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Nonpharmacologic adjuncts to training during pulmonary rehabilitation: The role of supplemental oxygen and noninvasive ventilation

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Abstract—Exercise training is the cornerstone of pulmonary rehabilitation. However, patients may not be able to exercise at a level that produces a training effect because of limitations related to their underlying lung disease. Adjuncts during exercise training may increase their exercise capacity and increase the benefit of pulmonary rehabilitation. The pathophysiology of exercise associated limitation is reviewed, as well as the role of supplemental oxygen and noninvasive ventilatory support as nonpharmacologic adjuncts to training. While most studies demonstrate benefit during exercise, the evidence of an added benefit during pulmonary rehabilitation is mixed. Work is needed to better define the benefits and appropriate patient populations. The subgroups that may derive the most benefit from these adjuncts are those with oxygen desaturation during exercise and those with severe chronic obstructive pulmonary disease (defined as a forced expiratory volume in 1 s (FEV_1) <1.0 L). Nocturnal noninvasive ventilation during pulmonary rehabilitation seems to be an effective adjunct and merits further study.

Key words: noninvasive ventilation, oxygen, pulmonary rehabilitation.

INTRODUCTION

The health burden of chronic obstructive pulmonary disease (COPD) is staggering. COPD constitutes the fourth leading cause of death in the United States. It is predicted to be the fifth (it is currently the 12th) leading cause of disability in the world by 2020 [1]. Since 1979, the number of deaths attributed to COPD has increased 118 percent, and it is the only condition in which the death rate has continued to rise [2,3]. In the United States, over 16 million patients are afflicted with COPD, and these account for over 17 million office visits and 700,000 hospitalizations annually [4]. This represents 5 percent of all office visits and over 13 percent of all hospitalizations in the United States [5,6]. Direct healthcare costs exceed $14 billion.

Abbreviations: BiPAP = bi-level positive airway pressure, COPD = chronic obstructive pulmonary disease, CPAP = continuous positive airway pressure, CRDQ = chronic respiratory disease questionnaire, EMG = electromyogram, EPAP = expiratory positive airway pressure, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, IPAP = inspiratory positive airway pressure, PaO_2 = partial pressure of oxygen in arterial blood, PAV = proportional assist ventilation, Pdi = transdiaphragmatic pressure, PEEP = positive end-expiratory pressure, PSV = pressure support ventilation, SEM = standard error mean, Ti = inspiratory time, TTdi = tension time index, Ttot = total respiratory cycle.

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Attempts to control the disease burden associated with COPD have met with limited success. Smoking cessation is clearly the most important intervention, with the greatest overall impact on morbidity and mortality [7]. The focus of other therapies has been on symptom relief and reducing the impact of exacerbations. Consensus guidelines, often referred to as the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines [1], include a strong recommendation for pulmonary rehabilitation in those with moderate to severe disease.

Pulmonary rehabilitation is designed to improve patients' functional status, disease management, and symptom control in conjunction with standard medical therapy [8–15]. A successful pulmonary rehabilitation program includes a structured training program with intense exercise, educational instruction, and other psychosocial and behavioral components. Proven benefits include improved quality of life and well-being, dyspnea relief, increased muscle strength, exercise endurance and a reduction in healthcare costs measured by hospitalizations and hospital days. There may be a survival benefit, although this has not been established conclusively [8–15].

Exercise and the exercise prescription form the cornerstone of successful pulmonary rehabilitation [16–18]. Much of the dyspnea and disability encountered by patients can be attributed to decreased strength and exercise capacity. This limits patient endurance and activity, which results in further deconditioning, creating a vicious cycle of progressive decline. Exercise training improves both strength and endurance, reducing energy expenditure, the work of breathing, and dyspnea. The benefit of exercise in improving dyspnea, exercise performance, endurance, and quality of life measures is greater than that achieved with all the other components of pulmonary rehabilitation (i.e., education, breathing strategies, psychosocial support) [13].

Intense research has been conducted to identify the optimal approach to exercise training (see other articles in this issue). Approaches taken to increase the training effect include different types of lower extremity exercise (treadmill vs. bicycle), upper extremity exercise training, increases in intensity and frequency of exercise schedules, weights, and breathing techniques. However, the dilemma is that patients may not be able to exercise at an intensity or duration sufficient to achieve a significant training effect. This has spurred the investigation of other strategies that may increase a patient's ability to increase his/her exercise capacity, and in turn, increase the benefits of and enable the patient to participate in exercise and pulmonary rehabilitation.

There are two main nonpharmacologic adjuncts to exercise training: supplemental oxygen therapy and noninvasive ventilatory support. The experience with these adjuncts and their role in pulmonary rehabilitation form the basis of this review.

PATHOPHYSIOLOGY OF EXERCISE LIMITATION

Understanding the pathophysiology of ventilatory compromise in severe obstructive lung disease will provide a better understanding of the use of oxygen and noninvasive ventilation. A general overview follows, with more specific details preceding each section on the adjuncts.

Patients with COPD characteristically have hyperinflated lungs. This places the ventilatory muscles, specifically the diaphragm, at a mechanical disadvantage. Hyperinflation flattens the diaphragm, creating a mechanically inefficient muscle, muscle fiber shortening, a less favorable length-tension relationship, and increasing the work of breathing, even at rest. Added factors that impair ventilatory muscle function include hypoxia, hypercapnia, increased airway resistance, and malnutrition [19]. Exercise may worsen hypoxemia and the increase in minute ventilation worsens dynamic hyperinflation, further compromising ventilatory muscle function [16,18,20].

This contributes to activity-limiting dyspnea. Dyspnea then occurs at lower levels of activity. Patients become deconditioned and eventually dyspneic at rest. Both peripheral and respiratory muscles are subject to deconditioning. The overall effect is a decrease in lean body mass, decreased endurance, and lower thresholds for anaerobic metabolism and lactic acidosis. Increasing oxygen requirements and/or increasing carbon dioxide production require further increases in ventilation, which may not be possible in ventilatory limited patients. This creates a vicious cycle, causing a further downward spiral that leads to eventual total disability and death.

NONPHARMACOLOGIC ADJUNCTS

Pathophysiology of Exercise Limitation: Effects of Hypoxemia

Patients may be hypoxemic at rest or develop oxygen desaturation with exertion or exercise. Hypoxemia is usually due to ventilation/perfusion inequalities from underlying emphysema or obstructed airways. The physiologic response to hypoxemia includes an increase in ventilatory drive, vascular bed dilatation, tachycardia, and increased cardiac output. There is hypoxic vasoconstriction of pulmonary vasculature, aimed at optimizing ventilation and perfusion. With chronic hypoxemia, pulmonary hypertension and cor pulmonale develops. Functional reserve is decreased, and exertion accentuates these limitations [21].

With exercise, heart rate and cardiac output increase, as well as oxygen use by contracting muscles. The transit time of blood in the capillary bed decreases, which may worsen hypoxemia in those with existing ventilation/perfusion abnormalities. Pulmonary pressures increase with hypoxemia, decreasing right heart function, which impairs cardiac output and oxygen delivery. Compound this with the effects of dynamic hyperinflation, and it becomes evident that these patients are susceptible to ventilatory muscle fatigue, lactic acidosis, and reduced exercise capacity [21].

Supplemental Oxygen

The effects of long-term oxygen therapy in hypoxemic patients have been well documented by two large, prospective randomized studies [22,23], with decreased mortality the most important benefit. In these trials, most of the patients used oxygen during sleep or delivered from a stationary source. There was an added survival benefit for those using oxygen continuously, including during ambulation. This benefit was attributed to decreased pulmonary hypertension, decreased right ventricular afterload, and improved right ventricular function [24]. However, the ambulatory patients constituted a minority of the patients involved in the two large supplemental oxygen trials. It follows that there would be additional benefit gained with supplemental oxygen during exertion or exercise.

In patients with resting or borderline hypoxemia, the use of supplemental oxygen during exertion provides obvious benefit by preventing oxygen desaturation. Innumerable studies document an increase in exercise duration or distance with the addition of supplemental oxygen. These studies will be reviewed in some detail and, unless otherwise stated, were randomized with treatment blinded to patients. Statistically significant differences are reported at either the $p < 0.05$ or $p < 0.01$ level.

The findings of Bradley and colleagues epitomize these findings [25]. They studied 26 patients with severe COPD (forced expiratory volume in 1 s, or $FEV_1 = 0.52 \pm 0.16$ L), during treadmill exercise, with random assignment to room air, compressed air at 5 L/min, or supplemental oxygen at 5 L/min. The group partial pressure of oxygen in arterial blood (PaO_2) was 69 ± 14.3 mm Hg, declining to 57.7 ± 10.8 and 59.8 ± 9.5 during exercise on room air or compressed air, but was 89.5 ± 21.5 with oxygen. The oxygen-treated group had about a 50 percent increase in endurance ($p < 0.01$). They noted mild CO_2 retention (41.8 ± 8.1 to 48.6 ± 9.9) during exercise with oxygen, but no change in the pH, suggesting that oxygen prevented not only oxygen desaturation, but also lactic acidosis.

Supplemental oxygen has been noted to reduce ventilation at the same workload. Stein and colleagues demonstrated this in 9 COPD patients ($FEV_1 = 0.87 \pm 0.32$ L) with a resting PaO_2 of 63 ± 10 mm Hg during treadmill exercise breathing compressed air or 30 percent oxygen [26]. The oxygen prevented exercise associated hypoxemia in all but two patients and was consistently associated with a lower minute ventilation at the same work load ($p < 0.05$). This group of patients was undoubtedly ventilatory limited with exercise, but because of their reduced ventilatory requirements with oxygen, did not reach that limit until much later, allowing them to exercise longer. These investigators also noted lower levels of lactate production at the same work loads ($p < 0.05$). Others have also confirmed that hyperoxia during exercise reduces lactate production at the same work load [27].

Although it would be expected that supplemental oxygen would benefit those with exertional oxygen desaturation, benefit has been noted also in patients who do not desaturate with exercise. Dean and colleagues studied 12 patients with COPD ($FEV_1 = 0.89 \pm 0.09$ L, with a resting PaO_2 of 71 ± 3 mm Hg) during cycle ergometry while breathing either compressed air or 40 percent oxygen [28]. As a group, the decline in PaO_2 was 64 ± 7 mm Hg at the end of exercise, with 4 subjects dropping below 55 mm Hg. They also used Doppler echocardiograms to measure right ventricular systolic pressures in a separate supine exercise test. As might be expected, there was improvement in duration of exercise (10.3 ± 1.6 to 14.2 ± 1.5 min, $p < 0.01$) and

dyspnea, and reduction in mean right ventricular systolic pressures, as well as the rise to maximal right ventricular pressures with oxygen ($p < 0.05$). The improvement was noted in all patients except one, and the most noteworthy finding was that these changes occurred even in those who were not hypoxemic with exercise during the compressed air trial. Woodcock and colleagues had also reported improvement in dyspnea and 6 min walk distance in a group of 10 COPD patients ($FEV_1 = 0.71 \pm 0.29$ L) [29]. These patients also maintained adequate oxygenation during exertion ($PaO_2 = 68 \pm 11$ mm Hg $\rightarrow 61 \pm 12$ mm Hg) during trials with compressed air and supplemental oxygen.

Other benefits of supplemental oxygen have been described. Hypoxemia can increase airway resistance in COPD patients. This bronchoconstriction can be reversed with supplemental oxygen, as demonstrated by Libby and colleagues in 10 COPD patients ($FEV_1 = 0.62 \pm 0.32$ L and $PaO_2 = 61 \pm 10$ mm Hg) [30]. They noted improvement in airway resistance and an increase in peak flow rates of almost 30 percent with their subjects breathing 30 percent supplemental oxygen compared to room air ($p < 0.05$). This was a sedentary study, but it can be envisioned that improvement in airway resistance and flow rates during exercise would translate to lower minute ventilation and less dynamic hyperinflation.

Supplemental oxygen also improves ventilatory muscle function during exercise. Bye and colleagues used esophageal and gastric balloons to evaluate the diaphragmatic electromyogram (EMG) and transdiaphragmatic pressures during exercise in eight patients with COPD ($FEV_1 = 32 \pm 4\%$ and $PaO_2 = 63 \pm 6$ mm Hg) during cycle ergometry with humidified air or 40 percent oxygen [31]. These subjects experienced an average decline in oxygen saturation of 11 ± 3 percent with exercise and were able to double their exercise time with oxygen (3.0 ± 0.6 to 6.4 ± 1.2 min, $p < 0.01$). Five demonstrated evidence of ventilatory muscle fatigue-manifested changes in the diaphragmatic EMG power spectrum, and two had evidence of abdominal paradox ($p < 0.01$). These conditions were either eliminated or delayed with supplemental oxygen. The mechanism of improvement correlated with a decline in minute ventilation and respiratory rate (13 and 17%, respectively) at comparable times in the exercise study ($p < 0.01$). Criner and Celli also demonstrated differences in the ventilatory muscle recruitment during exercise in a group of 6 COPD patients ($FEV_1 = 0.66 \pm 0.2$ L and $PaO_2 = 66 \pm 6$ mm Hg) in a crossover study, breathing either air or 30 percent oxygen during cycle ergometry [32]. Their patients had lower transdiaphragmatic pressures with oxygen and similar transdiaphragmatic pressures during exercise ($p < 0.05$). However, there were lower pleural (esophageal) pressures, with higher gastric pressures during exercise, suggesting a redistribution of ventilatory muscle recruitment with an overall effect of more efficient ventilatory work performed by the diaphragm. Exercise time almost doubled with oxygen ($p < 0.05$).

The benefit of supplemental oxygen may be tempered by the increased work associated with carrying the portable oxygen cylinder. Evaluation of exercise performance in ambulatory patients carrying oxygen cylinders may be more representative of its effect than the controlled exercise studies described above. Leggett and Flenley raised some questions about the benefit of ambulatory oxygen [33]. They evaluated 26 patients with severe COPD ($FEV_1 = 0.62 \pm 0.24$ L, resting $PaO_2 = 52 \pm 8$ mm Hg) and cor pulmonale (mean pulmonary artery pressure = 34 ± 12 mm Hg). In subgroups of these patients, they found that supplemental oxygen at 2 L/min improved their 12 min walk distance an average of 51.6 m ($p < 0.05$), but carrying a 4.5 kg portable oxygen cylinder reduced the walk distance by 73.6 m. Placing the oxygen cylinder in a trolley that allowed it to be wheeled increased walk distance by 59 m as they breathed 4 L/min nasal cannula oxygen ($p < 0.05$). However, the decrement in walk distance when carrying oxygen is not a uniform finding. Woodcock and colleagues noted improvement with oxygen and no difference in the improvement whether the oxygen cylinder was carried by the patient or by an assistant [29]. Davidson and colleagues evaluated 17 COPD patients ($FEV_1 = 0.79 \pm 0.03$ L (standard error of mean, or SEM) and resting $PaO_2 = 65 \pm 2$ mm Hg), using cycle ergometry, 6 min walk distance, and an endurance test, while patients received incremental flow rates of oxygen (2, 4, and 6 L/min) [34]. In addition to a dose response improvement with oxygen ($p < 0.05$), there was an average 51 m increase in walk distance in patients who carried their oxygen. This group further validated these findings in a similar study to evaluate a portable liquid oxygen container [35]. These disparate findings may be explained by the greater severity of lung disease in the group reported by Leggett and Flenley [33], as evidenced by a lower FEV_1 and lower baseline PaO_2.

As suggested in the report by Davidson and colleagues [34], there seems to be greater benefit with higher levels of supplemental oxygen, producing higher PaO_2 values beyond that required to correct oxygen desaturation [36–38]. Other investigators have confirmed this

observation. Somfay and colleagues evaluated 10 patients with COPD (FEV_1 = 0.92 ± 0.43 L and oxygen saturation 96 ± 0.8% → 92 ± 3%, resting → exertion) during cycle ergometry [37]. The subjects exercised breathing room air and oxygen at 30, 50, 75, and 100 percent. They noted increases in endurance time, with a dose response reduction in dyspnea, minute ventilation, and end-expiratory and end-inspiratory lung volumes, plateauing at 50 percent oxygen ($p < 0.01$). O'Donnell and colleagues evaluated a group of 11 COPD patients with more severe disease (FEV_1 = 0.65 ± 0.06 L and resting PaO_2 = 52 ± 2 mm Hg) [38]. Their patients exercised with either room air or 60 percent oxygen and had profound oxygen desaturation with exercise. They demonstrated improvement in exercise time, dyspnea, respiratory rate, carbon dioxide production, and lactate kineticis, with a reduction in the amount of dynamic hyperinflation noted on flow volume curves and end-expiratory lung volumes (all $p < 0.05$). This provides further support for the benefit of supplemental oxygen during exercise and, specifically, for its effects on reducing dynamic hyperinflation.

These studies with supplemental oxygen and hyperoxia all have a common theme in their mechanism of improvement. Patients uniformly have a reduction in dynamic hyperinflation as a result of decreased respiratory rate and minute ventilation. Improvement has been noted with or without oxygen desaturation. This improvement has led to a critical reexamination of the role of hyperoxia in the management of these patients. There definitely seems to be a dose response relationship with hyperoxia, and hyperoxia has not been associated with excessive hypercapnia. This has led to a call for more investigations into the possible benefit of this strategy [39]. These benefits of supplemental oxygen and hyperoxia are summarized in **Table 1**.

However, not all the evidence has supported the use of supplemental oxygen during exercise in severe COPD patients. This is not a new observation, and it has often been attributed to patient selection or testing modality. In a representative study, Longo and colleagues studied 27 COPD patients (mean FEV_1 percent predicted = 27%) during mild to moderate treadmill walking, breathing either compressed air or 2 and 4 L/min nasal cannula oxygen. They found no significant difference in ventilation, cardiac parameters, or exercise tolerance with supplemental oxygen, although all patients did improve their oxygen tension while breathing oxygen. No difference was noted in their patients, including a subgroup of six patients with oxygen desaturation during exercise (mean of 62 mm Hg declining to 54 mm Hg) [40]. Despite patients and methodology similar to other reported studies, the benefits of oxygen were not demonstrated.

Although the majority of studies demonstrate benefit with supplemental oxygen in short-term studies, the results of long-term studies have been mixed. Liker and colleagues evaluated the effect of oxygen in nine COPD patients

Table 1.
Benefits of supplemental oxygen during exercise.

Treatment	Mechanism of Benefit
Oxygen	Prevent oxygen desaturation
	Decrease tachycardia
	Decrease pulmonary artery pressure
	Improve right ventricular function
	Decrease minute ventilation
	Decrease dyspnea
	Decrease or delay diaphragmatic fatigue
	Decrease diaphragmatic work
	Reverse hypoxia-induced bronchoconstriction
	Increase exercise endurance
	Decrease serum lactate levels during exercise
Hyperoxia	All the above (probably dose-related effect)
(increasing benefit up to 6 L/min or FIO_2 = 0.50)	Decrease ventilatory drive
	Slow respiratory rate
	Decrease dynamic hyperinflation

FIO_2 = fractional inspired oxygen

(FEV_1 = 41 ± 17% and resting PaO_2 = 53 ± 8 mm Hg) [41]. They were randomized in a double-blind, crossover fashion to 5 weeks of either continuous air or oxygen at 2 L/min. Patients had completed pulmonary rehabilitation and were ambulatory with a portable cylinder (9 lb) that delivered either air or oxygen. Measurements were made within 24 hours after discontinuation of their assigned therapy. Findings include significant improvement only in room air oxygen (PaO_2 = 54 ± 9 vs 71 ± 8, $p < 0.05$), although improvement was also noted in resting heart rate, resting and maximal exercise minute ventilation, and oxygen saturation after oxygen use. A portion maintained improvement in dyspnea with an increase in exercise capacity after oxygen therapy. This improvement has been attributed to decreased hypoxic vasoconstriction and improved right ventricular hemodynamics. It should be emphasized that the testing was conducted and benefits documented as they breathed room air, but after a 5-week period of breathing either compressed air or oxygen. This illustrates that changes with oxygen persist, even with the patient off oxygen.

However, less impressive changes have also been noted. McDonald and colleagues reported a 12-week, double-blind, randomized crossover study of 26 COPD patients (FEV_1 = 0.9 ± 0.4 L) treated with air and oxygen [42]. These patients either had normal oxygenation or were mildly hypoxemic at rest (PaO_2 = 69 ± 8.5 mm Hg and oxygen saturation of 94 ± 2%). At the end of the trial, the improvement was noted primarily in the Guyatt chronic respiratory quality of life questionnaire ($p < 0.05$) [43]. The improvement in the 6 min walk distance was about 20 m and not significant (baseline = 326 ± 97 m). Patients were split equally in their preference of the two modalities (air or oxygen) during the study. Patients did not undergo any training program during the study and, during oxygen therapy, were noted to have only marginal benefit in functional performance. The quality of life improvement was also modest and found primarily in the "mastery" portion of the questionnaire. This group of patients was not as severely obstructed or hypoxemic as those in Liker's study [41]. This may explain the relatively modest benefit noted in this group.

Despite some trials demonstrating marginal benefit, the majority of studies support the use of oxygen, and it has become a mainstay of therapy. All patients are encouraged to use their oxygen, especially during periods of exertion. It follows that supplemental oxygen during pulmonary rehabilitation would be beneficial. Patients should improve their exercise capacity and endurance and be able to train longer or at a higher intensity, thereby increasing the benefits of pulmonary rehabilitation. However, despite the extensive literature investigating the use of oxygen, reports of oxygen use during a pulmonary rehabilitation program are sparse and show mixed results. A search of the National Library of Medicine PUBMED® and Cochrane Database of Systematic Reviews identified only three randomized trials assessing the merits of supplemental oxygen during exercise training (two pulmonary rehabilitation, one exercise program) in patients with COPD. These studies will be reviewed in further detail.

Rooyackers and colleagues studied 24 COPD patients with oxygen desaturation (defined as O_2 saturation <90%) during peak exercise while participating in a 10 week inpatient pulmonary rehabilitation program [44]. Although randomized, there were some differences at baseline between the two groups. The COPD patients who trained while breathing room air had a higher baseline FEV_1 (1.2 ± 0.5 L), with a higher minute ventilation (43 ± 21 L) achieved at maximal exercise, compared to the group who trained while breathing oxygen (FEV_1 = 0.9 ± 0.3 L and minute ventilation = 35 ± 15 L). Both groups had hypoxemia with exercise (PaO_2 = 55 ± 4 mm Hg and 54 ± 8 mm Hg, respectively). Subjects were randomized to training while breathing either room air or supplemental oxygen. Oxygen saturation was monitored during training and not allowed to decline below 90 percent. Both groups demonstrated improvement in 6 min walk distance, stair climbing, strength, and quality of life when tested breathing room air. The group that trained while breathing room air had a greater magnitude of improvement, but the differences were not significant. The average increase in 6 min walk distance breathing room air was 123 m, compared to 86 m in the oxygen-trained group. Maximum work load during exercise was significantly greater in those who trained breathing room air, with a mean increase in work load of 17 ± 15 W, compared to 7 ± 25 W in the oxygen-trained group. The investigators concluded that supplemental oxygen during pulmonary rehabilitation did not add to the training effect achieved with room air. One explanation for this lack of benefit may be that patients were not allowed to continue their exercise prescription if the oxygen saturation fell below 90 percent. Therefore, one would not expect much benefit from oxygen, since no abnormality would have

been corrected with supplemental oxygen. Although the differences in the groups were not statistically significant, the air-trained group was not quite as impaired as the oxygen-trained group, so they may have been able to train at a higher level and achieve a training effect that would have obscured a small benefit obtained with oxygen.

Waddell and colleagues randomized 20 COPD patients to a thrice weekly, 8-week treadmill exercise training program, breathing either room air or oxygen at 5 L/min [45]. No other components of the pulmonary rehabilitation program were provided. Exercise was stopped if a patient's oxygen saturation fell below 90 percent and resumed once the level rose again to above 90 percent. Although not statistically different, the group trained on air did have a slightly higher FEV_1 than the oxygen group (FEV_1 = 52 vs. 39%), less obstruction (FEV_1/forced vital capacity (FVC) = 49 vs. 45%), and similar baseline PaO_2 (70 vs. 71 mm Hg). The authors subjected their patients to testing breathing both air and supplemental oxygen. After training, both groups increased their 6 min walk distance, whether breathing air or supplemental oxygen, but the air-trained group had a greater percentage of improvement (20 vs. 14% when tested breathing air, 21 vs. 10% when tested breathing oxygen). The mean increase in these two groups was small, with the air group walking a little further (40 vs. 35 m when tested breathing air, 55 vs. 30 m when tested with oxygen). Improvement in dyspnea was mixed, with the air-trained group less dyspneic (based on Borg ratings at the end of the training) when tested while breathing room air; but the oxygen group was less dyspneic when tested while breathing oxygen. The dyspnea ratings did not change in the nontraining condition (air-trained breathing oxygen, oxygen-trained breathing air). The authors concluded that the use of oxygen during training did not further improve the training effect. As in the Rooyackers group [44], patients were not allowed to desaturate below 90 percent and therefore may not have been able to experience any of the potential benefits of oxygen. In addition, the lung function of the air-trained patients was a little better than the oxygen group, and this may also confound their results.

In the third trial, Garrod and colleagues studied a total of 25 COPD patients (FEV_1 = 0.76 ± 0.29 L) randomized to a 6 week pulmonary rehabilitation program, training using either compressed air or oxygen at 4 L/min [46]. Of note, in 11 patients previously receiving long-term oxygen, 5 trained with compressed air and 6 with supplemental oxygen. Patients were allowed to continue exercise, even if they developed oxygen desaturation (below 90%). As a group, oxygen desaturation with exercise was noted, with a mean oxygen saturation of 92 ± 4 percent, declining to 82 ± 10 percent with exercise. Subjects carried oxygen cylinders (containing either air or oxygen) during their exercise, so that training was similar in every respect, except for the use of oxygen or air. The only difference at the end of rehabilitation was a lower Borg dyspnea score in those who trained with oxygen ($p < 0.01$). There were no differences in other outcome measures, including the shuttle walk distance and three quality-of-life measures. Patients who trained using air actually walked a little further than their oxygen-trained counterparts: on average, patients who trained using oxygen walked an additional 20 m breathing room air on the repeat shuttle walk, while air-trained patients walked an additional 44 m. The results of the two pulmonary rehabilitation studies [44,46] are summarized in **Table 2**.

The accompanying editorial [47] identified some methodologic issues, including the limitations inherent in a small sample size and the possibility that the shuttle walk may not be sufficiently robust to detect a change in endurance, as would be expected of patients who train with oxygen [47]. The benefit of reduced dyspnea should also not be discounted, but the findings are intriguing. There may also be some benefit to using compressed air, since cool air has been demonstrated to have a beneficial effect on dyspnea in these patients [48]. The finding that oxygen does not seem to improve the training effect is somewhat counter intuitive, but it should be noted that training at altitude and under hypoxic conditions has been a long-standing strategy of competitive athletes. In addition, the use of oxygen is based on the premise that hypoxemia is a limiting factor during exercise. In fact, most of these patients are ventilatory limited as a result of their underlying lung disease, and this may be a greater factor in the intensity of training than hypoxemia. Although the benefits of supplemental oxygen extend beyond the simple correction of hypoxemia (improvement in dynamic hyperinflation, breathing patterns, right ventricular function, and dyspnea), the ventilatory limitation of exercise may be too great to overcome with oxygen alone.

The available data do not allow a general endorsement of training with supplemental oxygen during pulmonary

Table 2.
Randomized trials of oxygen supplementation during pulmonary rehabilitation.

Authors	**Room-Air Trained**		**Oxygen Trained**	
Rooyackers et al.*	*n* = 12		*n* = 12	
FEV_1	1.2 ± 0.5 L		0.9 ± 0.3 L	
% predicted	38 ± 11		29 ± 7	
Effects of Training	**Before**	**After**	**Before**	**After**
Work rate max (W)	70 ± 51	87 ± 58	58 ± 33	65 ± 39
6 min walk distance (m)	487 ± 191	610 ± 166	389 ± 140	475 ± 180
Dyspnea score (Borg score)	7.3 ± 2.4	5.8 ± 1.9	6.6 ± 2.1	5.3 ± 1.2
Authors	**Room-Air Trained**		**Oxygen Trained**	
Garrod et al.†	*n* = 12		*n* = 13	
FEV_1 (L)	0.84 ± 0.26		0.77 ± 0.26	
% predicted	35 ± 10		29 ± 10	
Effects of Training	**Before**	**After**	**Before**	**After**
Shuttle walk (m)	131 ± 103	Mean change = 44	160 ± 89	Mean change = 20
CRDQ	84.4 ± 21.2	Mean change = 5.6	77.9 ± 24.4	Mean change = 9.3

*Rooyackers JM, Dekhuijzen PN, Van Herwaarden EL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. Eur Respir J 1997;10:1278–84.
†Garrod R, Paul EA, Wedzicha JA. Supplemental oxgyen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. Thorax 2000;55:539–43.
CRDQ = chronic respiratory disease questionnaire

rehabilitation. However, this should not be interpreted as a proscription against oxygen use in this setting. Each patient should be evaluated individually to determine their oxygen needs during rehabilitation. Those with oxygen desaturation during exercise would be one group that would benefit from supplemental oxygen during rehabilitation. Preventing the potential adverse consequence of hypoxemia would be paramount in this recommendation. Its use in other groups is tempered by data that suggest that supplemental oxygen does not augment the training effect. However, oxygen definitely improves exercise time and endurance. The lack of training effect may be more a reflection of other limitations to exercise than the lack of benefit with oxygen. Additional work needs to be done to identify not only those who may benefit from training with oxygen during pulmonary rehabilitation, but also the optimal delivery methods and dose of therapy.

There are significant clinical and economic implications with this issue. If training with oxygen is determined beneficial, a large group of patients would qualify for oxygen therapy. Conversely, if oxygen is demonstrated to be of marginal or no benefit, its use during pulmonary rehabilitation would not be endorsed nor routinely reimbursed.

Pathophysiology of Exercise Limitation: Dynamic Hyperinflation

The other major limiting factor to exercise in COPD is dynamic hyperinflation. Hyperinflation worsens during hyperpnea and exercise. Decreasing exhalation time creates more air trapping, leading to higher end-expiratory lung volumes. Patients breathe on the less compliant portion of the pressure-volume curve, further increasing the work of breathing and decreasing muscle efficiency. They are unable to meet demands for increasing minute ventilation, as tidal volume increases are limited by existing hyperinflation. Their only recourse is increasing the respiratory rate, which further worsens dynamic hyperinflation [20].

This increased work of breathing creates an inspiratory threshold to breathing. The pressure needed to overcome dynamic hyperinflation encroaches on the maximal pressure-generating capacity, leading to a breathing pattern that cannot be sustained. This is similar to a concept identified during static conditions by Roussos and Macklem [49].

Their subjects could generate transdiaphragmatic pressure (Pdi) at 40 percent or less of their maximal pressures (Pdimax) indefinitely. Fatigue developed when breathing patterns exceeded a Pdi/Pdimax of 0.40. The higher the Pdi/Pdimax, the more rapidly fatigue ensued.

Fatigue is also influenced by the duty cycle (Ti/Ttot), reflecting the ratio of inspiratory time (Ti) to the total respiratory cycle (Ttot). Shorter duty cycles result in greater endurance at the same level of pressure generation (Pdi/Pdimax). A product of Pdi/Pdimax and Ti/Ttot, or tension time index (TTdi), greater than 0.15 can predict eventual ventilatory fatigue [50–52]. Diaphragmatic blood flow is also compromised during contraction at a TTdi of 0.15 or higher, leading to tissue hypoxia and acidosis.

These conditions are encountered routinely by patients with severe COPD. Their maximal diaphragmatic pressures are reduced because of hyperinflation, with further hyperinflation and increases in TTdi occurring during exercise and tachypnea.

Noninvasive Ventilation

Another approach to increasing exercise endurance or intensity has focused on the control of dynamic hyperinflation during exercise. During dynamic hyperinflation, dynamic airway compression leading to premature airway closure and air trapping also occurs. These changes are virtually identical to the intrinsic positive end-expiratory pressure (PEEP) that occurs in mechanically ventilated patients [53]. Treatment is patterned after the experience in that situation and involves means to unload the inspiratory muscles and prevent dynamic airway compression.

Continuous positive airway pressure (CPAP) is a mode of assisted ventilation that counters the effects of dynamic hyperinflation by providing added pressure during both inspiration and exhalation. This is the rationale for its use in patients with severe COPD during exercise [54–56]. Improvements with CPAP have been noted, with a decrease in dyspnea and increase in exercise capacity. Using CPAP levels of 4 to 5 cm H_2O, O'Donnell and colleagues noted that their COPD patients (FEV_1 = 0.88 ± 0.27 L) were able to exercise an average of 2.84 ± 0.7 min (mean ± SEM) or 48 percent longer than without CPAP ($p < 0.01$) [54,55]. These investigators delivered the CPAP using a pressure amplifier through a modification to the mouthpiece of their exercise testing equipment. This was obviously an experimental setup that cannot be widely duplicated.

At about the same time as the aforementioned reports, CPAP applied through a nasal mask was gaining widespread acceptance in the treatment of obstructive sleep apnea. This technology was quickly adapted to the treatment of patients with other respiratory disorders including obstructive lung disease [57]. Several investigators have demonstrated unloading of the ventilatory muscles with reduction in the work of breathing using noninvasive ventilation with either volume or pressure support ventilation (PSV) applied through a nasal or face mask [58–60]. Benefit in short-term studies led to its application in a wide range of respiratory conditions and acute and chronic respiratory failure, during the day, at night, and eventually during exercise.

Noninvasive assisted ventilation during exercise is particularly attractive as an adjunct to exercise because it provides a potential method of increasing the exercise capacity of patients. This is especially important since many patients have activity-limiting dyspnea that prevents them from exercising at sufficient intensity to achieve any benefit. Although there is no consensus as to the optimal training level, patients who train at a higher intensity (80 vs. 50% of maximum) achieve greater benefit than those who train at a lower level, although even low-level training (30% of maximum) provides some benefit [61,62]. It follows that an adjunct that would allow patients to train at higher intensities would be of both individual and clinical importance.

There have been over half a dozen studies using noninvasive assisted ventilation during exercise. These trials have focused on the use of PSV or proportional assist ventilation (PAV) during exercise. Except for one group, this assisted ventilation was delivered with commercially available portable ventilators via nasal or facemask in either the PSV or PAV mode. Some of the PAV studies used a ventilator prototype at the time of the study, but this modality is now also commercially available.

Similar to findings at rest, PSV during exercise unloads the respiratory muscles. Two studies have demonstrated a decrease in the work of breathing and respiratory muscle activity using PSV [63,64]. Both measured esophageal, gastric, and transdiaphragmatic pressures during exercise. Using a PSV of 11 ± 1 cm H_2O in 7 COPD patients (FEV_1 = 0.75 ± 0.09 L, SEM), Maltais and colleagues noted that mouthpiece PSV during cycle ergometry increased minute ventilation, with an increase in both tidal volume and respiratory rate ($p < 0.05$) [63]. There was also a reduction in the pressure-time product (a measure of oxygen consumption) of the diaphragm by 55 ± 8 percent of

control ($p < 0.01$). As expected, end-expiratory lung volume increased with exercise, but no further increases were noted with the application of PSV. Kyroussis and colleagues used facemask PSV during treadmill walking in 12 COPD patients ($FEV_1 = 0.7 \pm 0.2$ L) [64]. In 5 patients, there was an increase in walk time, from 6.8 ± 2.2 to 13.2 ± 3.8 min, and a 56 percent reduction in the diaphragmatic pressure time product ($p < 0.05$). Polkey and colleagues used face mask PSV during treadmill walking in eight COPD patients ($FEV_1 = 0.68 \pm 0.17$ L) [65]. They noted an increase in walk time, from 5.5 ± 1.5 to 13.6 ± 6 min, and a reduction in the serum lactate level at the end of exercise, from 2.96 ± 0.90 to 2.42 ± 1.01 mmol/L ($p = 0.01$). Patients were able to walk longer with less lactate production, evidence that PSV unloads the respiratory muscles and reduces the work of breathing during exercise.

Additional studies have compared the effects of different types of noninvasive support during exercise. Keilty and colleagues studied 8 COPD patients ($FEV_1 = 0.73 \pm 0.2$ L) during treadmill exercise, randomly administering face mask inspiratory PSV (12–15 cm H_2O), CPAP 6 cm H_2O, and oxygen at 2 L/min, comparing these to a sham control (air at 2 L/min) [66]. Although there was modest improvement from the sham arm with CPAP and oxygen, only PSV demonstrated a statistically significant improvement in median walk distance (188 ± 215 → 336 ± 282 m), or a 62 percent improvement from baseline ($p = 0.01$). Oxygen saturation declined an average of 6 percent during their control walk, and only oxygen and pressure support prevented oxygen desaturation with treadmill walking. There was also improvement in the time to development of severe dyspnea.

Others have studied the effect of PAV. This mode provides both flow and volume assistance proportional to the patient's inspiratory efforts, matching the end of the ventilator's inspiratory cycle with end of the patient's inspiratory cycle. The ventilator is able to adapt to the patient's support requirements with better patient-ventilator synchrony than conventional ventilators. It has also been demonstrated to be effective in unloading the ventilatory muscles [67,68].

Dolmage and Goldstein studied 10 COPD patients (FEV_1 percent predicted = 29 ± 7%) during cycle ergometry, comparing PAV (volume assist = 6 ± 3 cm H_2O/L, flow assist = 3 ± 1 cm H_2O/L/s), CPAP (5 ± 2 cm H_2O), PAV + CPAP, applied through a mouthpiece to sham support with 0 cm H_2O [69]. Exercise time increased with both CPAP and PAV (about 20%) compared to sham, but the difference was only significant for PAV + CPAP (6.6 ± 3.1 vs. 12.9 ± 8.7 min of cycle time, $p < 0.05$). There was a significant increase in minute ventilation only for PAV + CPAP, manifested primarily as in increase in tidal volume (1.14 ± 0.34 vs. 1.32 ± 0.33 L, $p < 0.05$).

Bianchi and colleagues studied 15 hypercapnic COPD (FEV_1 percent predicted = 32 ± 10%) patients during cycle ergometry [70]. They assigned patients to nasal mask PAV (volume assist = 8.6 ± 3.6 cm H_2O/L, flow assist = 3 ± 1.3 cm H_2O/L/s + 1 cm H_2O EPAP), PSV (12–16 cm H_2O + 1 cm H_2O EPAP), CPAP (6 cm H_2O), or sham support (1 cm H_2O). Oxygen was administered if necessary to maintain an oxygen saturation of 92 to 93 percent. All the support modes, CPAP, PSV, and PAV, demonstrated a longer cycle time with lower dyspnea scores than sham, with the longest cycle time noted during PAV (7.2 ± 4.4 vs. 12.5 ± 6 min; all modes $p < 0.05$). The other modes had intermediate improvement in cycle time (CPAP = 9.6 ± 4.6 min; PSV = 10.5 ± 2 min).

Hernandez and colleagues studied eight hypercapnic COPD patients ($FEV_1 = 0.7 \pm 0.2$ L) during cycle ergometry, comparing mouthpiece PAV (volume assist = 9.8 ± 2.1 cm H_2O/L, flow assist = 3.3 ± 1 cm H_2O/L/s) with unsupported breathing [71]. Their results were similar to those noted previously with PAV. Patients increased their minute ventilation primarily through an increase in tidal volume, associated with an increased exercise time of 72 percent (from 5.4 ± 4.1 to 8.5 ± 5.6 min, $p < 0.05$). Blood gases were measured during exercise, but there was no difference in the amount of end-exercise lactate production between supported and unsupported exercise.

Although there are differences in methodology, it is evident that noninvasive ventilation increases exercise capacity and decreases dyspnea during exercise in COPD patients. This has been a uniform finding, both as summarized above and in another review on the topic [72]. PSV and PAV seem to provide more benefit than CPAP, and PAV may be more effective than PSV. All modalities increase exercise capacity. However, the small number of patients who have undergone investigation tempers any conclusion. The findings in the review by van't Hull and colleagues were based on only 65 patients. A larger sample size would minimize the risk of a sample size effect and error (both in the ability to detect differences that do exist, and while minimizing the effect of a small sample size that may suggest a difference when one does not exist). The benefits of noninvasive ventilation during exercise and sleep are further summarized in **Table 3**.

Table 3.
Benefits of noninvasive ventilation during exercise and sleep.

Noninvasive Ventilation	Benefit
During Exercise	Unload ventilatory muscles
CPAP, PSV, PAV	Prevent dynamic airway compression
(PAV and PSV probably more effective than CPAP)	Reduce work of breathing
	Increase tidal volume
	Decrease minute ventilation
	Decrease heart rate
	Increase endurance during exercise
	Reduce serum lactate levels during exercise
During Sleep	All the above
	Possibly prevent or facilitate recovery from ventilatory muscle fatigue
	Decrease adverse effects of sleep
	Decrease upper airway resistance
	Prevent or decrease hypercapnia and hypoxemia

CPAP = continuous positive airway pressure
PSV = pressure support ventilation
PAV = proportional assist ventilation

These findings with noninvasive ventilatory support mirror somewhat the experience with supplemental oxygen. Short-term trials have uniformly demonstrated improvement in exercise capacity with a decrease in dyspnea. These findings provide a basis for the use of noninvasive ventilatory support during pulmonary rehabilitation. This support should translate into clinical improvement by allowing subjects to exercise longer and with greater intensity. However, the benefit with long-term application during exercise training, much less during a pulmonary rehabilitation program, has not been clearly established. A search of the National Library of Medicine PUBMED® and the Cochrane Database of Systematic Reviews identified only three randomized trials assessing the merits of noninvasive ventilation during exercise training (two pulmonary rehabilitation, one exercise program) in patients with COPD. One additional program used noninvasive ventilation nocturnally, but not during pulmonary rehabilitation, with striking results. These studies will be discussed in further detail.

Hawkins and colleagues randomized 29 patients with COPD (FEV_1 = 0.78 ± 0.2 L) to training with or without face mask PAV (volume assist = 12.7 ± 1.5 cm H_2O/L, flow assist = 3.6 ± 0.7 cm H_2O/L/s) during a supervised, 6-week outpatient cycle exercise program [73]. Educational efforts were not part of the program, and therefore this would not be considered a usual pulmonary rehabilitation program. This was not a blinded study, as there was no sham comparison group because patients did not tolerate the sham circuits in prior investigations. They set a 70 percent intensity target for training and were able to analyze results of 19 patients (10 assisted, 9 unassisted exercise). Of the 10 who did not complete the program, 6 had been assigned to unassisted training and 4 to assisted training. Four patients did not complete the program because of compliance issues, but the authors did not distinguish whether the noncompliant patients had been assigned to the assisted or unassisted ventilation group. Both groups underwent unassisted exercise testing before and after the program. Both demonstrated an increase in exercise capacity, with significantly higher peak work rates achieved by the PAV group (32.9% increase, compared to 14.5%; $p < 0.01$). There was an increase in exercise endurance by both groups during constant work rate exercise tests, but the difference between the two groups was not significant (PAV group: $8.7 \rightarrow 17.2$ min, unassisted group: $6.9 \rightarrow 13$ min). After training, PAV-supported patients had less lactate production, slower respiratory and heart rates, and lower minute ventilation for the same amount of workload ($p < 0.01$); but, except for the heart rate, the differences did not achieve statistical significance. These investigators were able to demonstrate that patients can undergo cycle exercise training over an extended timeframe using noninvasive assisted ventilation. This allowed their patients to train longer at higher intensity, with a net effect of modest improvement in exercise capacity and endurance.

Bianchi and colleagues randomized 33 patients with COPD in an outpatient, 6-week pulmonary rehabilitation program using cycle exercise. Patients were randomized to either nasal (13 patients) or face mask (5 patients) PAV (volume assist = 6.6 ± 2.2 cm H_2O/L, flow assist = 3.5 ± 1.6 cm H_2O/L/s + EPAP = 2 cm H_2O) or unassisted training (15 patients) [74]. The PAV patients had less severe COPD (FEV_1 = 1.43 ± 0.57 L) than the unassisted group (1.18 ± 0.39 L). A total of 19 (9 PAV) completed the program, with 5 (28%) of patients dropping out because they were unable to tolerate the mask. Two additional patients dropped out because of an exacerbation of their underlying lung disease, one due to hypertension and one due to coronary artery disease during training. In the unassisted group, five dropped out because of an exacerbation of their underlying lung disease. These authors used a 6 min walk distance as an outcome measurement. Both groups experienced an increase in exercise capacity and walk distance with a reduction in dyspnea scores, but the magnitude of the changes was essentially the same. No additional benefit was demonstrated with PAV compared to those with unassisted training. This group of patients was not as severely obstructed as the previous group, and this may explain their disparate results. The small sample size may have also limited the ability to detect a small difference. The failure of over a quarter of patients to tolerate PAV is also noteworthy and underscores this potential limiting factor in the use of assisted ventilation during exercise training.

Johnson and colleagues randomized 39 COPD patients (mean FEV_1 = 33.5%) in a 6 week treadmill exercise pulmonary rehabilitation program to one of three modalities [75]. These treatment arms were either 10 L/min humidified air, 10 L/min humidified heliox (79% helium, 21% oxygen), or noninvasive ventilatory support with bi-level positive airway pressure, BiPAP (inspiratory positive airway pressure, IPAP = 8–12 cm H_2O; expiratory positive airway pressure, EPAP = 2 cm H_2O). Heliox may reduce the work of breathing with increased forced expiratory flows, since there is less turbulent airflow with this gas mixture. Its use was extrapolated from beneficial results noted in asthma and COPD patients during acute exacerbations of their respiratory disease. Of the 39 subjects, 32 completed the program, with 4 dropouts from the noninvasive group, 2 from the unsupported group, and 1 from the heliox group. All the groups had a comparable level of lung function and oxygenation. They conducted short-term testing encompassing all three modalities. Subjects then underwent a 6-week program, using one of the three modalities, before testing was repeated, again with all three modalities. Supplemental oxygen was provided during training to maintain oxygen saturation above 90 percent, but the frequency of this use was not reported. There was no difference in any of the modalities in the short-term studies. At the end of the study, all the patients demonstrated an improvement in their exercise time and maximum workload. The noninvasive group had the greatest percentage of improvement in unassisted exercise time (90 ± 58% vs. 72 ± 51% [heliox] vs. 37 ± 33% [unassisted]), but there was no difference in the maximum workload achieved. However, despite a greater percentage of improvement in exercise time, the actual duration of unassisted exercise time was greatest for the heliox group (16.6 ± 4 min vs. 16.0 ± 5.8 min [unassisted] vs. 14.2 ± 5.6 min [noninvasive]). The noninvasive group had the lowest exercise capacity of the three groups at the start of training, despite comparable spirometry. The results provide support for the use of noninvasive ventilation, but are inconclusive with respect to its additional benefit during pulmonary rehabilitation. These three studies are summarized in **Table 4**.

The experience of Bianchi and colleagues [74] is telling. The logistics of noninvasive ventilation during exercise may be daunting for both patient and provider. In addition to identifying the appropriate group of patients, not all patients can tolerate noninvasive ventilation. Noninvasive ventilation needs to be delivered via a ventilator-patient interface, usually a facemask or nasal mask, or even a mouthpiece. Some patients cannot tolerate the mask because of claustrophobia or discomfort. Leaks due to facial deformities, beards, or poor positioning are the bane of noninvasive ventilation, limiting the amount of pressure that can be delivered [76]. Nasal masks are better tolerated in the awake patient, but are subject to inefficient ventilation due to mouth leaks. A mouthpiece may be uncomfortable during extended exercise. The need for a ventilator limits the use of noninvasive ventilation to stationary exercise (cycle or treadmill). The connecting hose must be of sufficient length to allow free movement without tethering the patient to the ventilator. The technical aspects make application during walking difficult, unless the ventilator can be battery operated and carried in a backpack or placed on a mobile stand for rolling.

A portable ventilator fulfilling those requirements has been evaluated and compared with oxygen in a short-term study [77]. This ventilator provides inspiratory pressure

Table 4.
Randomized trials of noninvasive ventilation during pulmonary rehabilitation.

Authors	**Room-Air Trained**		**Oxygen Trained**	
Hawkins et al.*	*n* = 9		*n* = 10	
FEV_1 (L)	0.78 ± 0.18		0.78 ± 0.22	
% predicted	28 ± 7		26 ± 7	
Effects of Training	**Before**	**After**	**Before**	**After**
Work rate max (W)	44 ± 12	57 ± 13	46 ± 11	52 ± 10
Exercise duration (min)	6.9	13	8.7	17.2
Peak lactate	3.0 ± 1.1	2.9 ± 0.83	2.84 ± 0.54	3.0 ± 1.1

Authors	**Room-Air Trained**		**Oxygen Trained**	
Bianchi et al.†	*n* = 15		*n* = 18	
FEV_1 (L)	1.18 ± 0.39		1.43 ± 0.57	
% predicted	40 ± 12		48 ± 19	
MIP (cm H_2O)	72 ± 23		83 ± 26	
Effects of Training	**Before**	**After**	**Before**	**After**
Work rate max (W)	81 ± 25	Mean change = 14	88 ± 25	Mean change = 20
6 min walk distance (m)	439 ± 77	Mean change = 47	490 ± 74	Mean change = 16

Authors	**Room-Air Trained**		**Heliox Trained**		**Noninvasive Ventilation (BiPAP)**	
Johnson et al.‡	*n* = 13		*n* = 11		*n* = 15	
FEV_1	—		—		4.1 ± 1.8	
% predicted	30.7 ± 11.3		34.1 ± 12.8		31.6 ± 9.3	
PaO_2 (mm Hg)	69.2 ± 9		70.3 ± 6.0		72.0 ± 10	
Effects of Training	**Before**	**After**	**Before**	**After**	**Before**	**After**
Exercise duration (min)	12.3 ± 5.2	16.0 ± 5.8	10.6 ± 4.7	16.6 ± 4.0	7.9 ± 3.5	14.2 ± 5.6
Max workload (METs)	3.9 ± 1.6	5.1 ± 1.7	3.2 ± 1.2	4.6 ± 1.4	2.7 ± 0.7	—

*Hawkins P, Johnson LC, Nikoletou D, Hamnegard C-H, Sherwood R, Polkey JI, Moxham J. Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. Thorax 2002;57:853–59.

†Bianchi L, Foglio K, Porta R, Baiardi P, Vitacca M, Ambrosino N. Lack of additional effect of adjunct of assisted ventilation to pulmonary rehabilitation in mild COPD patients. Respir Med 2002;96:359–67.

‡Johnson JE, Gavin DJ, Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. Chest 2002;122:464–72.

METs = 3.5–4.0 ml/O_2/kg/min

MIP = maximal inspiratory pressure

support, is battery operated, weighs 2.1 kg, and can be carried in a backpack. Revill and colleagues studied 10 COPD patients and randomly assigned the patients to inspiratory pressure support at 14 cm H_2O, sham pressure support (<8 cm H_2O), oxygen at 2 L/min, sham oxygen (compressed air), and no assistance, using the endurance shuttle walk test as their measurement tool. Only ambulatory oxygen was associated with an increase in walk distance and time (mean increase of 62 m and 70 s; $p < 0.05$). With all the other modalities, there was a reduction in walk distance and time (mean decrease of 88 s with the portable ventilator, sham, and supported breathing). The

investigators felt that the ventilator did not have enough power to support patients through the increased demands of exercise.

Given the difficulties associated with the application of noninvasive ventilation during exercise, another approach would be to provide noninvasive ventilatory support at home while patients participate in pulmonary rehabilitation. It would be much easier to provide noninvasive support in this setting, bypassing the logistical issues that arise by tethering the device to an exercising patient. Noninvasive ventilatory support can be used during the day or at night, as the patient is resting or engaged in quiet activity. The basis for improvement with noninvasive ventilation at home is multifactorial, based on unloading the inspiratory muscles and reducing the work of breathing. This strategy may prevent the development of ventilatory muscle fatigue; overcome increased upper airway resistance, hypercapnia, and hypoxemia that occur during sleep; and improve sleep quality. The use of noninvasive ventilation at home has demonstrated benefit, with both nasal CPAP and nasal mask BiPAP [78]. It follows that this strategy may be beneficial in patients undergoing pulmonary rehabilitation and an intense exercise program. Home noninvasive ventilation would allow patients to recover more quickly and completely from any fatigue associated with their exercise program. It may also prevent any adverse consequences of the hypoxemia or hypercapnia that may occur during sleep.

To address this issue, Garrod and colleagues randomized 45 COPD patients (FEV_1 = 0.92 ± 0.28 L) to a pulmonary rehabilitation program with or without home noninvasive ventilation (nasal mask BiPAP; median IPAP = 16 cm H_2O; EPAP = 4 cm H_2O) [79]. After a 4-week run-in period, 35 were eventually randomized to home noninvasive ventilation and exercise training (19 patients) or exercise training alone (16 patients). Two patients were unable to tolerate noninvasive ventilation; the other dropouts were due to other comorbidities, noncompliance, or exacerbations of their underlying COPD. Patients were either normocapnic or mildly hypercapnic (44 ± 7 mm Hg (BiPAP group) or 46 ± 9 mm Hg). After 12 weeks, a significant difference was noted in the group treated with BiPAP, with improvement in PaO_2 from 64 to 66 mm Hg and maximum inspiratory pressure from –60 to –67 cm H_2O ($p < 0.05$) and an increase in the shuttle walk distance from 169 to 269 m ($p < 0.01$). The change in inspiratory muscle strength was not different between the two groups, but the change in PaO_2 and shuttle walk distance was significant ($p < 0.05$). The mean increase in shuttle walk difference in the group treated only with the pulmonary rehabilitation program was 28 m. There was nearly uniform improvement in quality-of-life measures in both groups, but the BiPAP group had greater improvement in the chronic respiratory disease questionnaire and in the fatigue component of that questionnaire ($p < 0.05$). Only two patients could not complete the study, because of difficulty using nasal BiPAP. Based on the ventilator meter, the median daily use of the ventilator was only 2.08 hours per day, with 47 percent using the ventilator for more than 3 hours per day. This is a relatively short duration of use, when compared to the duration reported by sleep apnea patients and those using nocturnal ventilation because of neuromuscular disorders and hypercapnia (closer to 6 hours per day). Thus the findings are even more striking given the relatively short duration of its daily use. The investigators were also able to determine that the differences in the two groups were most evident after 4 weeks of the program. The patients in the two study arms experienced the same amount of improvement in exercise tolerance up to that point, after which only the BiPAP patients had continued improvement, while improvement in the other patients had plateaued. The benefit attained with this approach provides another option for the use of noninvasive ventilation during pulmonary rehabilitation. However, noninvasive ventilation may have a rather steep learning curve for those unfamiliar with the technique. The significant dropout rate and mask intolerance may be a limiting factor in its widespread use. The positive results from this one center with long-standing expertise needs to be replicated in a larger study involving multiple sites.

SUMMARY

Adjuncts to increasing the duration of training during pulmonary rehabilitation have met with limited success. There is general improvement in exercise performance and dyspnea with the use of oxygen or noninvasive ventilation. However, despite short-term improvement, these strategies have had mixed results during long-term use, specifically within the context of a pulmonary rehabilitation program. The lack of additional benefit or only modest effect may be due to a relatively small number of patients studied and inhomogeneity of the patient group. Some investigations included patients of moderate disease severity, who would not be expected to require nor benefit from these adjuncts. The most appropriate subgroups

await definition. Oxygen desaturation during exercise or an FEV_1 <1.0 L may identify those most likely to benefit from supplemental oxygen or noninvasive ventilation during training. Alternatively, nocturnal noninvasive ventilation may provide the most effective adjunct, allowing additional gain during pulmonary rehabilitation, but avoiding much of the logistic problems that occur with the use of noninvasive ventilation during exercise.

There is strong physiologic support for these strategies. Patients undergoing pulmonary rehabilitation are severely compromised by their advanced underlying disease. Their potential for improvement may be limited by their severe disease, which further limits the magnitude of additional benefit that can be achieved with any therapy. If that is the case, to definitively detect and demonstrate a relatively small magnitude of improvement would require a much larger sample size than has been studied to date. This not only requires careful patient selection, but also recruitment of dozens of patients that would be possible only in the context of a large, multicenter trial.

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