Combination therapy for exercise intolerance in COPD

R Casaburi

New combined approaches to reduce dynamic hyperinflation improve exercise intolerance in patients with COPD

Chronic obstructive pulmonary disease (COPD) is a miserable disease; exercise intolerance is one of its most troubling symptoms. Moreover, it has recently been discovered that poor exercise tolerance is highly predictive of poor survival. Those who care for these patients are therefore highly motivated to seek ways to ameliorate exercise intolerance. In recent years progress has come from what, at first glance, would seem to be an unlikely quarter. Although research expenditures for this disease are heavily weighted towards cell and molecular biology pursuits, physiological research (considered “old fashioned” in some quarters) has provided solid insights into rational treatment for exercise intolerance.

A key insight is that dynamic hyperinflation is a major mechanism limiting exercise tolerance in patients with COPD. This occurs when the increased metabolic requirements of exercise demand higher levels of pulmonary ventilation. This, in turn, requires that both tidal volume and respiratory rate increase. The patient with COPD is asked to exhale a larger volume in a shorter time, which becomes an impossible task given flow limitation imposed by the increased expiratory airflow resistance. At some point the exhalation cannot be completed in the allotted expiratory time, full exhalation cannot be accomplished, and end expiratory volume increases. Eventually, dynamic hyperinflation leads to end inspiratory lung volumes that approach a limiting value (total lung capacity). As the inspiratory reserve volume shrinks, additional inspiratory volume cannot be achieved without greatly increased elastic work of breathing, since the lung is increasingly on a shallow portion of its pressure-volume curve. Severe dyspnoea results and exercise terminates when this sensation becomes unbearable.

THERAPEUTIC APPROACHES

Pulmonary physiologists have been working to develop strategies to lessen dynamic hyperinflation at a given amount of exercise. Logically, approaches that either allow faster exhalation (reduced expiratory airflow resistance) or prolong the time allowed for exhalation (decreased respiratory rate) will allow fuller exhalation, thereby reducing dynamic hyperinflation and improving exercise tolerance. To date, four distinct approaches have been defined that either lower expiratory airflow resistance or slow respiratory rate:

- Oxygen supplementation.
- Treatment with bronchodilators.
- Heliox (79% helium, 21% oxygen).
- High intensity rehabilitative exercise training.

Oxygen supplementation

Oxygen supplementation reduces carotid body drive and slows respiration at a given level of exercise. Dynamic hyperinflation is reduced and exercise tolerance is substantially prolonged. Increasing inspired oxygen fraction up to roughly 50% confers progressively greater benefits. This occurs even in patients with COPD whose level of exercise desaturation does not meet the usual criteria for oxygen supplementation.

Treatment with bronchodilators

COPD is now recognised as distinctly not a disease of irreversible airflow obstruction. In a substantial majority of patients with COPD treatment with bronchodilators yields clinically useful improvements in expiratory airflow, allows fuller exhalation in a given period of time, reduces dynamic hyperinflation, and prolongs exercise tolerance. Reduced dynamic hyperinflation accompanied by exercise tolerance improvements has been best demonstrated with long acting anticholinergic agents.

Heliox

Heliox (79% helium, 21% oxygen) has a lower density than air and decreases airflow resistance. Breathing heliox lowers expiratory airflow resistance, decreases dynamic hyperinflation, and prolongs exercise tolerance.

Rehabilitative exercise training

High intensity rehabilitative exercise training has been widely acknowledged to substantially increase exercise tolerance in patients with COPD. An important mechanism of the benefits of exercise training has recently been defined. As the exercising muscles become more fit, they release less lactic acid at a given level of exercise. Since lactic acid stimulates respiration, after rehabilitative training exercise ventilation is lower, respiration is slowed, and dynamic hyperinflation is reduced.

COMBINATION THERAPY

If any one of these interventions improves exercise tolerance, it seems logical that a combination of any two (“combination therapy”) would yield even better results. There seems to be a minor competition among physiologically orientated laboratories to see which can demonstrate the effectiveness of these four treatments taken pairwise.

Our laboratory has shown that providing supplemental oxygen (3 l/min by nasal cannula) during a 7 week high intensity rehabilitation programme increased the tolerated work rates of patients during training and enhanced the improvements in exercise tolerance in comparison with COPD patients who trained while breathing room air. Patients who before training tolerated an average of 6 minutes of exercise at a given work rate breathing air tolerated an average of 26 minutes at the same work rate while breathing 30% oxygen after an oxygen supplemented training programme. For several participants it was apparent that, after training, their physiological capacity for exercise had improved to such a degree that the assigned work rate was now below the critical power; they were able to tolerate the work rate essentially indefinitely.

Peter Calverley’s laboratory investigated the combination of helium and oxygen breathing. In a crossover design, patients with COPD performed an endurance shuttle walk test while breathing air, 28% oxygen in nitrogen, 21% oxygen in helium, or 28% oxygen in helium. The latter mixture (high helium, high oxygen) yielded the highest shuttle walk distance. Whether 28% oxygen and 72% helium represents the optimal high oxygen/low density mixture for improving exercise tolerance remains to be determined. A multicentre study showed that the benefits of a rehabilitative treadmill training programme were enhanced in a group of COPD patients receiving an effective long acting anticholinergic...
In a crossover study in 16 patients, the mean tolerance of a constant work rate treadmill task was increased by 57% and 31% when inhalation of oxygen or receiving bronchodilator therapy (ipratropium bromide) to reduce hyperinflation and improve exercise tolerance in patients with COPD. In this study, the combination of oxygen and ipratropium increased exercise tolerance by an average of 87% over the control condition, demonstrating an approximately additive response.

The mechanism of increased exercise tolerance is thought to play a part. What is less clear is whether inflammation itself can feed back to the pathogenesis of CF. Further evidence suggests that they may play a part in the pathogenesis of CF. Further evidence to suggest that prostanoids have an important pro-inflammatory role in CF is provided by clinical trials which have shown that the broad spectrum COX inhibitor ibuprofen can delay the progression of CF lung disease.

Several questions are raised by these findings, including:

- What is the mechanism of increased prostanoid release and what is their role in regulating CF disease?

Possible role for COX-2 in the pathophysiology of CF

Lung disease in cystic fibrosis (CF) continues to be the major cause of morbidity and mortality, with the mechanisms whereby the biochemical defect causes lung disease receiving considerable attention. CF is caused by mutations in a 230 kbp gene located on chromosome 7 which codes for the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR functions in the main as a cAMP regulated chloride channel in epithelial and glandular structures. It has long been recognised that the abnormal chloride secretion by bronchial epithelial cells in CF predisposes to the development of bronchial damage and inflammation. The mechanism is under debate, but altered biochemical constituents of airway surface liquid, function of the mucociliary escalator, and the function of antibacterial defence molecules such as defensins are all thought to play a part. What is less clear is whether inflammation itself can feed back to further compromise the abnormalities in chloride transport leading to an amplificatory cycle of lung destruction. Studies of nasal potential difference in patients with CF have shown that there is a range in the severity of chloride flux reduction.

Lipid mediators such as prostanoids have an important role in regulating inflammation in most tissues including the lung. Prostanoids are produced from membrane phospholipids by a three step reaction involving arachidonic acid release via phospholipase A2, conversion of arachidonic acid into PGH₂ by cyclooxygenase (COX), followed by its conversion to terminal prostaglandins such as PGE₂ by specific synthases and isomerases. COX exists in three isoforms: COX-1 is constitutively expressed, COX-2 is inducible and therefore implicated in many inflammatory and malignant diseases, and a further enzyme, COX-3, has recently been described whose function is less well defined. Previous studies have shown that the levels of prostanoids such as PGE₂, PGF₂, PGF₁α, and thromboxane B₂ are raised in primary cultures of epithelial cells from the CF airway, suggesting that they may play a part in the pathogenesis of CF. Further evidence to suggest that prostanoids have an important pro-inflammatory role in CF is provided by clinical trials which have shown that the broad spectrum COX inhibitor ibuprofen can delay the progression of CF lung disease.

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