CLINICAL REVIEW

No room to breathe: the importance of lung hyperinflation in COPD

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) are progressively limited in their ability to undertake normal everyday activities by a combination of exertional dyspnoea and peripheral muscle weakness. COPD is characterised by expiratory flow limitation, resulting in air trapping and lung hyperinflation. Hyperinflation increases acutely under conditions such as exercise or exacerbations, with an accompanying sharp increase in the intensity of dyspnoea to distressing and intolerable levels. Air trapping, causing increased lung hyperinflation, can be present even in milder COPD during everyday activities. The resulting activity-related dyspnoea leads to a vicious spiral of activity avoidance, physical deconditioning, and reduced quality of life, and has implications for the early development of co-morbidities such as cardiovascular disease. Various strategies exist to reduce hyperinflation, notably long-acting bronchodilator treatment (via reduction in flow limitation and improved lung emptying) and an exercise programme (via decreased respiratory rate, reducing ventilatory demand), or their combination. Optimal bronchodilation can reduce exertional dyspnoea and increase a patient's ability to exercise, and improves the chance of successful outcome of a pulmonary rehabilitation programme. There should be a lower threshold for initiating treatments appropriate to the stage of the disease, such as long-acting bronchodilators and an exercise programme for patients with mild-to-moderate disease who experience persistent dyspnoea.

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Introduction

Worldwide, chronic obstructive pulmonary disease (COPD) is estimated to affect 10% of the population aged >40 years.¹ In primary care in the UK, the estimated prevalence of COPD is 7% of those aged ≥45, increasing to 8–9% of those aged >65.² However, underdiagnosis is a problem, and the true prevalence is likely to be much higher. Using specific screening for COPD, a study among primary care practices in Canada found a prevalence of 21% among those aged over 40.³ COPD is an important cause of mortality and morbidity,⁴ and even patients in the milder stages of disease are at increased risk.⁵

Many patients with COPD can no longer do the activities they used to do, or cannot sustain them to the same extent, because

they are limited by respiratory difficulty or dyspnoea.⁶⁻⁸ Activity-related dyspnoea is among the earliest and most troublesome symptoms of COPD, and it progresses over time to incapacitating levels.⁹ Limitations on activity often lead to feelings of social isolation and psychological problems and reduce a patient's perceived quality of life, which is further diminished by the resulting inactivity and physical deconditioning.⁶ The mechanisms underlying activity limitation and dyspnoea are complex, and the situation is further complicated by the problems of ageing and co-morbidity that are common in patients with COPD.

We performed a review of the current medical literature investigating the mechanisms of hyperinflation and its effects on the dyspnoea and activity limitation experienced by patients with COPD. Various treatment modalities have been employed to overcome the problem, and the effects of pharmacological treatment on hyperinflation are summarised. The summary of

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treatment effects was based on a literature search of the PubMed database (no date limits) for COPD and terms relating to hyperinflation, narrowed by individual drug name (see Appendix 1, available online at www.thepcrj.org, for complete search strategy).

Mechanisms underlying exercise limitation in COPD

COPD is a highly heterogeneous condition with many different factors contributing to its pathophysiology, and the relative contribution of these factors varies from patient to patient. The term COPD principally encompasses two conditions – chronic bronchitis and emphysema. Chronic bronchitis is characterised by airways obstruction resulting from inflammation and remodelling of the larger airways, with oedema and increased mucus production.¹⁰ Emphysema is characterised by irreversible damage to the lung parenchyma and adjacent vasculature. A recent study suggests that obliteration and narrowing of terminal bronchioles may precede the development of destructive emphysema.¹¹ The loss of lung elastic recoil pressure reduces the driving pressure for flow during expiration: expiratory flow rates are diminished at any given lung volume compared with health. In addition, the loss of alveolar walls and attachments, which normally help to maintain airway patency, renders the airways more liable to collapse during expiration. Collectively, these changes give rise to expiratory flow limitation.

Changes to the elastic properties of the lungs in emphysema alter the balance of forces between the lung (inward recoil) and chest wall (outward recoil), so that the relaxation volume of the respiratory system at the end of quiet expiration (end-expiratory lung volume; EELV) is reset to a higher volume than is predicted in health (i.e. static lung hyperinflation). In the presence of expiratory flow limitation, the ability to empty the lungs with each breath is critically dependent on the time available for expiration.

In many patients with flow-limited COPD, expiratory time during spontaneous resting breathing is simply insufficient to allow full lung emptying and gas trapping is the result (Figure 1).

EELV can increase temporarily and to a variable extent above the resting value in situations where expiratory flow limitation is suddenly worsened (i.e. bronchospasm or exacerbation) or when ventilatory demand is abruptly increased, such as with exertion, anxiety, or transient hypoxaemia.¹² This is termed 'dynamic lung hyperinflation'. In conditions of increased metabolic demand such as exercise, when breathing is accelerated, increased gas trapping becomes inevitable. The presence of lung overinflation limits the ability of tidal volume to expand, and ventilation can only be increased by faster breathing, contributing to further hyperinflation in a vicious cycle.

Although not discussed here, many other factors contribute to limiting a patient's activity in COPD, not least peripheral muscle weakness and deconditioning due to factors such as ageing, poor nutrition, and co-morbidities.¹³⁻¹⁵

Pressure–volume relationship

From the start of an intake of breath after fully emptying the lungs (residual volume, RV) to the finish (total lung capacity, TLC), the relationship between chest wall pressure and lung volume follows an S-shaped curve.¹⁶ Healthy subjects breathe at around the midpoint of the curve where volume can increase at comfortable pressure. With their larger lung volume due to gas

Figure 1. Schematic to illustrate how peripheral airway obstruction traps air during expiration in chronic obstructive pulmonary disease (COPD) resulting in hyperinflation. P_L =translung pressure, V =ventilation. Reproduced from O'Donnell and Laveneziana⁵⁶ with permission

Figure 2. Lung volumes at rest and during exercise in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). In normal lungs, end-expiratory lung volume (EELV) remains relatively constant during exercise as tidal volume can increase and inspiratory capacity (IC) is maintained. Patients with COPD breathe with a greater EELV and less IC. During exercise, as ventilation increases, the increased EELV (dynamic hyperinflation) pushes tidal volume closer to total lung capacity (TLC) where expansion is limited by high pressures. IC decreases and breathing becomes so restricted that patients have to stop activity. RV=residual volume, IRV=inspiratory reserve volume. Reproduced from O'Donnell *et al.*¹⁶ with permission

trapping, COPD patients breathe higher up the curve where the breathing muscles have to overcome relatively larger 'elastic' forces to achieve the same increase in lung volume during breathing (Figure 2).

Certain adaptive responses occur to compensate for chronic hyperinflation, including adaptations of the chest wall and diaphragm shape to accommodate the increased volume, and adaptations of muscle fibres to preserve strength and increase endurance in the face of chronic intrinsic mechanical loading.¹⁷ However, these compensatory mechanisms are quickly overwhelmed when ventilatory demand increases acutely (e.g. during exercise).¹⁸⁻²⁰

Exercise

Because of the already high operating volumes in COPD, any expansion in tidal volume during exercise can be gained only by greater force generation (and contractile effort) by the inspiratory muscles (see Figure 2). Expiratory flow limitation and the accompanying dynamic hyperinflation force the contractile units of the inspiratory muscles to operate at a shorter disadvantageous length, which ultimately weakens the muscles. Inflammation and oxidative stress increase the susceptibility of respiratory muscles to contractile dysfunction under acute inspiratory loading.²¹

Exacerbations of COPD

An acute increase in hyperinflation can also occur during exacerbations, and is believed to be an important contributor to the characteristic symptom of worsening dyspnoea.^{12,22,23} COPD exacerbations differ greatly in their clinical presentation, reflecting differences in patients' clinical characteristics, the presence of co-morbidities such as chronic heart failure, the underlying pathophysiology of COPD, and causative factors.²⁴ Exacerbations involve increased airway inflammation and worsening airway obstruction, in variable contributions. The effectiveness of various non-steroidal treatment modalities in reducing the severity and frequency of exacerbations (bronchodilator drugs, surgery)^{25,26} and the differential effect of bronchodilators and corticosteroids on exacerbations²⁷ suggest that exacerbations can involve worsening airway obstruction in the absence of airway inflammation,¹² assuming that these bronchodilators do not exert anti-inflammatory effects in patients with COPD *in vivo*.

Studies in hospitalised patients with acute respiratory failure undergoing mechanical ventilation have shown that severe exacerbations involve a mechanism of critical expiratory flow limitation with lung hyperinflation, with serious mechanical consequences.²⁸ This can cause fatigue or overt failure of the respiratory muscles. Less is known about the mechanisms behind symptomatic deterioration during mild-to-moderate exacerbations that are commonly encountered in clinical practice, but the underlying physiology is likely to be similar to that of severe exacerbations.^{12,22}

Sensory experience of breathlessness in COPD

In conditions such as exercise and exacerbation, the drive to

breathe is increased but the ability of the respiratory system to respond appropriately is greatly hindered. This disparity between the increased central drive to breathe and the mechanical/muscular response of the respiratory system is termed 'neuromechanical uncoupling' or dissociation. Although patients try to meet the increased ventilatory demand, they cannot increase the tidal volume very much (constrained at one end by increased EELV and at the other by the fact that they are forced to breathe close to TLC; Figure 2). With literally no room to breathe despite near-maximal neural drive, patients experience intolerable dyspnoea very quickly.

While COPD patients – in common with healthy subjects – describe their dyspnoea on exercise in terms of increased effort and heaviness of breathing, they also describe some unique sensations such as "can't get enough air in" or "unsatisfied inspiratory effort" (Figure 3).²⁹ This is somewhat akin to 'air hunger' which can be induced experimentally in healthy volunteers when CO₂ loading is combined with mechanical restriction of lung volume expansion.³⁰ This suggests that COPD patients are receiving abnormal peripheral neurosensory information from various mechanical receptors in the respiratory muscles and chest wall, signalling that respiration is inadequate for the excessive effort expended. The perception of unsatisfied effort is rarely reported in healthy subjects.

The change in description of the sensation from 'work and effort' to one of 'unsatisfied inspiration' occurs when the drive to

Figure 3. Qualitative descriptors of exertional dyspnoea (at the end of symptom-limited cycle exercise) of 'unsatisfied inspiration', 'inspiratory difficulty', and 'shallow breathing' were more common among patients with chronic obstructive pulmonary disease (COPD) than in healthy subjects (* $p < 0.05$). Modified from O'Donnell *et al.*²⁹ with permission

Figure 4. In a study in hyperinflated subjects with chronic obstructive pulmonary disease (COPD), with increasing breathing frequency, tidal volume (VT) expanded to a maximal value of approximately 75% of the concurrent inspiratory capacity (IC) (left). When this plateau in VT/IC occurs, and regardless of baseline differences in lung function, dyspnoea rises sharply to intolerable levels (right). Q=quartile of COPD severity (airflow limitation). Forced expiratory volume in 1 second quartiles were mean 62%, 49%, 39%, and 27% predicted. Modified from O'Donnell et al.³² with permission)

breathe continues to increase without a corresponding increase in lung volume, and the intensity of dyspnoea rises sharply. This inflection point in the relationship between volume and effort during exercise, when tidal volume can no longer increase in line with increasing ventilatory drive, is depicted in Figure 4.^{31,32} The relationship between the increase in dyspnoea and the point where tidal volume is close to TLC is similar across differing levels of baseline airway obstruction.³²

The perception of unsatisfied inspiration is likely to evoke a powerful fear response that escalates to panic, or respiratory distress.²⁹ In general, COPD subjects are distinct from healthy subjects in describing their sensation of breathlessness in terms such as 'frightening', 'helpless', and 'awful'.³³ The descriptions of dyspnoea that reflect fear and anxiety become more common with increasing severity of COPD.³⁴ This powerful affective dimension of dyspnoea has been highlighted in a recent American Thoracic Society statement.³⁰

Hyperinflation and relationship with COPD progression and co-morbidities

Cross-sectional studies have demonstrated the presence of hyperinflation in milder stages of COPD, including dynamic hyperinflation during everyday activities.^{9,35-37} The early stages of hyperinflation and its progression may not be perceived by patients because of adaptive changes that compensate for the mechanical disadvantages (e.g. chest wall reconfiguration to accommodate overextended lungs and partially preserved function of the diaphragm despite operating at shortened muscle fibre length).^{20,38} Pathological changes in the muscle fibres of the diaphragm may be evident even in the milder stages of COPD.³⁹

Hyperinflation, physical inactivity, and physical deconditioning may be related to the early development of co-morbidities. Inactivity and muscle wasting are present in the earliest stages of COPD⁴⁰⁻⁴³ and may be important for the development of co-morbidities that can also occur in milder

stages of COPD.^{44,45} For example, subclinical left ventricular dysfunction in milder COPD was found to be especially marked in patients with resting hyperinflation.⁴⁶

The presence of hyperinflation may influence the progression of disease: resting hyperinflation (inspiratory capacity (IC)/TLC ratio <25%) has been associated with increased frequency of COPD exacerbations,⁴⁷ and is an independent predictor of mortality in COPD.⁴⁸ Of potential relevance, hyperinflation of the lung (assessed by quantitative computed tomography) was found to predict a rapid annual decline in forced expiratory volume in 1 second (FEV₁) in smokers with normal FEV₁.⁴⁹ If, as recently shown, most of the decline in lung function occurs in milder disease,^{44,50-52} it may be hypothesised that some form of early intervention could prevent progressive functional deterioration and maintain organ function at a higher level.

Measurement of hyperinflation in COPD

Hyperinflation is difficult to measure with the investigations usually available in general practice. Relevant measures in COPD are functional residual capacity (the volume of air remaining in the lungs at the end of tidal expiration, an index of hyperinflation), and RV (the volume of air remaining in the lungs at the end of a maximal expiration, an index of air trapping), but both of these volume measurements require relatively sophisticated equipment (body plethysmography or spirometers with inert gas analysers).⁵³

IC is often used as a surrogate measure of hyperinflation. This is the maximal volume of air that can be inspired after a quiet breath out, which is the difference between TLC and EELV. IC can be measured by simple spirometry using a closed-circuit system.⁵³ Provided TLC remains constant, reduced resting IC indicates the presence of hyperinflation in the setting of expiratory flow limitation.⁵⁴ IC may not always be a reliable measure in conditions of severe hyperinflation or over time (when TLC changes).^{55,56} IC measurements during exercise reflect the

increase in dynamic EELV and are more relevant physiologically with respect to exertional dyspnoea and exercise intolerance than resting IC.⁵⁷ A recent study has shown that critical reduction of the inspiratory reserve volume (IRV; calculated as IC minus tidal volume), an index of 'the room to breathe', is more closely related to dyspnoea intensity during exercise in COPD than is the extent of air trapping *per se*.^{58,59}

Effect of treatment

Treatment strategies

A treatment that can bring about a reduction in EELV (and increase in IRV) should enable a patient to increase tidal volume more for a given effort, and thus lessen exertional dyspnoea. A treatment that improves expiratory flow limitation or decreases ventilatory demand will interrupt the vicious cycle of faster breathing and worsening hyperinflation. Thus, there is a range of treatment strategies^{60,61} that may be employed in different settings, from drug treatments and supplemental oxygen for patients with hypoxia or oxygen desaturation available in primary care, to assisted ventilation for hospitalised patients and surgical options for those with advanced emphysema.

Treatments that primarily decrease respiratory rate (reducing ventilatory demand) and increase ventilation include rehabilitative exercise training (pulmonary rehabilitation) and supplemental oxygen. Assisted ventilation counterbalances the negative effects of lung hyperinflation on the respiratory muscles. Treatment with bronchodilators primarily reduces flow limitation and improves lung emptying. Lung volume reduction surgery reduces EELV by favourably altering the elastic properties of the remaining lung, thus increasing lung emptying. The different mechanisms by which these interventions operate suggest that combinations would provide additional benefits, an example being the additive benefits shown by the combination of tiotropium (reduced hyperinflation) with supplemental oxygen (reduced ventilatory drive),⁶² and ipratropium bromide or supplemental oxygen with rehabilitation.⁶³⁻⁶⁵ This review will focus on the treatments that are available in the primary care setting, principally pharmacotherapy and exercise programmes.

Pulmonary rehabilitation/exercise training

Increasing activity levels is a key part of interrupting the downward spiral of disability and premature death for COPD patients.⁶⁶ Pulmonary rehabilitation is a cornerstone in the comprehensive management of patients with COPD, and has recognised benefits for improved exercise endurance, dyspnoea, functional capacity, and quality of life (Table 1).⁶⁷ The strength of evidence is reflected in its prominence in global and national COPD management guidelines.⁶⁷⁻⁷³ Pulmonary rehabilitation is currently the best way to improve quality of life in patients with COPD.^{71,74} Comprehensive pulmonary rehabilitation programmes include exercise training, smoking cessation, nutrition counselling, and education.⁶⁷

Exercise training improves skeletal muscle function and leads to less ventilatory requirement for a given work rate, which in

Table 1. Benefits of pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD)⁶⁷

Strength of evidence	Benefit
A	Improves exercise capacity
	Reduces the perceived intensity of breathlessness
	Improves health status
	Reduces number of hospitalisations and days in hospital
	Reduces anxiety and depression associated with COPD
B	Upper limb strength/endurance training improves arm function
	Benefits persist beyond training period
	Improves survival
	Improves recovery after hospitalisation for exacerbation
	Enhances the effect of long-acting bronchodilators
C	Respiratory muscle training can be beneficial (dyspnoea, health status, exercise capacity), especially when combined with general exercise training
A=randomised controlled trials (rich body of data), B=randomised controlled trials (limited body of data), C=non-randomised trials (observational studies).	

turn may reduce dynamic hyperinflation, thus reducing exertional dyspnoea.⁷⁰ Because exercise capacity is limited by both skeletal muscle fatigue and exertional dyspnoea due to dynamic hyperinflation, bronchodilator therapy may help improve the effectiveness of exercise training by lowering the barrier of activity-limiting dyspnoea and allowing patients to exercise their peripheral muscles to a greater degree.^{70,75} Practice guidelines recommend that optimal bronchodilator therapy should be given prior to exercise training.⁷⁰ Even if a formal exercise programme is not available, patients should be encouraged to undertake regular exercise such as walking for 20 minutes a day.⁶⁷

Effect of pharmacotherapy on hyperinflation

Evidence for the effects of pharmacotherapy on hyperinflation was gathered using the search strategy shown in Appendix 1 (online at www.thepcrj.org). Single-dose studies were not included.

Bronchodilators

Bronchodilators work by relaxing smooth muscle tone in the airways, leading to reduced respiratory muscle activity and improvements in ventilatory mechanics.⁷⁶ In addition, reduced abdominal muscle activation and the consequent fall in gastric pressure following bronchodilator therapy may contribute to relieving the load on the respiratory system, similar to the relief provided by non-invasive ventilatory support.⁷⁶⁻⁷⁸ Bronchodilators have been associated with reduced airways resistance and elastic loading of the inspiratory muscles during constant work rate exercise.⁷⁹ The lower operating lung volume allows patients to achieve the required alveolar ventilation during rest and exercise at a lower oxygen cost of breathing. By deflating the lungs,

Table 2. Effect of long-acting bronchodilators on resting and dynamic lung volumes and exercise measures (results are differences versus placebo unless otherwise stated)

Reference	Treatments (doses in µg)	n	FEV ₁ % pred	FRC % pred	Duration	Design	Resting measurements (post-dose)		Exercise (post-dose)			
							FRC (L)	IC (L)	Endurance (time or distance)	Borg dyspnoea score	IC	Tidal volume
O'Donnell et al. ⁷⁵	TIO 18 once daily PBO	187	41–42	160–161	6 weeks	R, PG, DB	Trough –0.30* Peak –0.45*	Trough 0.10* Peak 0.24*	105 s*	Isotime –0.9* Peak –0.1	Isotime 0.18* Peak 0.15*	Isotime 0.11* Peak 0.10*
Maltais et al. ¹¹⁸	TIO 18 once daily PBO	261	43	172–176	6 weeks	R, PG, DB	Trough –0.17* Peak –0.40*	Trough 0.17* Peak 0.22	236 s*	Isotime –1.05* to –0.97* (2 and 8 h post-dose)	Isotime 0.22* to 0.14* (2 and 8 h post-dose)	Isotime 0.09* to 0.05* (2–8 h post-dose)
Travers et al. ¹¹⁵	TIO 18 once daily PBO	18	40	171	7–10 days	R, XO, DB	–0.29*	0.23*	0.9 min	Peak –0.5 Isotime –0.8	Peak 0.31* Isotime 0.23*	Peak 0.11* Isotime 0.06
Berton et al. ¹¹⁹	FOR 12 twice daily + TIO 18 once daily FOR 12 twice daily + PBO	33	47	–	2 weeks	R, XO, DB	–	0 vs FOR (both 2.20)	124 vs 68% increase from B/L*	Isotime 0 (both 5)	Isotime 0.13 vs FOR	Isotime: 0.04 vs FOR
Beeh et al. ⁹¹	Glycopyrronium 50 once daily PBO	108	57	–	3 weeks	R, XO	–0.46*	0.22–0.23*	89 s*	Isotime –1.16*	Isotime 0.20* Peak 0.19*	–
O'Donnell et al. ⁹⁷	IND 300 once daily PBO	90	61 (post-BD)	–	3 weeks	R, XO, DB	–	Predose 0.14* Post-dose 0.17*	111 s*	End-exercise: no difference†	End-exercise 0.28*	–
Beeh et al. ⁹⁴	IND 300 once daily PBO	27	52 (post-BD)	>120	2 weeks	R, XO, DB	–0.34	0.18*	1.46 min*	Isotime –1.5* Peak –0.6	Isotime 0.27* Peak 0.32*	–
Maltais et al. ⁹⁶	ACL 200 once daily PBO	181	49–52	152–159	6 weeks	R, PG, DB	–0.28*‡	0.3*‡	116 s*	Isotime –0.7* Peak –0.3	Isotime: 0.04 Peak 0.02	Isotime 0.11* Peak 0.10*
O'Donnell et al. ⁹⁵	SLM 50 twice daily PBO	23	42	172	2 weeks	R, XO, DB	–0.35*	0.33*	96 s*	At 75% max. work rate –0.5 Isotime –0.9	At 75% max. work rate 0.22* Isotime 0.17*	At 75% max. work rate 0.15* Isotime 0.11*
Man et al. ⁷⁶	SLM 50 twice daily PBO	16	31	(RV 139% pred)	2 weeks	R, XO, DB	–	0.16*	14 s	Isotime –0.84*	Isotime 0.29*	–
Neder et al. ¹²⁰	FOR 12 once daily PBO	21	39	(RV 203% pred.)	2 weeks	R, XO, DB	–	0.28*	130 s	Isotime –1.5	Isotime 0.22*	Isotime 0.14*

ACL=acitininum, IND=indacaterol, SLM=salmeterol, TIO=tiotropium, FOR=formoterol, PBO=placebo, BD=bronchodilator, R=randomized, PG=parallel group, XO=crossover, DB=double-blind;

FEV₁=forced expiratory volume in 1 second, FRC=functional residual capacity, pred=predicted, RV=residual volume, IC=inspiratory capacity, B/L=baseline maximum; maximum.

*p<0.05. †As expected, at the end of exercise (i.e. when the patients stopped exercising owing to symptom limitation) the level of symptoms was the same in the two treatment arms. ‡Estimated from figure.

bronchodilators effectively improve ventilatory muscle performance resulting in greater tidal volume expansion. Thus, neuromechanical coupling is enhanced and dyspnoea is lessened. Reduction in absolute lung volume results in a delay in the time for end-inspiratory lung volume to reach the minimal dynamic IRV; the mechanical limitation of ventilation is postponed and exercise endurance time is prolonged.⁷⁹ With short-acting inhaled bronchodilators, three multiple-dose studies reported improvements in lung volume and exercise measures with single or combined treatments (β_2 -agonist plus anticholinergic; β_2 -agonist plus theophylline).⁸⁰⁻⁸²

Multiple-dose studies that have investigated the effects of long-acting bronchodilators on both resting hyperinflation and dynamic hyperinflation during exercise are summarised in Table 2 and Appendix 2 (available online at www.thepcrj.org). The results demonstrate improved IC throughout rest and exercise, in association with numerical or significant improvement in dyspnoea intensity ratings during exercise and increased exercise endurance (Table 2 and Appendix 2). Many other studies have investigated the effects on resting hyperinflation alone, and report improvements measured by IC and volume measurements during treatment with indacaterol,⁸³ formoterol,^{84,85} salmeterol,⁸⁶ tiotropium,^{55,87-90} and glycopyrronium.⁹¹ Furthermore, a study investigating the effects of bronchodilator therapy on ventilatory mechanics during exercise showed that significant reductions in dynamic hyperinflation and dyspnoea were paralleled by decreased respiratory muscle activity.⁷⁶

There are few published comparisons of long-acting bronchodilators. Tiotropium was reported to be superior to salmeterol in improving resting volumes and exercise endurance,^{92,93} and indacaterol was reported to be superior to salmeterol for its effect on resting inspiratory capacity.⁸³

The additive effects of combining a long-acting bronchodilator and pulmonary rehabilitation have been discussed above.^{64,70} Because the beneficial effects of long-acting bronchodilators on exercise and associated hyperinflation are observed as early as day 1 of treatment,⁹⁴⁻⁹⁷ these agents may be particularly useful in the context of exercise programmes to provide patients with an initial 'boost' that may help them achieve successful rehabilitation.

Table 3. Effect of ICS and ICS+LABA on resting and dynamic lung volumes and exercise measures (results are differences versus placebo unless otherwise stated)

Reference	Treatments (doses in µg)	n	FEV ₁ % pred	FRC % pred	Duration	Design	Resting measurements (post-dose)			Exercise (post-dose)			
							FRC (L) (or % change)	IC (L) (or % change)	Endurance time (s)	Borg dyspnoea score	IC (L) (or % change)	Tidal volume	
Guenette <i>et al.</i> ⁵⁸	FP 500 twice daily PBO (added to bronchodilator Tx)	17	54	144	2 wks	R, XO, DB	-0.31*	0 (both 2.71)	Isotime 0 Peak 188*	Isotime -0.7 Peak 0.6	Isotime 0.05 Peak -0.04	Isotime 0.04 Peak 0.04	
O'Donnell <i>et al.</i> ¹⁰⁶	FP/SLM 250/50 twice daily SLM 50 twice daily PBO	185	40-43	154-157	8 wks	R, PG, DB	-0.35 FP/SLM* -0.26 SLM*	0.33 FP/SLM* 0.27 SLM	132 FP/SLM* 86 SLM	Isotime -0.5 FP/SLM -0.4 SLM Peak -0.4 FP/SLM -0.3 SLM	Isotime 0.20 FP/SLM* 0.15 SLM* Peak 0.17 FP/SLM* 0.11 SLM	Isotime 0.10 FP/SLM* 0.08 FP/SLM* Peak 0.14 FP/SLM* 0.06 SLM	
Worth <i>et al.</i> ¹⁰⁷	BUD/FOR 320/9 twice daily FOR 9 twice daily PBO	111	38	-	1 wk	R, XO, DB	1 h post-dose: -4% BUD/FOR* -1% FOR -3% BUD/FOR vs FOR 6 h post-dose: -5% BUD/FOR* -3% FOR -2% BUD/FOR vs FOR	1 h post-dose: 14% BUD/FOR* 12% FOR* 2% BUD/FOR vs FOR 6 h post-dose: 14% BUD/FOR* 9% FOR* 5% BUD/FOR vs FOR	1 h post-dose: 105 BUD/FOR* 36 FOR 69 BUD/FOR vs FOR* 6 h post-dose: 62 BUD/FOR* 20 FOR 42 BUD/FOR vs FOR*	Isotime 1 h post-dose: -0.8 BUD/FOR* ~ -0.3 FOR ~ -0.5 BUD/FOR vs FOR Isotime 6 h post-dose: -1.1 BUD/FOR* -1.1 FOR* ~ 0 BUD/FOR vs FOR			

ICS=inhaled corticosteroid, LABA=long-acting β_2 -agonist, FP=fluticasone propionate, SLM=salmeterol, BUD=budesonide, FOR=formoterol, PBO=placebo, R=randomised, PG=parallel group, XO=crossover, DB=double-blind, Tx=treatment, pred=predicted, FEV₁=forced expiratory volume in 1 second, FRC=functional residual capacity, IC=inspiratory capacity. *p<0.05.

Combining two bronchodilators may extend the improvements seen with single agents – for example, resting IC was increased with indacaterol plus tiotropium compared with tiotropium alone⁹⁸ or with formoterol plus tiotropium versus tiotropium alone.⁹⁹⁻¹⁰¹ The addition of tiotropium to an inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) combination has been reported to improve resting lung volumes compared with either individual component.¹⁰²⁻¹⁰⁴ The bronchodilator combination of tiotropium and salmeterol was more effective than an ICS/LABA for improving resting lung volumes in hyperinflated patients, although exercise endurance time was not significantly increased.¹⁰⁵

ICS and ICS/LABA combinations

Two studies have compared the effects of ICS/LABA treatment with a LABA alone. O'Donnell *et al.* reported that fluticasone/salmeterol reduced resting and dynamic hyperinflation and increased exercise endurance time compared with placebo but not compared with salmeterol (Table 3 and Appendix 2).¹⁰⁶ A later study with a higher ICS dose found that adding fluticasone to long-acting bronchodilator therapy decreased EELV during exercise without improvements in dyspnoea or IC.⁵⁸ The budesonide/formoterol combination was reported to increase exercise endurance and reduce dynamic hyperinflation compared with both placebo and formoterol.¹⁰⁷ The mechanism for an effect of ICS on hyperinflation is unclear, but may involve a direct local action on pulmonary cells or vasculature (e.g. vasoconstriction).^{58,107} The budesonide/formoterol combination was reported to improve resting lung volumes more than salmeterol/fluticasone,¹⁰⁸ and with a faster onset of effect.^{109,110}

Other treatments: roflumilast, theophylline, mucoactive treatment (acetylcysteine)

The oral phosphodiesterase-4 inhibitor roflumilast had no effect on hyperinflation or exercise times compared with placebo after 12 weeks of treatment.¹¹¹ Theophylline has been reported to reduce lung volumes and improve exercise endurance,^{112,113} possibly through improved respiratory muscle performance likely secondary to unmeasured lung volume reduction.^{114,116} Reduced hyperinflation and improved exercise endurance were reported following treatment with the mucoactive/antioxidant treatment acetylcysteine.¹¹⁷

Conclusions

While persistent and progressive expiratory flow limitation is the hallmark of COPD, its consequence – lung hyperinflation – importantly contributes to the exertional dyspnoea that limits activity and prevent patients from going about their normal everyday activities. Such inactivity can have a detrimental effect on physical conditioning and health-related quality of life. Acute increases in hyperinflation above the already increased resting level are likely to underlie the acute worsening of symptoms during increased activity and during exacerbations of COPD. Reducing hyperinflation and its

consequences will have important benefits for COPD patients by interrupting the vicious cycle of dyspnoea, activity limitation, deconditioning, and impaired health-related quality of life. Some of the common co-morbidities in COPD start early in the disease and may be related to inactivity and physical deconditioning.^{44,45} It seems logical that the earlier the vicious cycle is interrupted, the better the outcome for patients, and there should be a lower threshold for initiating treatments appropriate to the stage of the disease (e.g. long-acting bronchodilators and an exercise programme for patients with mild-to-moderate disease who experience persistent dyspnoea). Exercise and pulmonary rehabilitation have a valuable effect at all stages of the disease.

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Conflicts of interest Neither MT nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings from the following companies marketing respiratory and allergy products: AstraZeneca (AZ), Boehringer Ingelheim (BI), GlaxoSmithKline (GSK), MSD, Napp, Schering-Plough, Teva. He has received honoraria for attending advisory panels with Almirall, AZ, BI, Chiesi, GSK, MSD, Merck Respiratory, Schering-Plough, Teva, and Novartis. He has received sponsorship to attend international scientific meetings from GSK, MSD, AZ, and Mundipharma and he has received funding for research projects from GSK, MSD, and Napp. He held a research fellowship and is Chief Medical Advisor to Asthma UK. He is a member of the UK Department of Health Asthma Strategy Group and Home Oxygen Group. He is a member of the MHRA Respiratory and Allergy Expert Advisory Group, the BTS SIGN Asthma Guideline Group and the EPOS Rhinosinusitis Guideline Group. MT is an Associate Editor of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article.

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Appendix 1.

Search no. 5 was taken as starting point, followed by selection based on relevance of abstracts; narrower searches were thought possibly restrictive. Results were cross-checked by conducting separate searches for 'inspiratory capacity' and individual drug names. Search last updated 11 September 2012 (no starting date limit).

Search	Query	Items found
#10	Search #1 AND #4 AND #9 therapeutics subset	521
#9	Search "therapeutics"[MeSH] OR "therapy"[tiab] OR "treatment"[tiab] OR "treatments"[tiab]	5272386
#6	Search #5 NOT #3	768
#5	Search #1 AND #4 all results	1069
#4	Search "Functional Residual Capacity"[MeSH] OR "Expiratory Reserve Volume"[MeSH] OR "Residual Volume"[MeSH] OR "air trapping" OR "air-trapping" OR "gas trapping" OR "gas-trapping" OR "hyperaerated" OR "hyperaeration" OR "hyperinflated" OR "hyperinflation" OR "functional residual capacity" OR "residual volume" OR "over distended" OR "over-distended" OR "over distension" OR "over-distension" OR "overinflated" OR "over-inflated" OR "overinflation" OR "over-inflation"	10017
#3	Search #1 AND #2 effects subset	301
#2	Search "Functional Residual Capacity/drug effects"[MeSH] OR "Expiratory Reserve Volume/drug effects"[MeSH] OR "Residual Volume/drug effects"[MeSH] OR (("air trapping" OR "air-trapping" OR "gas trapping" OR "gas-trapping" OR "hyperaerated" OR "hyperaeration" OR "hyperinflated" OR "hyperinflation" OR "functional residual capacity" OR "residual volume" OR "over distended" OR "over-distended" OR "over distension" OR "over-distension" OR "overinflated" OR "over-inflated" OR "overinflation" OR "over-inflation") AND ("effects of treatment" OR "effects of therapy" OR "therapeutic effect" OR "treatment effect" OR "therapeutic effects" OR "treatment effects"))	2072
#1	Search "Pulmonary Disease, Chronic Obstructive"[MeSH] OR "COPD" OR "chronic obstructive pulmonary disease"	32912

Appendix 2

Figure 5. Summary of key differences with long-acting bronchodilators, ICS, or ICS+LABA versus placebo or comparator in post-dose exercise measures: (A) exercise endurance time; (B) Borg dyspnoea score; (c) inspiratory capacity (IC); and (d) tidal volume (data are presented as mean treatment $\pm$ SE (solid line) or with 95% CI (dashed lines), where available; * $p<0.05$, ** $p<0.01$, *** $p<0.001$). (A) †Change from baseline in limit of exercise tolerance was significantly greater for FOR+TIO than FOR+PBO ($124\pm 27\%$ vs $68\pm 14\%$; $p<0.05$). ‡Added to bronchodilator therapy. (B) †As expected at end of exercise (i.e. when patients stopped exercising owing to symptom limitation) the level of symptoms was the same in the two treatment arms. ‡Added to bronchodilator therapy. (C) †Measured at end of exercise, not isotime. ‡Added to bronchodilator therapy. (D) †Added to bronchodilator therapy. ACL=acclidinium; BUD=budesonide, FOR=formoterol, FP=fluticasone propionate, ICS=inhaled corticosteroid, IND=indacaterol, LABA=long-acting β -agonist, SLM=salmeterol, PBO=placebo, TIO=tiotropium