

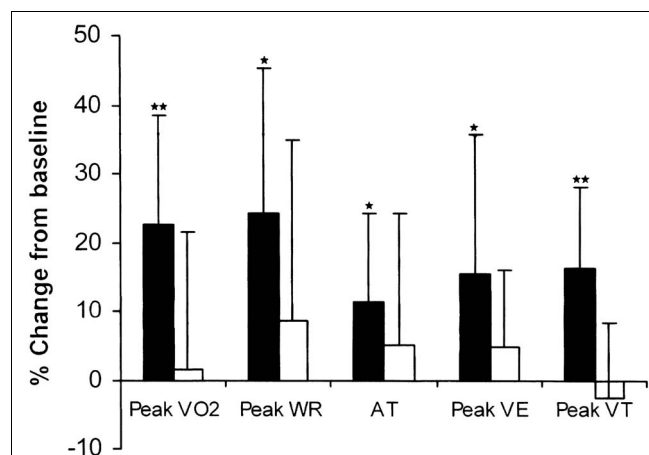


Figure 1. Changes from baseline in a number of parameters recorded at the peak of incremental exercise test, following the training period of 8 weeks, for the ventilated (■) and control (□) groups.

* Significant difference from pre-training response at $P < 0.05$, ** significant difference from pre-training response at $P < 0.005$. Comparisons are within, not between, groups. WR = work rate, VE = expired ventilation.

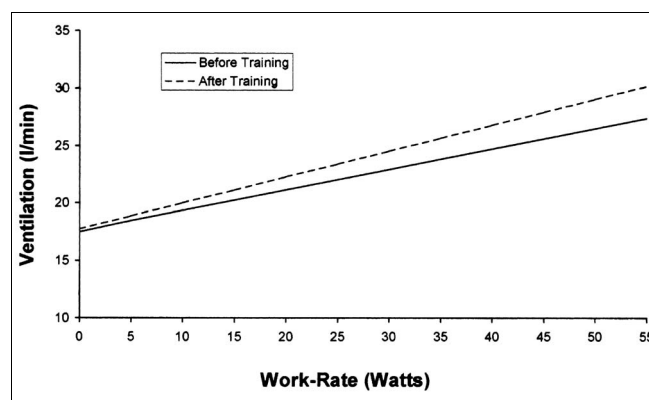


Figure 2. Minute ventilation in the patients with COPD who underwent training with pressure support ventilation. The solid line shows the pre-training and the dashed line the post-training linear regression. The slopes are significantly different ($P < 0.05$).

in the BiPAP group. The rise in the control group was not significant [Table 2]. In addition, in the BiPAP group, V_T max increased by $16 \pm 12\%$ as compared to a fall of $3 \pm 11\%$ in the control group ($P < 0.005$).

Changes in the breathing pattern in the BiPAP group after training

As expected, as work rate increased, V_E increased proportionally throughout exercise. However, as noted in Figure 2, the slope of the V_E rise was significantly higher after training ($P < 0.05$). This excess post-training rise was induced by the steeper slope of the V_T ($P = 0.001$), while the slope of the respiratory ventilation did not change. The higher ventilation was associated with a lower P_{ET}CO₂ that had been compared at the lower peak work rate of 55 watts, and was 40 ± 4 and 38 ± 4 mmHg respectively ($P < 0.05$).

Discussion

The main finding in this study is that training with ventilatory support was advantageous for patients with severe COPD who had ventilatory limitation during exercise, and that the advantage was carried over to unsupported exercise. In contrast, physical fitness of the control group who underwent standard training did not improve.

How could the supported training lead to higher unsupported exercise capacity? Our hypothesis was that the ventilatory support would enable higher ventilation (by tethering the airways and/or by unloading the respiratory muscle) and hence higher training intensity, and lower exercise-induced lactic acidosis and, thus, lower ventilatory demand for a given task (even when unsupported) [4]. We did not find significantly lower post-training lactate, but despite higher post-training peak exercise intensity, post-exercise lactic acid in the BiPAP group was not higher, suggesting that lactic acid produced during a given task was indeed lower after training. It is not clear, however, if the use of BiPAP enabled higher training intensity, since only the percent rise (but not the absolute final training speed) was higher in the supported group. Furthermore, even though lactic acid for a given exercise intensity was probably lower, the post-training ventilatory demand for a given intensity was surprisingly higher [Figure 2].

In light of this experience, the following questions arise: How could BiPAP induce a superior training effect? By what mechanism was the ability to increase ventilation with support carried over to the unsupported test? Why did the ventilatory response to a given task increase (an apparent disadvantage in COPD)? The answers to these questions are not known. A higher post-training ventilatory response may have resulted from a change in the central respiratory center set-point for ventilation [24], from peripheral effects such as better endurance of the respiratory muscles, or due to attenuation of the perception of dyspnea. One or more of these three effects may have been induced in the supported training group. The observation that $P_{ET}CO_2$ was lower after training does not distinguish between these three putative mechanisms. To distinguish among these putative mechanisms, there is a need to measure, before and after supported training, end-exercise lung volume, ventilation during training, exercise partial pressure of CO_2 in arterial blood, respiratory muscle strength and endurance, and the perception of dyspnea. The carry-over effect of BiPAP was also observed in another study, in a setting of standard training in COPD [25]. A subgroup in this study had, in addition to training, nocturnal BiPAP. It is interesting that in this subgroup the training effect exceeded that induced in the subgroup that did not receive nocturnal ventilation [25]; however, the authors do not report on the ventilatory pattern during exercise.

In our study, no improvement was found in the control group. This may have been due to the relatively short twice-weekly training, while effective protocols reported in the literature utilized between three and five sessions per week [2,5,12,13]. The fact that BiPAP training induced a measurable effect despite the limited number of sessions further emphasized its added value.

Three recently published studies report the use of ventilatory support during training in COPD [18–20]. In one study [18], exercise

time and load were increased after training, but this benefit was observed only when the exercise test itself was done while on the ventilatory support. The second group [19] used proportional assisted ventilatory support, demonstrating higher training intensity and some evidence of true physiologic adaptation in the support group, but in contrast to our study they did not measure the $\dot{V}O_2$ max. The third group [20] failed to achieve any benefit with assisted ventilation in mild to moderate COPD patients compared to unsupported training. In contrast, the patients in our study had severe disease and were therefore more likely to be ventilatory-limited and to benefit from the support ventilation.

In conclusion, in severe COPD, exercise training in conjunction with positive pressure ventilatory support induces a higher training effect even during subsequent unsupported exercise. This improvement was associated, unexpectedly, with higher ventilatory response to any given exercise intensity and with lower $P_{ET}CO_2$. Whether BiPAP increases ventilation by affecting the ventilatory set-point (regulated by a central mechanism), respiratory muscle endurance, or by attenuating the perception of dyspnea is not known.

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