The Roles of Bronchodilators, Supplemental Oxygen, and Ventilatory Assistance in the Pulmonary Rehabilitation of Patients With Chronic Obstructive Pulmonary Disease

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In patients with chronic obstructive pulmonary disease, pulmonary rehabilitation significantly improves dyspnea, exercise capacity, quality of life, and health-resource utilization. These benefits result from a combination of education (especially in the promotion of collaborative self-management strategies and physical activity), exercise training, and psychosocial support. Exercise training increases exercise capacity and reduces dyspnea. Positive outcomes from exercise training may be enhanced by 3 interventions that permit the patient to exercise train at a higher intensity: bronchodilators, supplemental oxygen (even for the nonhypoxemic patient), and noninvasive ventilatory support. *Key words: bronchodilators, oxygen, mechanical ventilation, pulmonary rehabilitation, chronic obstructive pulmonary disease, COPD, dyspnea, exercise capacity, quality of life, exercise training, exercise capacity, noninvasive ventilation*. [Respir Care 2008;53(9):1190–1195.

Introduction

A recent statement from the American Thoracic Society and European Respiratory Society defines pulmonary rehabilitation as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health-care costs by stabilizing or reversing systemic manifestations of the disease."[1] Although individual pulmonary rehabilitation programs differ considerably in setting, staff, composition, approach, and duration, most have components of patient assessment, exercise training, education (especially promoting self-management strategies), psychosocial intervention, and outcome assessment.

What Pulmonary Rehabilitation Does and How It Works

It is still surprising to some that pulmonary rehabilitation, which has no significant effect on the physiologic and

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functional respiratory impairments of individuals with chronic lung disease, often substantially improves multiple outcomes important to patients.[2] In fact, for patients with chronic obstructive pulmonary disease (COPD), pulmonary rehabilitation improves dyspnea, exercise capacity, and health status more than any other therapy, including bronchodilators or supplemental oxygen. Newer studies also suggest that pulmonary rehabilitation also reduces subsequent health-care utilization.[3,4]

Pulmonary rehabilitation works because patients with chronic respiratory disease usually have associated morbidity and comorbidity that are often very responsive to therapy. For example, patients with lung disease often unconsciously adopt a sedentary lifestyle, probably because of distressing exertional dyspnea and fatigue. Exertional dyspnea usually develops gradually, and a patient might attribute it to the normal aging process. The resultant physical deconditioning and alterations in structure and function of the peripheral muscles results in even more exertional dyspnea and fatigue, which, in turn, leads to even more sedentarism. Pulmonary rehabilitation interrupts this vicious circle, especially by increasing exercise capacity and promoting physical activity. Exercise training, especially at a higher intensity, can even cause favorable biochemical alterations in exercising muscles, even in patients with COPD with "pump limitation."[5]

It is very important to recognize that, although exercise training is integral to comprehensive pulmonary rehabilitation, other components of pulmonary rehabilitation are also important in enhancing outcomes. In the vicious circle of sedentarism → dyspnea/fatigue → more sedentarism, pulmonary rehabilitation also increases self-efficacy for exercise,[6] promotes increased physical activity at home, and provides techniques for pacing; these also enhance benefits.

Enhancing the Effectiveness of Pulmonary Rehabilitation Exercise Training

"If little labor, little are our gains; Man's fortunes are according to his pains."[7] Exercise intolerance is a major problem in patients with COPD, and strategies to improve the functioning of exercising muscles are needed to improve this functional limitation.[8] This often involves an appropriate, patient-specific exercise prescription. The above quotation from Robert Herrick (1591−1674) can be applied to the importance of training intensity (although without inflicting pain) in getting the most out of pulmonary rehabilitation. Even in patients with COPD, who have ventilatory pump and gas-exchange limitations, higher exercise training intensity provides more physiologic benefit and greater increase in exercise capacity.[9-13] Training intensity in the patient with COPD is affected by respiratory, cardiovascular, and peripheral-muscle impairments, and motivation. In pulmonary rehabilitation, training intensity up to or exceeding 60% of maximum symptom-limited exercise capacity is a reasonable goal.[1] Interventions that allow the patient to exercise-train at a higher intensity should promote greater post-rehabilitation improvement.

The following discussion will focus on 3 available therapies that may enhance the benefits from pulmonary rehabilitation exercise training: bronchodilators, supplemental oxygen, and noninvasive ventilation (NIV). These interventions may enhance the benefits of exercise training by allowing the symptom-limited COPD patient to train at a higher intensity.

Pulmonary rehabilitation is often complementary to other therapies in this regard:

1. Pulmonary rehabilitation often adds to the improvements in dyspnea, functional status, and health status obtained by therapies such as bronchodilators and supplemental oxygen.
2. Bronchodilators, oxygen, and (occasionally) NIV can enhance the effectiveness of pulmonary rehabilitation exercise training.

Bronchodilators

There are undoubtedly multiple mechanisms by which bronchodilators reduce dyspnea in patients with COPD, but bronchodilators' effects on reducing the resistive work of breathing (by increasing airway caliber) and the elastic work of breathing (by decreasing hyperinflation) are probably most important.[14-19] It is important to recognize that bronchodilators decrease breathlessness by decreasing lung volumes.[20] Hyperinflation, from decreased elastic recoil, increases the elastic work of breathing and reduces the mechanical advantage of the respiratory muscles.[21] Additionally, the increased metabolic requirements from exercising muscles demand increased minute ventilation, usually from an increased tidal volume, then an increased respiratory rate. However, expiratory time in COPD is prolonged, which makes it problematic to exhale completely when forced to breathe at a higher frequency. The combination of exertional dyspnea, the prolonged expiratory time, and the increased respiratory rate lead to more hyperinflation (dynamic hyperinflation) that further aggravates dyspnea.

Saey and colleagues[22] demonstrated an important concept that explains some of the variability in improvement in exercise capacity following bronchodilator therapy in COPD. Of the 18 patients they studied, 9 demonstrated muscle fatigue following constant-work-rate cycle exercise after placebo inhalation. Muscle fatigue was defined by a post-exercise reduction in quadriceps twitch force ≥ 15%. After nebulization with a short-acting anticholinergic bronchodilator, exercise endurance increased

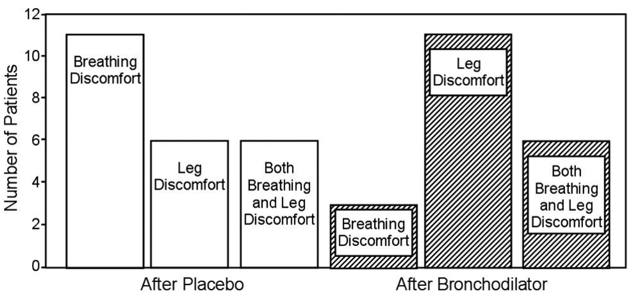

Fig. 1. Effect of bronchodilator on symptom-limitation during high-intensity constant-load exercise testing in 23 patients with chronic obstructive pulmonary disease. Without bronchodilator they were more frequently limited by breathing discomfort than by leg discomfort, whereas the reverse was true when they exercised following bronchodilator. With bronchodilator, 3 patients (not shown) listed "other" as their reasons for exercise termination. (Adapted from Reference 14.)

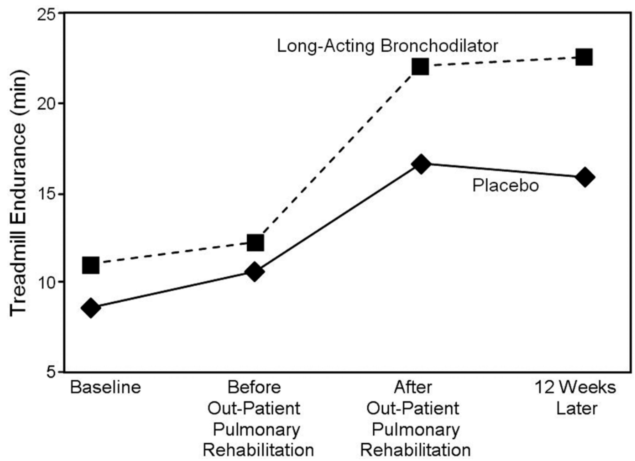

Fig. 2. Effect of long-acting bronchodilator on treadmill endurance in patients with chronic obstructive pulmonary disease, before, during, and after a pulmonary rehabilitation program. The patients were randomized to receive either placebo plus as-needed albuterol or a long-acting bronchodilator plus as-needed albuterol. Both groups had significantly increased treadmill endurance after the 8-week pulmonary rehabilitation exercise training, but those who took the long-acting bronchodilator improved more ($P < 0.05$). The differences in exercise capacity persisted 12 weeks after pulmonary rehabilitation. This study illustrates the additive effect of bronchodilator to pulmonary rehabilitation exercise training. (Adapted from Reference 23.)

significantly more in the 9 patients without muscle fatigue. This underscores the importance of ambulatory muscle fatigue in COPD and explains some of the variability in the exercise response to bronchodilator.

A study by O'Donnell and colleagues[14] illustrates an important concept in the effect of bronchodilator and exercise capacity. They evaluated the effect of a long-acting β-agonist bronchodilator on the ventilatory response to exercise in 23 patients with COPD. Of interest to this discussion is the patients' "locus of symptom limitation" (ie, the primary reason for stopping constant-load, high-intensity exercise on a cycle ergometer) (Fig. 1). Exercise without bronchodilator was more likely to be limited by dyspnea, whereas exercise with bronchodilator was more likely to be limited by leg fatigue. Thus, bronchodilator shifted the locus of symptom limitation somewhat away from "pump-limitation," so the patients could, presumably, get more out of lower-extremity exercise training.

With the knowledge that bronchodilators allow some patients to exercise at a higher intensity and that higher-intensity exercise promotes greater physiologic improvements, the combination of these 2 modalities makes sense. This additive relationship was demonstrated by Casaburi and colleagues in 2005, in an often-cited, double-blind placebo-controlled trial.[23] Patients with COPD who were pulmonary rehabilitation candidates were randomized into 2 groups: daily administration of a long-acting anticholinergic bronchodilator plus as-needed albuterol (n = 47); and daily administration of an inhaled placebo plus as-needed albuterol (n = 44). Both groups participated in an 8-week pulmonary rehabilitation program that included relatively high-intensity treadmill exercise training. Though both groups improved their exercise capacity with pulmonary rehabilitation, those who took the long-acting bronchodilator improved more (Fig. 2). Thus, bronchodilators can enhance gains in exercise capacity from pulmonary rehabilitation. This concept is important.

Supplemental Oxygen

Patients with COPD are aerobic organisms, and long-term supplemental oxygen for those with severe hypoxemia prolongs survival.[24,25] It stands to reason that supplemental oxygen is also clinically indicated for these patients during the exercise training in pulmonary rehabilitation, and, in fact, the oxygen flow often has to be increased during exercise. From a safety perspective, it is reasonable to also administer supplemental oxygen during exercise training in patients who are not hypoxemic at rest but have substantial exercise-induced hypoxemia. From a practical viewpoint, patients who have COPD and require oxygen are generally very sedentary and deconditioned, and ambulatory oxygen may not increase their activity level or health status.[26] These patients stand to benefit from pulmonary rehabilitation as an adjunct to their oxygen therapy.

This discussion will focus on the concept of supplemental oxygen therapy as an adjunct to pulmonary rehabilitation. A distinction should be made between the short-term effect of oxygen on enhancing exercise capacity in the laboratory and the long-term effect of oxygen on enhancing outcomes from exercise training in pulmonary rehabilitation. Supplemental oxygen increases exercise capacity in the laboratory in hypoxemic and nonhypoxemic patients with COPD.[27,28] The rationale for using oxygen to increase exercise capacity is that it reduces exertional breathlessness, probably through several mechanisms, including reducing hypoxic ventilatory drive, delaying the metabolic acidemia from exercise, and (indirectly) reducing dynamic hyperinflation[28] (presumably by reducing the ventilatory drive and respiratory rate), which permits a longer expiratory time and more complete lung emptying.

If oxygen increases exercise capacity in the laboratory, can it enhance exercise training in pulmonary rehabilitation? As stated earlier, the safety requirement usually requires supplemental oxygen in patients who have substantial hypoxemia during exercise training. Can oxygen enhance exercise-training effects in the nonhypoxemic patient, in whom oxygen is not clinically indicated? A recent systemic review of patients with COPD who did not require long-term oxygen addressed this issue. The analysis of the 5 randomized controlled trials that compared supplemental oxygen to compressed air or room air in the exercise training component of pulmonary rehabilitation had mixed results.[29] On pooled analyses, patients who received supplemental oxygen had longer exercise endurance but did not have significantly greater improvement in maximal exercise capacity, functional exercise capacity (6-min walk distance), shuttle-walk distance, or health status. The total number of patients in those studies is relatively small and the study designs differed.

A double-blinded study of 29 nonhypoxemic patients with COPD, by Emtner et al,[30] illustrates the potential usefulness of supplemental oxygen in pulmonary rehabilitation. These patients had severe COPD, as evidenced by a mean forced expiratory volume in the first second of 36% of predicted, but the study-inclusion criterion required arterial oxygen saturation (measured via pulse oximetry) of ≥ 88% during a constant-work-rate test. The patients exercised at high intensity, under supervision, on cycle ergometers, for 21 sessions over 7 weeks. One group received oxygen at 3 L/min. The other group received compressed air at 3 L/min. Compared to those who breathed compressed air, those who received oxygen increased their work rate more rapidly (Fig. 3), trained at higher intensity, and by the completion of the program had a greater increase in exercise endurance. The improvement in exercise performance was accompanied by an iso-time reduction in respiratory rate hyperinflation at iso-time. A lower respiratory rate in this setting would probably reduce the amount of dynamic hyperinflation.

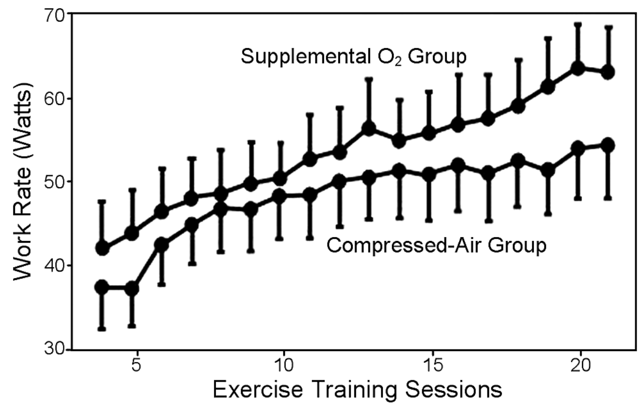

Fig. 3. Work rate during exercise training sessions in a double-blinded study. Twenty-nine nonhypoxemic patients with chronic obstructive pulmonary disease were randomized to receive either supplemental oxygen (at 3 L/min) or compressed air (at 3 L/min) during supervised, high-intensity cycle ergometry training. Those who received oxygen increased their work rate more rapidly than those who received compressed air. (Adapted from Reference 30, with permission.)

Noninvasive Ventilation

NIV may serve as an adjunct to exercise training in pulmonary rehabilitation by unloading the respiratory muscles. Additionally, there is some evidence that short-term administration of NIV to stable hypercapnic patients with COPD decreases hyperinflation,[31] probably by increasing expiratory time, allowing for more complete emptying of slow lung units.[32] This might allow for a higher exercise intensity.[33] A systematic review found that NIV significantly improves dyspnea and exercise endurance.[34] However, these benefits in the laboratory should be differentiated from the ability to enhance outcomes from exercise training in pulmonary rehabilitation. The discussion below will focus on the latter.

Three clinical trials have evaluated NIV as an adjunct to an exercise training program. One trial used NIV at night only; the other 2 trials used NIV during the exercise training program. The rationale for nocturnal NIV is to rest respiratory muscles in patients with severe COPD between pulmonary rehabilitation exercise training sessions. In the study by Garrod et al, 45 patients were randomized to 12 weeks of exercise training either with or without nocturnal NIV via nasal mask.[35] The median NIV inspiratory and expiratory pressure settings were 16 cm H_2O and 4 cm H_2O, respectively. Nighttime NIV was associated with a significantly greater increase in shuttle-walk test distance and improved health status following pulmonary rehabilitation.

Several trials have evaluated the adjunctive effect of NIV during supervised exercise training. Small numbers of subjects were studied, the study designs differed considerably, and drop-outs complicated the analyses. Most, but not all, showed some advantage to NIV in some exercise outcomes.[36-38] A recent evidence-based-guidelines statement on pulmonary rehabilitation concluded that NIV may enhance outcomes in the immediate post-rehabilitation period in patients with more advanced COPD.[39] It could be anticipated that NIV in that setting would be limited by several important factors, including problems with patient acceptance and tolerance, and an inordinate amount of pulmonary-rehabilitation staff time required.

Summary

Pulmonary rehabilitation significantly benefits several outcomes important to patients, including dyspnea, exercise tolerance, health status, and health-care utilization. Bronchodilators, oxygen (even in patients who are not severely hypoxemic), and NIV may allow patients to exercise-train at higher intensity during pulmonary rehabilitation exercise training and thus provide greater improvement in exercise capacity. However, these additive effects would probably be diminished or eliminated if the pulmonary rehabilitation involves only low-intensity exercise.

Bronchodilator is an established standard of care for symptomatic patients with COPD,[40] so its use in the pulmonary rehabilitation setting is natural. Administering short-acting bronchodilator before beginning exercise is reasonable. Supplemental oxygen for hypoxemic patients is also obviously indicated. There is also a rationale for its use in nonhypoxemic patients, that it may allow the patients to exercise at a higher intensity, but the evidence on this is not particularly strong, so the jury is still out on whether to administer oxygen to nonhypoxemic patients during exercise. NIV enhances outcomes in some patients with severe COPD, but using NIV during exercise training would present problems.

Of course, these exercise enhancers can be combined. A recent crossover-design study[41] found that the combination of bronchodilator plus supplemental oxygen in mildly hypoxemic patients ($P_{aO_2} > 65$ mm Hg) increased exercise endurance more than did either bronchodilator or supplemental oxygen alone. The authors[41] concluded that the additive effect was caused by the reduced hyperinflation from the bronchodilator and the reduced ventilatory drive from the oxygen. It would be reasonable to expect that this combination would also enhance the effects of pulmonary rehabilitation exercise training.

One important question that needs answering is, assuming the strategies listed above allow patients to exercise-train at a higher intensity and thereby achieve greater increases in exercise capacity, does the increased exercise capacity have any longer-term benefits? What does the increased treadmill endurance from supplemental oxygen really do for the patient? Is it translated into more activities at home? Is it maintained once the patient leaves the formal pulmonary rehabilitation program and has to do things without the aid of supplemental oxygen? Are the benefits of high-intensity exercise more likely to drop off with time?

Finally, it should be emphasized again that pulmonary rehabilitation is more than just exercise training. Though adjunctive therapies to enhance exercise outcomes make sense, they should be viewed as only one aspect of a patient-individualized, multidisciplinary, comprehensive intervention. The complete package works best.

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