Reduction of Hyperinflation by Pharmacologic and Other Interventions

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Hyperinflation of the lungs is associated with activity limitation and reduced quality of life of patients with chronic obstructive pulmonary disease (COPD). Cardiopulmonary exercise testing has proven useful, not only in establishing this link, but also in determining which interventions modify exercise endurance and the mechanisms by which this is achieved. In COPD, dynamic hyperinflation is reduced during exercise by interventions that either increase the potential for expiratory flow or increase the time available for expiration. Two classes of intervention improve exercise tolerance by increasing expiratory flow. Bronchodilators reduce expiratory airflow resistance by increasing the diameter of the airways. An alternative intervention, though less practical, is to reduce the density of the gas exhaled through obstructed airways, such as occurs when breathing a mixture of helium and oxygen (heliox). In contrast, supplemental oxygen and exercise rehabilitation programs improve endurance by reducing respiratory ventilatory drive and, therefore, respiratory rate. The different mechanisms exploited by these interventions to reduce dynamic hyperinflation suggest that combination treatments should yield additive benefits. This has been proven in the case of combinations of rehabilitative exercise training with supplemental oxygen, or with the bronchodilator tiotropium, both of which have been found to yield additive effects. With such interventions, we already have options for improving the mobility of patients with COPD. With a firm understanding of the physiologic basis of exercise limitation, we can focus on defining new and better strategies to improve exercise tolerance.

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The chief complaint of many patients with chronic obstructive pulmonary disease (COPD) is that they are no longer able to carry out or maintain an activity of which they were previously capable (1, 2). The mechanism of activity limitation is now felt to be multifactorial, related to muscle dysfunction as well as to pulmonary factors. A key concept is that activity limitation (or exercise intolerance) in COPD is linked to hyperinflation, particularly dynamic hyperinflation (see article by O’Donnell in this issue, pages 180–184). Discovery of this link between airway obstruction and activity limitation has led us to seek physiologic-based strategies to reduce hyperinflation and, thereby, improve the exercise tolerance of patients with COPD. Four interventions that reduce hyperinflation during exercise have been identified and are discussed in this article, with particular respect to their mechanism of action and with reference to selected literature citations. These are bronchodilator therapy, inhalation of supplemental oxygen or a helium/oxygen mixture, and rehabilitative exercise programs.

ASSESSING ACTIVITY LIMITATION

Before discussing interventions that influence activity limitation, a brief discussion of how it can be assessed is warranted. There are now a number of methods for assessing activity limitation, the choice of which will depend on availability of resources and the intended use of the data.

Perhaps the simplest method of assessment of activity levels is to seek the opinion of the patients themselves, which is aided by standardized and validated activity-related scales within quality of life questionnaires, such as the St. George’s Respiratory Questionnaire or the Short Form–36 (3, 4). Another method, which is still in development and not yet widely used in clinical practice, is the use of triaxial accelerometry to monitor patient activity in their everyday activities (5, 6). A patient can wear a triaxial accelerometer over periods of days or weeks before and after an intervention; this allows objective determination of differences in a patient’s activity level induced by the intervention (7).

However, most intervention trials assess the degree of activity limitation using laboratory exercise tests. Of these, the distance walked in 6 min is the simplest (8, 9), but does not provide any information on the mechanisms of exercise intolerance. More advantageous in investigating an effect of an intervention are the more complex cardiopulmonary exercise tests performed using treadmills or cycle ergometers (10, 11). These assessments include the changes in lung volume during activity, which yields information on the pulmonary mechanisms of activity limitation and defines the mechanism by which activity limitation is improved by interventions. Exercise testing at a constant work rate has proven to be a valuable outcome measure because it is sensitive to improvements in the ability to perform exercise and allows assessment of exercise-induced hyperinflation over time.

PHARMACOTHERAPY

At present, bronchodilators are the main pharmacologic options for improving hyperinflation. The efficacy of bronchodilators in reducing hyperinflation during exercise has been shown with various agents (12–15). These trials will not be reviewed comprehensively. Instead, a large, long-term trial with tiotropium has been selected as a representative study (12). Tiotropium is a once-daily anticholinergic with a prolonged bronchodilator effect (16).

In this multicenter study, 198 patients with moderate to severe COPD were randomized to a 6 wk treatment with either tiotropium (18 μg) or placebo, once daily (12). On average, patients had a resting residual volume approximately double that predicted, suggesting hyperinflation at rest. Exercise tolerance was determined by serial constant work-rate tests at 75% of initial peak work rate obtained during an incremental exercise test. Hyperinflation during exercise was measured by serial inspiratory capacity (IC) maneuvers, which require the patient to breathe in as deeply as possible every 2 minutes during exercise. As IC is the
total lung capacity (TLC) minus the end-expiratory lung volume, and TLC can be assumed to remain constant during exercise, IC is reduced proportionally as end-expiratory lung volume increases during exercise through dynamic hyperinflation (see article by Ferguson in this issue, pages 176–179).

IC data from this study is shown in Figure 1A. Data are shown at a standardized time, defined as the duration of the shortest exercise test for a given subject (isotime). Patients taking placebo showed little change in isotime IC over the 6-wk study. In contrast, patients taking tiotropium had an increase in isotime IC as compared with the baseline exercise test of approximately 200 ml that was maintained over the 6-wk period. This represents an appreciable decrease in dynamic hyperinflation. Tiotropium-treated patients also increased Ve by approximately 4 L/min at end of exercise compared with patients taking placebo, suggesting that treatment ameliorates the ventilatory limitation to exercise.

As expected, this reduction in hyperinflation corresponded with an increase in exercise tolerance (Figure 1B). At the end of the 6-wk trial, patients taking tiotropium were able to continue exercising for a mean of 21% (1.75 min) longer than patients taking placebo. Although a small initial increase in endurance time was seen with placebo, there was no further change over the 6 wk. In contrast, endurance time in the tiotropium group increased over time. This continued improvement may conceivably be due, at least in part, to a habitual increase in activity level that chronic improvement in lung mechanics allows. Bronchodilators, therefore, improve exercise tolerance by decreasing the expiratory airflow resistance, which decreases dynamic hyperinflation during exercise, yielding less dyspnea at a given level of exercise.

INHALED OXYGEN

Another approach to improving the exercise tolerance in patients with COPD is to increase the fraction of oxygen inhaled. Supplemental oxygen is an established treatment for hypoxemic patients with COPD, in whom it improves exercise tolerance and is proven to prolong life (17). Evidence also supports benefits of supplemental oxygen in nonhypoxemic patients—patients for whom supplemental oxygen would not normally be considered (18–21). For example, in our laboratory we investigated the effects of altering the FIO2 over the range from 21% (room air) through to 100% in 10 patients with COPD (19). These patients had severe airway obstruction (mean FEV1, ~30% predicted) and a substantial degree of hyperinflation at rest (mean residual volume approximately twice the predicted value), but did not have clinically significant reductions in arterial oxygen saturation (determined by pulse oximetry) at rest or during exercise.

Patients performed five constant work-rate exercise tests on a cycle ergometer at 75% peak work rate, each at a different oxygen fraction (performed in randomized order). Dynamic hyperinflation during exercise was again assessed by IC maneuver. The key results are shown in Figure 2. Inspiratory reserve volume (IRV) is the difference between TLC and end-inspiratory lung volume during spontaneous breathing. In other words, it is the IC minus the tidal volume. When breathing air (21% O2), isotime IRV is reduced to about 290 ml (compared with healthy subjects in the same study whose mean IRV when breathing air was 950 ml). When end-inspiratory volume approaches the TLC so closely, elastic work of breathing increases substantially (because the lungs are on a shallow portion of their pressure–volume relationship), which results in greatly increased dyspnea. Dynamic hyperinflation thus forces the patients to stop exercise. When these patients breathed 30 and 50% oxygen, mean IRV at the same isotime increased to 480 and 540 ml, respectively, suggesting that hyperinflation was reduced. There were no further increases in IRV at isotime with 75 and 100%. These increases in IRV were correlated with decreases in respiratory rate (data not shown). Hyperoxia decreased pulmonary ventilation; the fall in ventilation was wholly due to respiratory rate decrease. The lower respiratory rate allowed more time for exhalation, presumably yielding less hyperinflation. These changes were associated with an impressive increase in exercise endurance time, which showed a plateau at 50% oxygen and a peak increase of 160% above that for room air (Figure 2B). Breathing 30% oxygen was also very effective, suggesting that, at least in these patients, only a modest increase in oxygen fraction is required for an improvement in exercise endurance.

As supplemental oxygen is unlikely to impact airways resistance in COPD, the mechanism for reducing hyperinflation must differ from that of bronchodilators. A mechanism supported by these results is that, in nonhypoxemic patients, supplemental oxygen during high intensity exercise lowers ventilatory drive, which decreases respiratory rate. This, in turn, allows more time

![Figure 1. Effect of tiotropium on inspiratory capacity at isotime (ICstd) (A) and exercise duration (B) in patients with chronic obstructive pulmonary disease (COPD). Results are the mean values of 91 patients taking placebo and 96 patients taking tiotropium (18 μg once daily). Subjects performed constant work-rate exercise tests on a cycle ergometer at 75% of the peak work rate tolerated in a pre-intervention incremental exercise test. Isotime was defined as the response at the time at which the shortest test ended among the four performed by a given subject over the 6-wk period. Placebo (open circles, broken line) had little effect on ICstd over the 6-wk study (A). In contrast, tiotropium (triangles, solid line) significantly increased IC. Change from baseline in mean exercise endurance time increased significantly more with tiotropium (closed circles) compared with placebo (open circles) (B). *p < 0.05; **p < 0.01. See text for more details (12). Figure 1B reprinted by permission from Reference 12.]
when breathing heliox was no different from breathing room air, suggesting that both groups had the same degree of ventilatory drive when doing the same amount of work. Comparing responses at end-exercise, however, $V_{E}$ was significantly increased with heliox compared with normal air, supporting the theoretical mechanism of action of heliox. The key improvement was mean IC, which was significantly increased at isotime by approximately 200 ml with heliox compared with room air, and continued to increase significantly, even at peak exercise. Furthermore, the increase in endurance time with heliox correlated significantly with the increase in IC at isotime ($r = 0.70$).

Heliox breathing, therefore, functions in a similar way to bronchodilators, in that it decreases airflow resistance, albeit via a different physical mechanism. By the same physiologic mechanism, however, dynamic hyperinflation during exercise is reduced and exercise tolerance is improved.

**REHABILITATIVE EXERCISE TRAINING**

Of all the interventions available, a program of rehabilitative exercise training, when optimally delivered, generally yields the greatest improvements in exercise tolerance. Rehabilitation programs used in studies invariably include an element of exercise training, but may also include other elements, such as psychosocial, behavioral, and educational components. A review of the clinical trial evidence supporting the efficacy of these various components suggests that training the muscles of the lower limbs is the clearly beneficial component (25). In some studies, impressive improvements occurred even after the simplest of exercise-based rehabilitation programs (26). Exercise training is, however, muscle specific. Hence, training of lower limb muscles is not an optimal approach for improving upper body exercise endurance, and *vice versa* (25, 27).

The mechanisms by which exercise tolerance is improved by rehabilitative exercise have been progressively revealed. The first insight was that training muscles decreases ventilatory stimulation at a given level of activity due to a reduction in lactic acid production in the muscles. Another cause of exercise cessation is muscle fatigue, the onset of which is slowed by exercise training. We now realize that dynamic hyperinflation is also reduced after a rehabilitative exercise training program, as evidenced by the results of a recent study from our laboratory (28).

In this study, we investigated the effects of a training program on 24 patients with severe COPD (mean age, 66 yr; mean $FEV_1$, 1.02 L). The training program consisted of 45-min sessions of high-intensity exercise on a cycle ergometer three times/wk for 7 wk. Constant work-rate cardiopulmonary exercise tests at 75% of peak work rate in the initial incremental exercise test, featuring serial IC maneuvers, were performed before and after the training program. Figure 3 shows the $V_{E}$ and IC in a typical patient from this study. Before the training program, $V_{E}$ reached a peak after approximately 5 min, at which time the patient had to stop exercising (Figure 3A). After training, although $V_{E}$ initially increased with the same gradient as before, $V_{E}$ tended toward a plateau after a few minutes, which was lower than the peak $V_{E}$ in the pretraining study, and the patient was able to continue exercise for approximately four times as long as in the pretraining study (Figure 3A). Similar differences were seen in the IC time course, which decreased rapidly during exercise before training, but tended to level off after training (Figure 3B). Mean difference at isotime for the whole group showed that exercise training lowered $V_{E}$ by approximately 2 L/min, lowered the rate of breathing by approximately 3 breaths/min, and increased IC by approximately 130 ml.

Endurance exercise training, therefore, similar to supplemental oxygen, reduces ventilatory drive and slows breathing frequency

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**INHALATION OF HELIUM/OXYGEN MIXTURES**

Lung mechanics in ventilatory-limited patients with COPD may also be improved by breathing a low-density gas mixture, such as a mixture of 79% helium, 21% oxygen (heliox). The principle is that breathing heliox reduces the turbulence caused by flow resistance at high rates of ventilation (22) and, thereby, improves exercise tolerance by increasing the maximal $V_{E}$ possible. This theory has been substantiated in a study by Palange and colleagues (23), the results of which have recently been confirmed in a study by our group (24). In the former study, 12 patients with moderate to severe COPD (mean $FEV_1 = 1.15$ L) underwent two constant-work exercise tests at 80% maximum on a cycle ergometer while breathing either room air or heliox in a double-blinded fashion. As before, dynamic hyperinflation was measured by IC maneuvers during exercise.

Patients breathing heliox more than doubled their endurance time for a constant work-rate cycle ergometer test, from a mean of 4.2 min with room air to a mean of 9.0 min. At isotime, $V_{E}$

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**Figure 2.** Effect of breathing increasing oxygen concentrations on inspiratory reserve volume at isotime (A) and exercise endurance time tolerance (B) in patients with COPD performing cycle ergometer constant work-rate tests while inhaling different FIO₂. Results are the mean ± SEM of 10 patients. Increasing the FIO₂ from room air (0.21) to 0.3 or 0.5 increased the inspiratory reserve volume (A). No further changes beyond those observed at an FIO₂ of 0.5 were observed with FIO₂ of 0.75 and 1.00. Exercise endurance time showed a similar pattern (B). See text for more details (19).

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**Figure 3.** Endurance exercise training, therefore, similar to supplemental oxygen, reduces ventilatory drive and slows breathing frequency
during exercise. This allows more time to exhale between breaths, and the resultant reduction in dynamic hyperinflation allows activity to be maintained longer.

IMPROVING REHABILITATIVE EXERCISE PROGRAMS

It is postulated that improving exercise endurance will have a positive effect on the activity of patients, which itself will further improve exercise endurance. The key initiator of this positive reinforcement cycle is the attainment of an initial exercise tolerance improvement that is as large as possible. To achieve this, patients need to train at higher exercise intensities to gain a better initial effect. Mechanistically, this can be achieved by reducing the degree of hyperinflation through a combination of exercise training with one or more of the other interventions discussed previously here, or perhaps other interventions, such as pressure support ventilation or interval training.

Supporting data from specific studies for these combination approaches currently exist only for bronchodilators and supplemental oxygen (29, 30). Focusing on the bronchodilator–exercise combination, a report testing tiotropium in combination with an 8-wk rehabilitation program in a 25-wk, placebo-controlled trial has recently been published (29). The study randomized 108 patients with severe COPD (mean FEV1, 34% of predicted) to either tiotropium or placebo once daily. The study drug was administered 5 wk prior to the rehabilitation program, and continued for 12 weeks after completion of the program. The rehabilitation program was rigorous, with three 45-min treadmill exercise sessions carried out at the highest intensity of exercise the patient could achieve.

Figure 4 shows the changing exercise endurance time on a treadmill set at 80% of the maximum speed that the patient could reach during an incremental test performed before the intervention. Both groups began the study being able to endure the exercise test for a mean of approximately 9 min. The placebo group showed little improvement above baseline before rehabilitation, but improved to approximately 16 min by the end of rehabilitation, followed by a small decline at 12 wk after cessation of rehabilitation. In contrast, all responses were improved with tiotropium. As expected, tiotropium alone improved exercise endurance above placebo (by an average of 16%). However, this improvement doubled to 32% over placebo by the end of rehabilitation, and the improved endurance continued after cessation of rehabilitation, so that the improvement over placebo was 42% by the end of the study.

Therefore, improvement in exercise endurance with the combination of tiotropium and rehabilitation was more than additive. This was presumably the result of patients with tiotropium being effectively bronchodilated, which enabled exercise at a higher intensity during rehabilitation, and provided a greater benefit from the rehabilitation program.

CONCLUSIONS

Reducing hyperinflation in patients with COPD is a key mechanism for improving their exercise tolerance and activity. This article has discussed four physiologically based interventions that are able to improve exercise tolerance through a mechanism linked to a reduction in dynamic hyperinflation.

![Figure 3. Effect of a high-intensity cycle ergometer exercise training program in a representative patient with COPD on responses to constant work-rate cycle ergometer exercise performed at 75% of the peak work rate achieved in an incremental exercise test. Ve (A) and IC (B) time courses shown are before (open circles, broken line) and after (closed circles, solid line) a series of 45-min training sessions, three times a week for 7 wk. Although Ve increased at the same rate for the first 3–4 min of exercise, the peak ventilation that occurred at end of exercise before training was not achieved after training, and exercise continued for approximately five times longer (A). Similarly, IC decreased rapidly and continuously until end of exercise before training, whereas it leveled off after training (B). See text for more details.](image-url)

![Figure 4. Combined effect of tiotropium (18 µg once daily) and an 8-wk rehabilitation program on duration of exercise tolerated by patients with COPD. Results show the mean endurance time for a constant work-rate treadmill exercise test at 80% of the maximum speed tolerated in an incremental test in 53 patients taking placebo (circles) and 55 patients taking tiotropium (triangles). Study drug started after the baseline measurements and then continued throughout the study. Rehabilitation included three 45-min high-intensity treadmill exercise sessions per week. Exercise endurance time was measured at baseline, after 4 wk on study drug, after the 8-wk rehabilitation program, and 12 wk after completion of the rehabilitation program. In the placebo group, little improvement was seen before rehabilitation. In the tiotropium group, an effect of tiotropium was observed before rehabilitation, but this was smaller than the observed increase in the effect of rehabilitation compared with that of the placebo group. The increased endurance time after rehabilitation in the tiotropium group continued to the end of the study. *p < 0.05. See text for more details (29). Reprinted by permission from Reference 29.](image-url)
Dynamic hyperinflation can be reduced by either improving airflow during expiration or by reducing the rate of breathing to increase the time for expiration. Bronchodilators and heliox decrease airflow resistance, allowing more rapid airflow during expiration. In contrast, supplemental oxygen and rehabilitative exercise training decrease ventilatory drive, slow respiration rate, and allow the patient more time to exhale.

The different mechanisms employed in these interventions suggest that combinations would provide additional benefits. This has already been demonstrated by the supra-additive benefits shown by combining tiotropium or supplemental oxygen with rehabilitation. With such interventions, we have the capacity to reduce hyperinflation, thereby providing options for improving the potential for living a fuller life for patients with COPD.

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