Lung hyperinflation in COPD: the impact of pharmacotherapy

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ABSTRACT: Improvement in airway function in response to bronchodilator therapy is generally confirmed by simple spirometry. However, improvements in maximal expiratory flow rates have been shown to correlate poorly with important patient-centred outcomes, such as reduced exertional dyspnoea and improved exercise performance. Recent studies have suggested that attendant reductions in end-expiratory lung volume as a result of bronchodilator-induced improvements in lung emptying may be more closely associated with symptom relief and increased exercise capacity than traditional spirometric indices. To the extent that chronic lung hyperinflation and the superimposition of acute dynamic hyperinflation (in response to increased ventilation or expiratory flow limitation) result in excessive loading and weakening of the inspiratory muscles, then pharmacological lung volume reduction should have important mechanical and sensory benefits for the patient.

The present article will examine the mechanisms of lung deflation following short-term bronchodilator therapy. The physiological links between reduced hyperinflation, improved dyspnoea and exercise endurance will be examined, and the emerging evidence for the additive effects of combining various modern pharmacological therapies will be reviewed.

KEYWORDS: Bronchodilators, chronic obstructive pulmonary disease, dynamic hyperinflation, dyspnoea, exercise, respiratory mechanics

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All classes of bronchodilators (BD) act by relaxing airway smooth muscle tone. Traditionally, improvement in airway function after BD is assessed by spirometric measurements of maximal expiratory flow rates [1]. Improvements in the forced expiratory volume in one second (FEV1) post-BD signify reduced resistance in the larger airways, as well as in alveolar units, with rapid time constants for lung emptying. In more advanced chronic obstructive pulmonary disease (COPD; in contrast to asthma), post-BD increases in FEV1 mainly occur as a result of lung volume recruitment; the ratio of FEV1 to forced vital capacity (FVC) is unaltered or actually decreases in response to BD [2–6]. Measurements of timed vital capacity or forced expiratory volume in six seconds appear to be more sensitive than FVC in detecting enhanced lung emptying after pharmacotherapy [7, 8]. Improvement in small airway function is more difficult to measure but reduced lung volume (residual volume (RV) and end-expiratory lung volume (EELV)), as a consequence of reduced airway closure and enhanced gas emptying in alveolar units with slower time constants, provides indirect evidence of a positive effect. Recent studies have shown that substantial reductions (*i.e.* >0.5 L) in lung hyperinflation can occur after acute short- and long-acting BD treatment in the presence of only modest improvements in FEV1 [2–6, 9–11]. BD therapy is often associated with small but consistent increases in maximal expiratory flow rates in the effort-independent mid-volume range where tidal breathing occurs [3, 4]. BD therapy does not necessarily abolish resting expiratory flow limitation (especially in more severe disease) but changes the conditions under which it occurs (fig. 1) [10]. Thus, patients may remain flow-limited but can now accomplish the required alveolar ventilation at a lower operating lung volume and, therefore, at a reduced oxygen cost of breathing. Patients who show expiratory flow limitation during spontaneous resting breathing (as determined by the negative expiratory pressure technique) and those with more severe resting lung hyperinflation have demonstrated the greatest lung volume reduction with BDs [6, 10, 11].

A recent mechanical study on the mechanisms of dyspnoea relief following tiotropium therapy showed that release of cholinergic tone was associated with improved airway conductance at all lung volumes, from total lung capacity to RV [12]. Static elastic recoil of the lung was unchanged after acutely administered tiotropium and expiratory timing during spontaneous
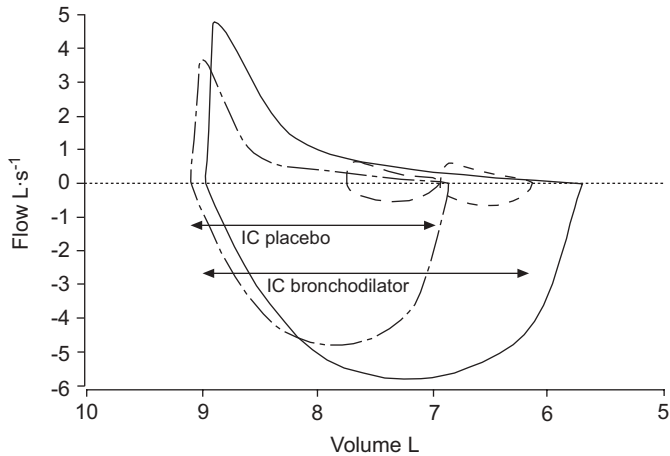
FIGURE 1. In a typical patient with severe chronic obstructive disease, maximal expiratory flows increased from placebo (– - –) with bronchodilator (——) in association with a decrease in end-expiratory lung volume as reflected by an increase in inspiratory capacity (IC). Tidal volume (– – – and -----) was positioned at a lower operating lung volume and inspiratory reserve volume was increased after bronchodilation compared with placebo.

resting breathing was unaffected. Lung deflation therefore primarily reflected improvements in the mechanical time constants for lung emptying (*i.e.* reduced airway resistance). In contrast to the situation following lung volume reduction surgery [13], acute BD administration was not associated with increased elastic lung recoil pressure and is not, therefore, likely to affect the statically determined relaxation volume of the respiratory system. The main impact is therefore on the dynamically determined resting EELV through pharmacological manipulation of resistance in the airways upstream from the flow-limiting segments [14, 15].

EFFECT OF BDs ON DYNAMIC VENTILATORY MECHANICS DURING EXERCISE

Improvements in resting inspiratory capacity (IC) have been shown to occur as a result of treatment with all classes of BDs and this indirectly signifies reduced EELV [3, 16–18]. A BD-induced increase in the resting IC (indicating reduced lung hyperinflation) in the order of 0.3 L or ~10% predicted, appears to be clinically meaningful and corresponds to important improvements in exertional dyspnoea and exercise endurance [3–5, 16–19]. Several studies have shown that BD therapy does not alter the rate of dynamic hyperinflation (or air trapping) during exercise [3–5, 16–20]. In fact, the rest to peak exercise reduction in IC may actually increase as a result of the higher levels of ventilation permitted by BD therapy [3–5, 16–20]. 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 break-point of exercise during the placebo arm of the treatment [3–5, 16–20]. In other words, BD treatment (compared with placebo) is associated with a parallel downward shift in the EELV over the course of the exercise test (fig. 2).

The resting IC (standardised as a percentage of the predicted normal value) has been shown to correlate well with peak symptom-limited oxygen uptake during incremental exercise
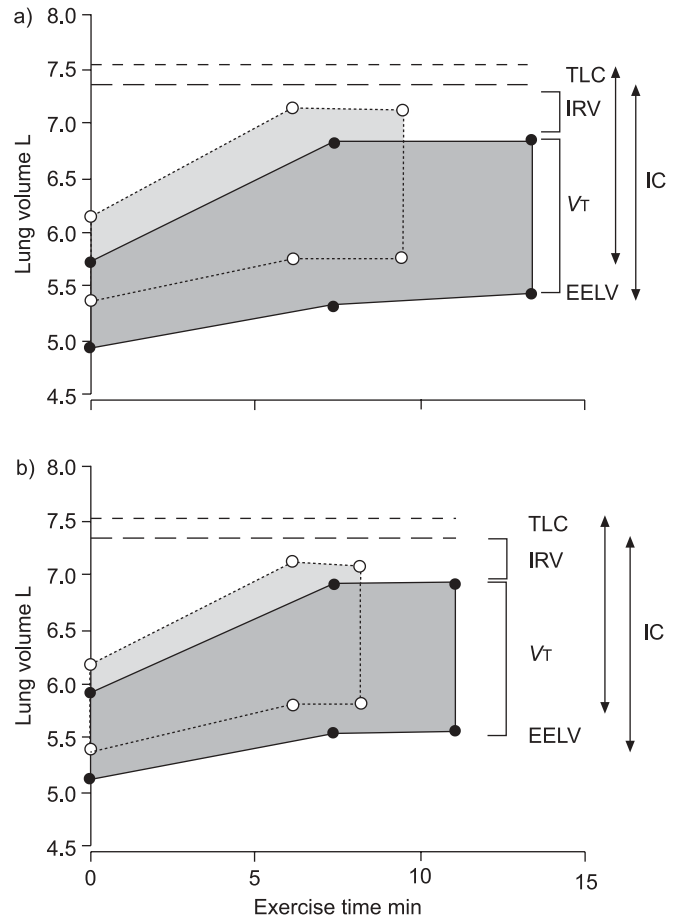

FIGURE 2. Operating lung volumes during constant work-rate cycle ergometry to symptom limitation at 75% of maximal work capacity on day 42 of treatment at a) 2.25 h post-dose and b) 8 h post-dose. At 2.25 h post-dose, the total lung capacity (TLC) corresponds to body plethysmography measurements at 1 h 20 min post-dose; at 8 h post-dose, TLC corresponds to values calculated by linear interpolation using values at trough (pre-dose) and 1 h 20 min post-dose. ○: placebo; ●: tiotropium; - - - -: placebo TLC; – – –: tiotropium TLC. IRV: inspiratory reserve volume; V_T: tidal volume; EELV: end-expiratory lung volume; IC: inspiratory capacity. Reproduced and modified from [5] with permission from the publisher.

testing in demonstrably flow-limited patients [21, 22]. It follows that improvements in this variable should be linked to improved exercise performance. Several studies, which used various BDs, have now shown that increased IC both at rest and during exercise is associated with increased tidal volume (V_T) and ventilatory capacity [3–5, 16–20]. Greater V_T expansion is accompanied by reduced breathing frequency throughout exercise, which, in turn, results in increased dynamic lung compliance [12]. Moreover, reduced airways resistance, together with reduced inspiratory threshold and elastic loading of the inspiratory muscles, means that a lower inspiratory effort is now required for a given ventilation. 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. Lung volume deflation, by increasing sarcomere fibre length in the diaphragm, may also favourably affect this muscle's force-generating capacity, which again would
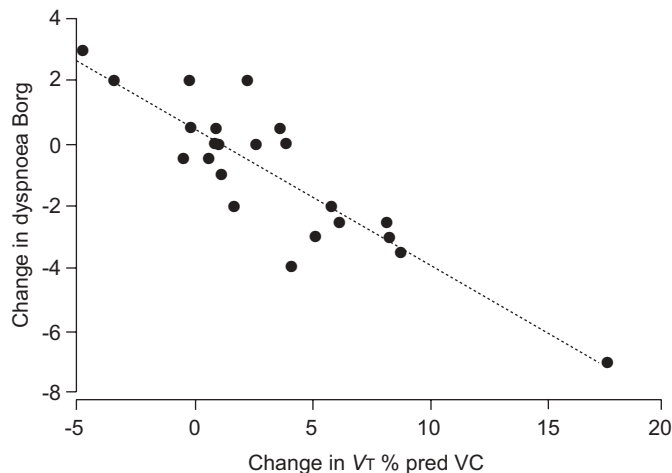
FIGURE 3. A significant correlation was found between differences in dyspnoea intensity and tidal volume (V_T; standardised as a % of the predicted vital capacity (VC)) at a standardised exercise time after salmeterol compared with placebo (n=23, r= -0.88, p<0.0005). -----: significant correlation (r=-0.88, p<0.0005) between differences in dyspnoea intensity and V_T at a standardised exercise time after salmeterol compared with placebo. Reproduced from [18] with permission from the publisher.

contribute to reduced effort requirements (and central neural drive) for a given V_T displacement. Thus, avoidance of ''high-end'' mechanics (where the respiratory system's pressure–volume relation is relatively flat) as a result of BD-induced reductions in EELV and increases in inspiratory reserve volume (IRV) should contribute importantly to exertional dyspnoea alleviation and improved exercise performance [2–4, 6, 9, 11]. This hypothesis has been bolstered by a number of BD studies, which have shown that reduced dyspnoea ratings at a standardised exercise time correlate well with reduced operating lung volumes (*i.e.* reduced EELV and increased IRV) and improved breathing pattern (increased V_T and reduced breathing frequency; fig. 3) [2, 3, 9].

IMPROVED VENTILATORY MECHANICS AND DYSPNOEA RELIEF

The strongest correlate of improved exercise endurance in a number of BD trials has been reduced exertional dyspnoea intensity [3, 4]. The precise neurophysiological mechanisms of dyspnoea relief remain speculative. In one study, treatment with the long-acting anticholinergic agent, tiotropium, was associated with consistent reductions in the ratio of respiratory effort to volume displacement throughout exercise, suggesting a more harmonious relation between neural drive and the mechanical response (fig. 4) [12]. BD-induced unloading of the ventilatory muscles must mean that less neural activation is required for a given force generation. Reduced motor command output (and central corollary discharge) may be sensed directly as a decrease in perceived effort. Improvement in the operating characteristics of inspiratory muscles secondary to lung deflation would be expected to enhance neuromuscular coupling; the muscle spindles may have an important role in sensing this [23, 24]. To the extent that restriction of the normal volume response to the increased neural drive of exercise contributes to perceived respiratory
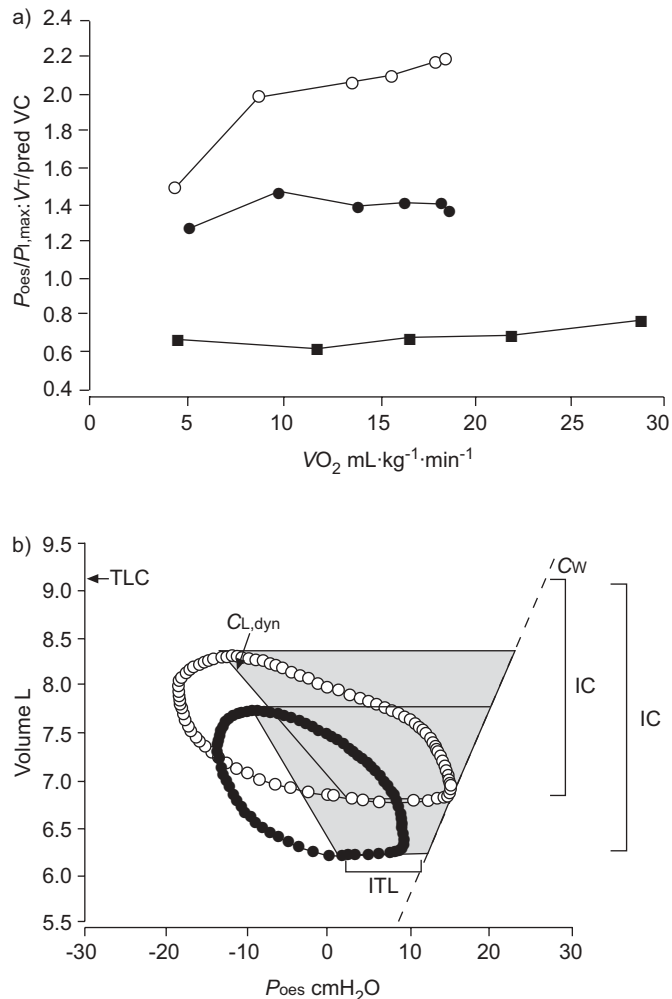

FIGURE 4. a) The relationship between respiratory effort (oesophageal pressure/maximal inspiratory volume ($P_{oes}/P_{I,max}$)) and tidal volume displacement (V_T; standardised as a fraction of predicted vital capacity (VC)), an index of neuromechanical coupling, is shown during constant work-rate exercise after tiotropium (●) and placebo (○) in a patient with severe chronic obstructive pulmonary disease (COPD; forced expiratory volume in one second=29% predicted; forced spirometry for this patient is shown in fig. 1). Data from a group of age-matched healthy subjects during exercise is also shown (■; data from [30]). Compared with placebo, tiotropium enhanced neuromechanical coupling throughout exercise in COPD. b) Campbell diagrams are shown at a standardised time during constant-load exercise for the same patient. After tiotropium (●) compared with placebo (○), there were decreases in the inspiratory threshold load (ITL), the elastic work of breathing (▨), the resistive work of breathing (area within volume–P_{oes} loops), and the effort/displacement ratio. The point at which total lung capacity (TLC) was reached is indicated by the arrow. V'_{O_2}: oxygen uptake; $C_{L,dyn}$: dynamic compliance; C_W: chest wall compliance, IC: inspiratory capacity.

discomfort [25], then the new-found ability to increase V_T after BDs may form the basis, at least in part, for reduced dyspnoea intensity or for alteration in its quality. Interestingly, in two studies, patients selected qualitative descriptors of dyspnoea in the ''unsatisfied inspiration'' cluster less frequently after BDs compared with placebo [18, 19]. There are numerous mechanosensors throughout the respiratory system whose afferent inputs can convey the sense of improved thoracic motion or

volume displacement for a given electrical activation of the muscle [26–30]. Altered peripheral sensory inputs from these sources, together with reduced central corollary discharge, culminate in reduced perceived respiratory discomfort during physical exertion in ways that are not yet fully understood. Although the precise mechanisms remain to be elucidated, the emerging evidence supports the idea that the salutary effects of BDs on respiratory sensation in COPD patients are ultimately linked to enhanced neuromechanical coupling of the respiratory system as a result of improved dynamic ventilatory mechanics [12].

COMBINED THERAPIES

Recent studies in patients with moderate-to-severe COPD have indicated that combined long-acting anticholinergic and β_2-agonist BDs have additive effects on airway function [31, 32]. A recent study by VAN NOORD et al. [33] showed that tiotropium (once daily) combined with formoterol (twice daily) was associated with sustained lung volume reduction as assessed by serial IC measurements over a 24-h period. The mean 0–24 h increase in IC after this BD combination was 0.29 L, with an impressive daytime peak effect of 0.55 L. The question arises whether this peak effect could be sustained throughout the 24 h by the addition of further BD therapy or possibly by adding inhaled corticosteroid therapy. A recent study confirmed that fluticasone propionate/salmeterol combination (FSC 250/50) was associated with reduced lung hyperinflation, improved IC and increased cycle exercise endurance time when compared with placebo [19]. Improvements in exercise endurance time during constant work-rate cycle exercise (at 75% of each patient's peak work-rate) averaged 130 s and were seen after the first dosing. The magnitude of the effect associated with FSC 250/50 was similar to that previously reported after 42 days of treatment with tiotropium in a similar COPD population [4, 5]. However, differences in study design, particularly the exercise testing protocol, preclude any direct comparison of the physiological and clinical benefits of these two therapies. Based on the results of studies that have examined the effects of combining long-acting BDs (as previously discussed), there is every indication that the combination of tiotropium and FSC will have additive clinical benefits with a greater impact on impairment, disability and handicap than with either treatment alone.

It now appears that it is possible to achieve sustained lung volume reduction by pharmacological means that is comparable in magnitude to that obtained by lung volume reduction surgery. What remains to be determined is whether modern pharmacotherapy will favourably alter, in an unprecedented manner, the natural history of this devastating disease.

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