Richard Casaburi

Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, Stany Zjednoczone

Strategies to reduce dynamic hyperinflation in chronic obstructive pulmonary disease

Sposoby zmniejszania dynamicznego rozdęcia płuc w przewlekłej obturacyjnej chorobie płuc

Pneumonol. Alergol. Pol. 2009; 77: 192–195

Introduction

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. 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. These are bronchodilator therapy, inhalation of supplemental oxygen or a helium/oxygen mixture, and rehabilitative exercise programs.

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 [3–6]. A large, long-term trial with tiotropium has been selected as a representative study [3]. Tiotropium is a once-daily anticholinergic with a prolonged bronchodilator effect. In this multicenter study, 198 patients with moderate to severe COPD were randomized to 6 weeks of treatment with either tiotropium (18 mg) or placebo, once daily. 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 (EELV), and TLC can be assumed to remain constant during exercise, IC is reduced proportionally as EELV increases during exercise through dynamic hyperinflation.

Patients taking placebo showed little change in isotime IC over the 6-week 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-week period. Tiotropium-treated patients also increased minute ventilation by approximately 4 L/min at end of exercise compared with patients taking placebo, suggesting that treatment ameliorates the ventilatory limitation to exercise. This reduction in hyperinflation yielded an increase in exercise tolerance. At the end of the 6-week trial, patients taking tiotropium were able to continue

Address for correspondence: Richard Casaburi, PhD, MD, Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Building J-4, 1124 W. Carson Street, Torrance, CA 90502, USA, tel.: 001 310 222–8249, fax: 001 310 222–8200, e-mail: casaburi@ucla.edu

Praca wpłynęła do Redakcji: 21.01.2009 r.

ISSN 0867–7077

exercising for a mean of 21% (1.75 minutes) longer than patients taking placebo. 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 exercise tolerance in 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 [7]. Evidence also supports benefits of supplemental oxygen in nonhypoxemic patients — patients for whom supplemental oxygen would not normally be considered [8–11].

In a study performed in our laboratory, 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. When breathing air (21% O_2), isotime IRV (the difference between TLC and end inspiratory lung volume) is reduced to about 290 mL, compared to healthy subjects in the same study whose end-exercise 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 mL and 540 mL, respectively, suggesting that hyperinflation was reduced. There were no further increases in IRV at isotime with 75% and 100%. Hyperoxia decreased pulmonary ventilation; the fall in ventilation was wholly due to respiratory rate decrease. The lower respiratory rate allowed more time for exhalation, 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. Breathing 30% oxygen was also quite effective, suggesting that, at least in these patients, only a modest increase in oxygen fraction is required for an improvement in exercise endurance.

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 to exhale, and hence, reduces dynamic hyperinflation, which results in increased exercise endurance.

Inhalation of helium/oxygen mixtures (heliox)

Lung mechanics in ventilatory-limited COPD patients may also be improved by breathing a low--density gas mixture, such as heliox (79% helium and 21% oxygen). The principle is that breathing heliox reduces the turbulence caused by flow resistance at high rates of ventilation and, thereby, improves exercise tolerance by increasing the maximal minute ventilation possible. This theory has been substantiated in a study by Palange et al. [12], the results of which have recently been confirmed by a study from our group [13]. 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 minutes with room air to a mean of 9.0 minutes. At isotime, minute ventilation when breathing heliox was no different to when breathing room air, suggesting both groups had the same degree of ventilatory drive when doing the same amount of work. Comparing responses at end- exercise, however, minute ventilation 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 be significantly increased, even at peak exercise.

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 of lower limb exercise training, a clearly beneficial component [14]. 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, onset of which is slowed by exercise training. It is now established that dynamic hyperinflation is also reduced following a rehabilitative exercise-training program [15].

In this study, the effects of a training program on 24 patients with severe COPD (mean age 66 years, mean FEV_1 1.02 L) were investigated. The training program consisted of 45-minute sessions of high intensity exercise on a cycle ergometer, 3 times a week for 7 weeks. 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. Mean difference at isotime for the group showed that exercise training lowered minute ventilation by approximately 2 L/min, lowered the rate of breathing by approximately 3 breaths/minute, and increased IC by approximately 130 mL. Exercise tolerance was substantially prolonged.

Endurance exercise training, therefore, similarly 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 to obtain 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 combination of exercise training with one or more of the other interventions discussed above, or perhaps other interventions such as pressure support ventilation or interval training.

Supporting data from specific studies for these combination approaches currently exists for bronchodilators and supplemental oxygen [16, 17]. A report studying tiotropium in combination with an 8-week rehabilitation program in a 25-week, placebo-controlled trial randomized 108 patients with severe COPD (mean FEV_1 34% of predicted) to either tiotropium or placebo once daily [16]. Study drug was administered 5 weeks prior to the rehabilitation program and continued 12 weeks after completion of the 8 week program. The rehabilitation program was rigorous, with three 45-minute treadmill exercise sessions carried out at the highest intensity of exercise the patient could achieve.

The primary outcome was exercise endurance time on a treadmill set at 80% of the maximum speed the patient could sustain during an incremental test performed prior to the intervention. Both groups began the study being able to endure the exercise test for a mean of approximately 9 minutes. The placebo group showed little improvement above baseline prior to rehabilitation, but improved to approximately 16 minutes by the end of rehabilitation, followed by a small decline at 12 weeks 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, thereby providing a greater benefit from the rehabilitation program.

Conclusions

Reducing hyperinflation in patients with COPD has been shown to be a key mechanism for improving exercise tolerance. This article has discussed four physiologic-based interventions that are able to improve exercise tolerance through a mechanism linked to a reduction in dynamic hyperinflation.

Dynamic hyperinflation can be reduced by either improving airflow during expiration or by reducing the rate of breathing allowing more 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 additive benefits shown by combination of 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.

References

1. Rennard S., Decramer M., Calverley P.M.A. et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur. Respir. J. 2002; 20: 799–805.
2. Katula J.A., Rejeski W.J., Wickley K.L., Berry M.J. Perceived difficulty, importance, and satisfaction with physical function in COPD patients. Health Qual. Life Outcomes 2004; 2: 18.
3. O'Donnell D.E., Flüge T., Gerken F. et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in patients with COPD. Eur. Respir. J. 2004; 23: 832–840.
4. O'Donnell D.E., Voduc N., Fitzpatrick M., Webb K.A. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. Eur. Respir. J. 2004; 24: 86–94.
5. O'Donnell D.E., Lam M.I.U., Webb K.A. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 1999; 160: 542–549.
6. Liesker J.J., Van De Velde V., Meysman M. et al. Effects of formoterol (Oxis Turbuhaler) and ipratropium on exercise capacity in patients with COPD. Respir. Med. 2002; 96: 559–566.
7. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; 1: 681–686.
8. O'Donnell D.E., Bain D.J., Webb K.A. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. Am. J. Respir. Crit. Care Med. 1997; 155: 530–535.
9. Somfay A., Porszasz J., Lee S.M., Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. Eur. Respir. J. 2001; 18: 77–84.
10. Dean N.C., Brown J.K., Himelman R.B., Doherty J.J., Gold W.M., Stulbarg M.S. Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am. Rev. Respir. Dis. 1992; 146: 941–945.
11. Woodcock A.A., Gross E.R., Geddes D.M. Oxygen relieves breathlessness in „pink puffers". Lancet 1981; 1: 907–909.
12. Palange P., Valli G., Onorati P. et al. Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J. Appl. Physiol. 2004; 97: 1637–1642.
13. Goto S., Porszasz J., Sakurai S., Whipp B.J., Casaburi R. Effect of helium breathing on dynamic hyperinflation, minute ventilation and exercise tolerance in severe COPD patients. Am. J. Respir. Crit. Care Med. 2004; 169: A467.
14. Lacasse Y., Guyatt G.H., Goldstein R.S. The components of a respiratory rehabilitation program: a systematic overview. Chest 1997; 111: 1077–1088.
15. Porszasz J., Emtner M., Goto S., Somfay A., Whipp B.J., Casaburi R. High intensity training decreases exercise-induced hyperinflation in patients with COPD. Chest 2005; 128: 2025––2034.
16. Casaburi R., Kakafka D., Cooper C., Witek J., Kesten S. Improvement in endurance time with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005; 127: 809–817.
17. Emtner M., Porszasz J., Burns M., Somfay A., Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am. J. Respir. Crit. Care Med. 2003; 168: 1034–1042.