Educational aims

- To review current concepts of the mechanisms of symptom relief and improved exercise tolerance following pharmacological treatment in chronic obstructive pulmonary disease (COPD).
- To examine the relative responsiveness of new physiological outcome parameters in clinical trials.

Summary

Bronchodilator therapy is the first step in improving dyspnoea and exercise endurance in patients with COPD. Recent studies have challenged the long-held view that airway obstruction in COPD is irreversible. We now know that even in the setting of minor or no change in traditional spirometry, bronchodilator therapy is associated with consistent, and often impressive, reduction in lung hyperinflation. This pharmacological lung volume reduction is linked to improved inspiratory muscle function and enhanced neuro-mechanical coupling of the respiratory system during activity, even in those with advanced disease. Moreover, these improvements in dynamic mechanics provide a sound physiological rationale for observed bronchodilator-induced improvements in the important patient-centred outcomes of reduced dyspnoea and activity limitation.
Bronchodilator therapy

Recent international guidelines have correctly highlighted dyspnoea alleviation and improvement in exercise tolerance as among the most important management goals in COPD.

All classes of bronchodilators act by relaxing airway smooth muscle tone. Improvements in forced expiratory volume in one second (FEV1; beyond the natural variability of the measurement) after inhaled bronchodilators signify reduced resistance in the larger airways, as well as in alveolar units, with rapid time constants for lung emptying. In more advanced COPD (in contrast to asthma), post-bronchodilator increases in lung emptying (i.e., reduced airway resistance). The main impact of bronchodilator therapy is, therefore, on the dynamically determined resting EELV through pharmacological manipulation of airway resistance.

Improvements in resting IC, which indirectly signify reduced EELV, have been shown to occur as a result of treatment with all classes of bronchodilators (figure 2) [1–14]. A bronchodilator-induced increase in the resting IC (indicating reduced lung hyperinflation), in the order of 0.3 L or ~10–15% predicted (or 15–17% of baseline value), appears to be clinically meaningful and corresponds with important improvements in exertional dyspnoea, and exercise endurance measured during constant work rate cycle exercise at 60–75% of the patients’ pre-determined maximal work rate [1–3].

A number of studies have shown that bronchodilator therapy, alone or in combination with inhaled corticosteroids, does not alter the rate of dynamic hyperinflation (or air trapping) during exercise [1–3]. In fact, the magnitude of the rest-to-peak exercise reduction in IC may actually as measured by “trough”, or morning, pre-bronchodilator EELV or IC [1, 2, 7, 14] Combined long-acting bronchodilators have additive effects on lung volume deflation [14].

A recent mechanical study on the mechanisms of dyspnoea relief following therapy with the long-acting bronchodilator tiotropium showed that release of cholinergic tone was associated with improved airway conductance at all lung volumes from total lung capacity to residual volume (RV). Static elastic recoil of the lung was unchanged after acutely administered tiotropium, and expiratory timing during spontaneous resting breathing was unaffected. Lung deflation, therefore, primarily reflected improvements in the mechanical time constants for lung emptying (i.e., reduced airway resistance). The main impact of bronchodilator therapy is, therefore, on the dynamically determined resting EELV through pharmacological manipulation of airway resistance.

Improvements in resting IC, which indirectly signify reduced EELV, have been shown to occur as a result of treatment with all classes of bronchodilators (figure 2) [1–14]. A bronchodilator-induced increase in the resting IC (indicating reduced lung hyperinflation), in the order of 0.3 L or ~10–15% predicted (or 15–17% of baseline value), appears to be clinically meaningful and corresponds with important improvements in exertional dyspnoea, and exercise endurance measured during constant work rate cycle exercise at 60–75% of the patients’ pre-determined maximal work rate [1–3].

A number of studies have shown that bronchodilator therapy, alone or in combination with inhaled corticosteroids, does not alter the rate of dynamic hyperinflation (or air trapping) during exercise [1–3]. In fact, the magnitude of the rest-to-peak exercise reduction in IC may actually...
COPD feature: Bronchodilator therapy in COPD: physiological effects

Suggested answers
1: Bronchodilator therapy facilitates lung emptying and reduces air trapping. The resultant improvement in inspiratory muscle function and neuromechanical coupling of the respiratory system contribute to dyspnoea relief. This pharmacological lung volume reduction can occur in the absence of change in FEV1, particularly in advanced COPD.
2: In COPD, IC represents the true operating limits for tidal volume expansion during exercise. Recruitment of IC (which reflects reduced air trapping) following bronchodilatation allows for greater tidal volume expansion during exercise, with consequent reduced breathing frequency.

Bronchodilator responses in COPD
- Volume (functional residual capacity, RV) and flow responses (FEV1) to bronchodilators are independent
- Bronchodilators often do not abolish expiratory flow limitation [9–13]
- IC responses are more likely in patients with resting expiratory flow limitation (IC <80% pred) [6]
- IC responses are more pronounced in those with expiratory flow limitation and severe resting hyperinflation [5, 6]
- Changes in IC correlate better with improved outcomes than changes in FEV1 [1, 4, 13]

increase as a result of the higher levels of ventilation permitted by bronchodilator therapy. However, because of recruitment of the IC at rest, the dynamic EELV at peak exercise is lower, in absolute terms, than the value obtained at the breakpoint of exercise during the placebo arm of the treatment. In other words, bronchodilator treatment (compared with placebo) is associated with a parallel downward shift in the EELV over the course of the exercise test.

Improvements in the resting IC (as % pred) following bronchodilator therapy has been shown to correlate well with: 1) improved peak symptom-limited oxygen uptake; 2) increased peak tidal volume; 3) reduced dyspnoea ratings; and 4) increased endurance time during constant work rate cycle exercise testing in moderate-to-severe COPD patients [1, 4, 13]. In all of the studies, increased resting IC permitted greater tidal volume expansion with reduced breathing frequency throughout exercise [9–13]. Moreover, in a recent mechanical study, tiotropium was found to be associated with reduced airways resistance and elastic loading of the inspiratory muscles, which resulted in a reduced work and oxygen cost of breathing, compared with placebo [3]. A reduced inspiratory threshold load, reflecting reduced intrinsic positive end-expiratory pressure, would be expected to enhance neuromechanical coupling of the respiratory system during exercise.

The strongest correlate of improved exercise endurance in a number of bronchodilator trials has been reduced exertional dyspnoea intensity [9–13]. Several bronchodilator studies have shown that reduced dyspnoea ratings at a standard exercise time correlated well with reduced operating lung volumes (reduced EELV and an increased inspiratory reserve volume) and improved breathing pattern (increased tidal volume and reduced breathing frequency) [1, 4, 13]. The emerging evidence supports the idea that the beneficial effects of bronchodilators on respiratory sensation in COPD patients are ultimately related to enhanced neuromechanical coupling of the respiratory system as a result of improved dynamic ventilatory mechanics.

References