Assessment of Bronchodilator Efficacy in Symptomatic COPD*

Is Spirometry Useful?

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Bronchodilator therapy in COPD is deemed successful if it improves ventilatory mechanics to a degree where effective symptom alleviation and increased exercise capacity are achieved. A greater understanding of the pathophysiologic mechanisms of dyspnea and exercise intolerance in COPD has prompted a reevaluation of the manner in which we currently assess therapeutic efficacy. The traditional reliance on an improved postbronchodilator FEV_1 as indicative of a positive clinical response has recognized limitations. To the extent that pharmacologic volume reduction is a desirable therapeutic goal with favorable implications for dyspnea relief and increased exercise tolerance, the potential value of bronchodilator-induced changes in lung volume measurements is currently being studied. It is unlikely, however, given the multifactorial nature of dyspnea and exercise limitation in COPD, that resting spirometric measurements of maximal flows and volumes alone will be sufficiently sensitive to adequately predict a positive clinical response to bronchodilator therapy. Thus, additional direct measurements of exercise dynamic hyperinflation and exercise endurance together with reliable subjective measurements of dyspnea and quality of life are recommended in the setting of a suitable placebo-controlled design. ***(CHEST 2000; 117:42S–47S)***

Key words: bronchodilators; COPD; dyspnea; exercise; inspiratory capacity; lung hyperinflation; spirometry

Abbreviations: DH = dynamic hyperinflation; EELV = end-expiratory lung volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; Pes = tidal esophageal pressure swing; TLC = total lung capacity; VC = vital capacity; V_T = tidal volume

In patients with symptomatic COPD, desirable therapeutic goals include improvement of ventilatory mechanics, alleviation of dyspnea, increased activity levels, and improved quality of life. Studies designed to evaluate the efficacy of interventions, such as bronchodilator therapy, increasingly incorporate these important clinical outcomes. Traditionally, the primary outcome measure for clinical trials has been the measurement of FEV_1. The recognition that meaningful improvements in symptoms, exercise capacity, and quality of life can occur in the presence of minimal changes in FEV_1 has prompted the search for better evaluative methods.

Recent studies have provided greater appreciation that symptomatic benefit in COPD patients with lung hyperinflation is clearly linked to effective pharmacologic volume reduction. In this review, we will briefly discuss the mechanical abnormalities of advanced COPD, the mechanisms of dyspnea and exercise intolerance, and the means by which bronchodilator therapy can favorably affect each of these variables. Specifically, we will review the role of spirometry in evaluating therapeutic responses in advanced COPD, and consider the potential value of broadening existing bronchodilator "responsiveness" criteria to include spirometric lung volumes.

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Nature of the Mechanical Abnormalities in COPD

In COPD, the most obvious pathophysiologic abnormality is expiratory flow limitation; however, the main consequence of this is a restrictive mechanical deficit as a result of lung hyperinflation because of air trapping (Fig 1).[1] Although breathing at a high lung volume optimizes tidal expiratory flow generation, it results in serious negative mechanical and sensory consequences. The deleterious effects of resting hyperinflation are amplified during exercise when increased ventilatory demands (and reduced expiratory timing) result in further air trapping, dynamic hyperinflation (DH), and increased mechanical restriction.[1] Thus, the inspiratory capacity (IC)

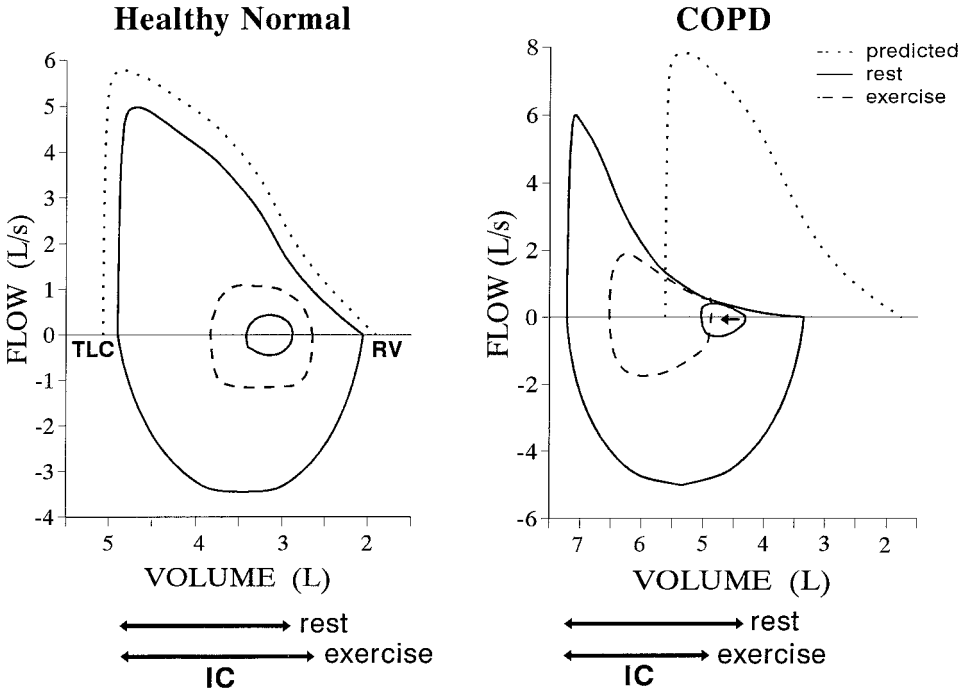

FIGURE 1. Comparison of maximal and tidal flow-volume loops in a healthy subject and a patient with COPD, at rest and at a standardized exercise level (oxygen consumption 30% predicted max). Volume compartments of the VC are also depicted at rest and at a standardized exercise level. In normal subjects, minimal expiratory flow limitation is evident during exercise, there is no ventilatory limitation, and IC increases during exercise. By contrast, expiratory flow limitation is evident at rest in COPD, with dynamic lung hyperinflation as evidenced by the reduced IC during exercise. IC = inspiratory capacity; RV=residual volume.

that indirectly reflects the end-expiratory lung volume (EELV), and which is already diminished at rest in COPD, progressively decreases further during exercise as dynamic EELV increases (Fig 1).[2–4] The inability to expand tidal volume (VT) appropriately in response to increasing respiratory drive results in greater reliance on increasing breathing frequency to increase ventilation; the resultant tachypnea, however, further increases DH in a vicious cycle.[1] As IC diminishes during exercise (Fig 2), VT and end-inspiratory lung volume become positioned closer to total lung capacity (TLC) and the upper alinear extreme of the respiratory systems pressure-volume relationship, where there is increased elastic loading. The greater the dynamic EELV is relative to passive functional residual capacity, the greater the inspiratory threshold load on the inspiratory muscles. This hidden load (*ie*, auto-positive end-expiratory pressure, intrinsic-positive end-expiratory pressure) can be substantial, particularly in the setting of severe DH during exercise. DH also compromises the ability of the inspiratory muscles to generate pressure and results in dynamic functional muscle weakness and altered patterns of ventilatory muscle recruitment. It follows that during exercise, tidal inspiratory pressure excursions represent a much higher fraction of their maximal force-generating capacity in COPD than in health (Fig 2).[5] The net mechanical effect of DH is that there is a marked disparity between the level of inspiratory effort (which approaches maximum) and the actual mechanical response of the respiratory system (which is greatly diminished; *ie*, reduced VT response and diminished thoracic displacement; Fig 2).[5] The coexistence of higher ventilatory demands during exercise in COPD (as a result of high physiologic dead space, metabolic acidosis, or hypoxemia) results in worsening expiratory flow limitation with consequent mechanical restriction, (*ie*, end-inspiratory lung volume/TLC ratio $> 90\%$), earlier attainment of ventilatory limitation, and intolerable dyspnea at relatively low exercise work rates (Fig 1).[5]

LUNG HYPERVENTILATION AND DYSPNEA

The intensity of exertional dyspnea in COPD has been shown to correlate well with the level of acute DH during exercise and also with the increased disparity between effort and volume displacement (*ie*, Pes/maximal inspiratory pressure: VT/% predicted vital capacity [VC]; Fig 2).[4,5] This disparity is

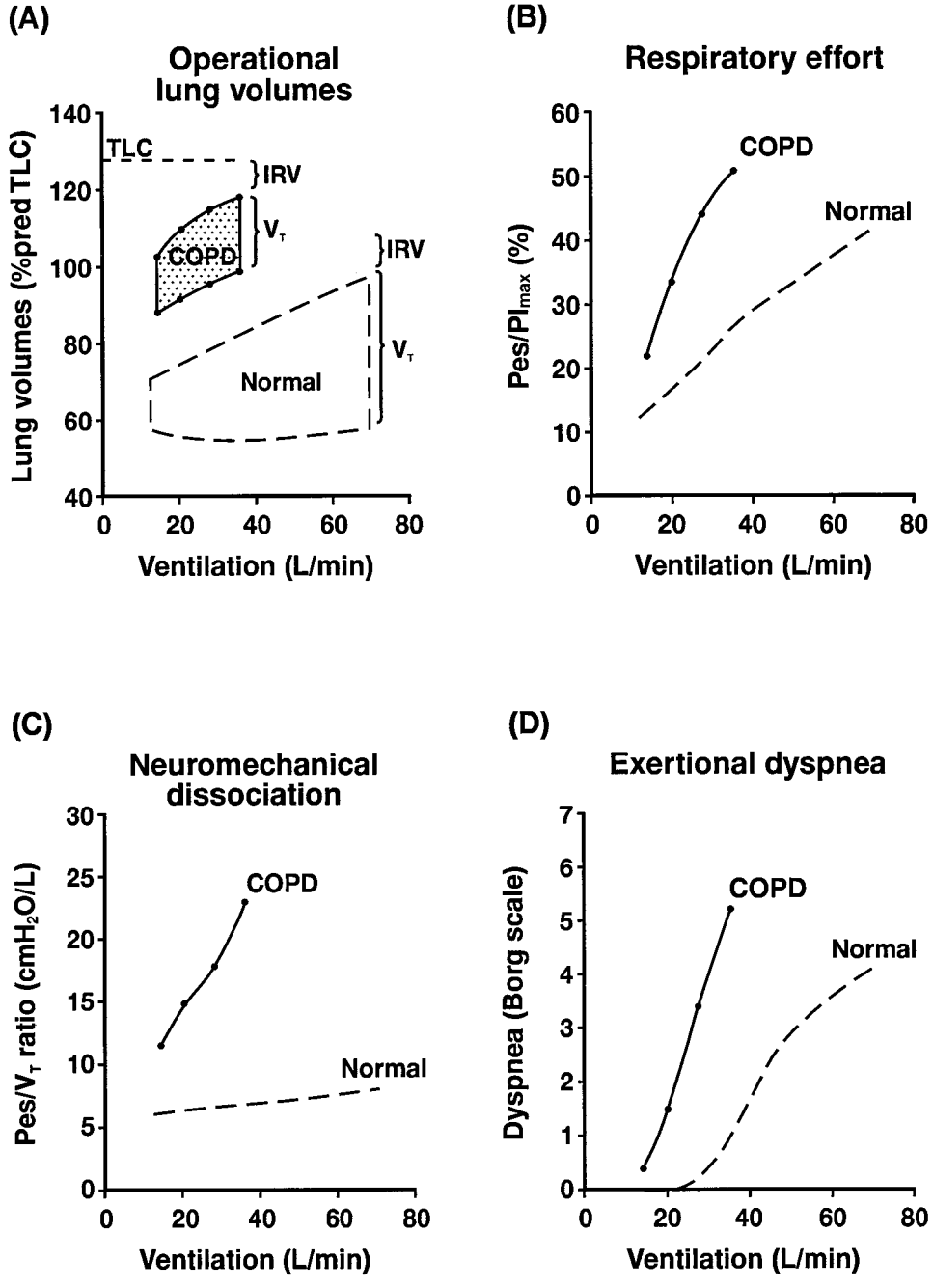

FIGURE 2. Comparison of (*top left, A*) operational lung volumes; (*top right, B*) inspiratory effort relative to maximum; (*bottom left, C*) the ratio of effort (Pes/maximal inspiratory pressure) to VT (% predicted VC), *ie*, an index of neuromechanical dissociation; and (*bottom right, D*) exertional dyspnea, each expressed as a function of ventilation during exercise in normal subjects and COPD patients. Note that in COPD, despite increased inspiratory effort, the VT response is seriously constrained, in part because of dynamic hyperinflation, with severe encroachment on the IRV at low ventilation levels (*top left, A*, and *top right, B*). The relationship between effort and VT is constant throughout exercise in health but increased markedly in COPD, partly as a result of dynamic hyperinflation and mechanical restriction. The increased dyspnea at any given ventilation in COPD (*bottom right, D*) is explained in part by this high ratio, which is an index of neuromechanical dissociation of the respiratory system. Reprinted with permission from O'Donnell et al.[5]

a consequence of DH and ultimately reflects neuromechanical dissociation of the ventilatory pump. It follows that interventions that successfully reduce hyperinflation should enhance neuromechanical coupling, and improve dyspnea and exercise tolerance (see below).

Chrystyn et al[6] demonstrated an association between improved exercise endurance following increasing theophylline therapy (in a dose-response manner), and reduced plethysmographic thoracic gas volume. Belman et al,[7] in an elegant mechanical study, have shown that exertional dyspnea relief following salbutamol therapy in COPD correlated well with a reduction in operational lung volumes during exercise, which, in turn, was related to enhanced neuroventilatory coupling (*ie*, improved effort-displacement ratio). O'Donnell et al[8] have recently reported similar findings in response to acute high-dose anticholinergic therapy in advanced COPD. In this study of 29 patients (FEV_1 = 40 ± 2% predicted), dyspnea relief correlated best with reduced dynamic EELV (*ie*, increased IC) at submaximal levels of exercise. Moreover, improved exercise endurance after anticholinergic therapy was explained by the reduced dyspnea and reduced operational lung volumes. Recently, dyspnea relief following surgical volume reduction in COPD has also been shown to correlate well with reduced dynamic EELV (*ie*, increased IC), and enhanced neuromechanical coupling of the diaphragm.[9–11] These studies collectively point to the importance of DH in dyspnea causation and exercise intolerance in COPD. It follows that systematic assessment of the therapeutic efficacy of bronchodilator therapy should ideally include measurements of DH (*ie*, IC at a standardized work rate), endurance time (for example, at a constant load of 75% of the predetermined maximal work rate), and dyspnea (measured by Borg or visual analog scales). Measurements of these three variables during constant load submaximal cycle exercise in advanced COPD have recently been shown to be reliable, being both reproducible and responsive.[8] However, this comprehensive therapeutic assessment of bronchodilator efficacy may be unrealistic for many clinicians managing COPD. The question arises, therefore, whether spirometry alone, which includes resting lung volumes, provides sufficient information to predict a positive clinical response.

The Role of Spirometry in Therapeutic Evaluation

Bronchodilator reversibility criteria have traditionally been based on changes in the FEV_1. Thus, acceptable minimum spirometric improvements by American Thoracic Society criteria,[12] (increase in FEV_1 by 12%, and at least 0.2 L), or by European Respiratory Society criteria[13] (increase by 10% predicted) are more likely to indicate actual reversible airway obstruction than random variation of the measurement. The FEV_1 is a simple, reliable measurement that is of unquestionable diagnostic utility and allows an accurate assessment of disease progression. However, the FEV_1 correlates only weakly with exercise capacity and dyspnea,[14–17] and the change in FEV_1 following bronchodilator therapy is poorly predictive of improved symptoms and exercise endurance in advanced COPD.[18–20] In COPD of moderate severity, change in FEV_1 is possibly a better predictor of exercise performance after bronchodilators than in severe disease, but considerable intersubject variability remains.[21] The FEV_1 gives no information about the extent of expiratory flow limitation, the shape of the maximal expiratory flow curve over the operating VT range, or the extent of resting hyperinflation required to maximize tidal expiratory flow rates. All of these parameters are relevant with respect to dyspnea causation and exercise limitation in COPD. Each can vary greatly for a given FEV_1.[16] Furthermore, resting maximal spirometric tests, which are prone to measurement artifact (volume history and gas compression effects) give little information about dynamic airway function and the attendant mechanical abnormalities during exercise.

The pattern of spirometric response to bronchodilators varies greatly between patients with COPD and may depend in some instances on the dose and type of bronchodilator agent used. Some patients show increases in both FEV_1 and FVC, others show changes in each of FEV_1 or FVC alone, and a minority do not show changes in either.[20] In many patients, changes in FEV_1 after bronchodilators simply reflect lung volume recruitment (*ie*, FEV_1/FVC ratio does not change).[20,22]

As with the FEV_1, improvement in FVC after bronchodilator therapy, which generally reflects a reduction in residual volume, is poorly predictive of improved dyspnea and exercise tolerance.[20] This, in part, reflects the variability of this measurement, especially if the time of exhalation is not standardized. Slow VC or timed VC may be more reproducible and responsive than the FVC and may correlate better with improved clinical outcomes,[22] but this requires further study. Similarly, it is not known whether direct plethysmographic measurements of thoracic gas volume or trapped gas volume (body box–helium-derived lung volumes) are stronger predictors of improved activity levels and symptoms than spirometric volume measurements.

Spirometric IC and derived measurements (*ie*, VT/IC ratios and inspiratory reserve volume [IRV]) provide indirect measures of resting lung hyperinflation and the extent of mechanical restriction and may provide complementary information to the FEV_1 in therapeutic evaluation.[20] Resting and dynamic spirometric IC measurements have recently been shown to be both reproducible and responsive.[8] In a recent

study, the change in IC after high-dose anticholinergic therapy emerged as the only spirometric correlate ($p < 0.02$) with improved exercise endurance and reduced exertional dyspnea.[20] Resting IC, and not the VC, represents the true operational limits for VT expansion during exercise. Thus, as a result of improved airway function, resting IC and IRV were significantly increased after ipratropium bromide inhalation, and this meant that patients could maintain the same exercise ventilation for a longer duration with a more efficient breathing pattern (*ie*, slower and deeper), at lower dynamic operational lung volumes (Fig 3). Thus, improved resting IC delayed ventilatory limitation during exercise: IRV was significantly greater after ipratropium than after placebo at end of exercise.[20] In that study, a mean improvement in resting IC by 14% predicted was associated with an improvement in exercise endurance time of 32%.[20]

Two recent studies[23,24] have shown that a lack of increase in resting IC after β_2-agonist bronchodilator therapy in a subset of patients with COPD may indicate the absence of true expiratory flow limitation and resting dynamically determined lung hyperinflation. It is also possible that an unchanged IC after bronchodilator therapy may occasionally obscure a true clinical benefit if TLC reduction is relatively greater than EELV reduction. In general, however, an increase in IC, regardless of the behavior of TLC, is likely to be clinically beneficial to patients.

Summary

In conclusion, exclusive reliance on the change in FEV_1 as the primary outcome measure in assessing therapeutic efficacy can lead to underestimation of a true clinical benefit in some patients with advanced COPD. Additional consideration of bronchodilator-induced changes in spirometric lung volumes (or capacities) can provide clinically useful information. In this respect, the spirometric resting IC, which is a simple reproducible measurement, is an acceptable surrogate for direct measurements of resting lung hyperinflation. Improved resting IC following anticholinergic therapy has been shown to correlate significantly, albeit weakly, with improved exercise performance and dyspnea alleviation, and provides a reasonable mechanistic rationale for these benefits. Clearly, further studies are required to determine the ultimate clinical utility of IC and other lung volume measurements. For a comprehensive therapeutic evaluation of bronchodilator therapy, detailed resting spirometric assessments, however, are unlikely to obviate the need for direct measurements of dynamic lung hyperinflation, symptom intensity, ex-

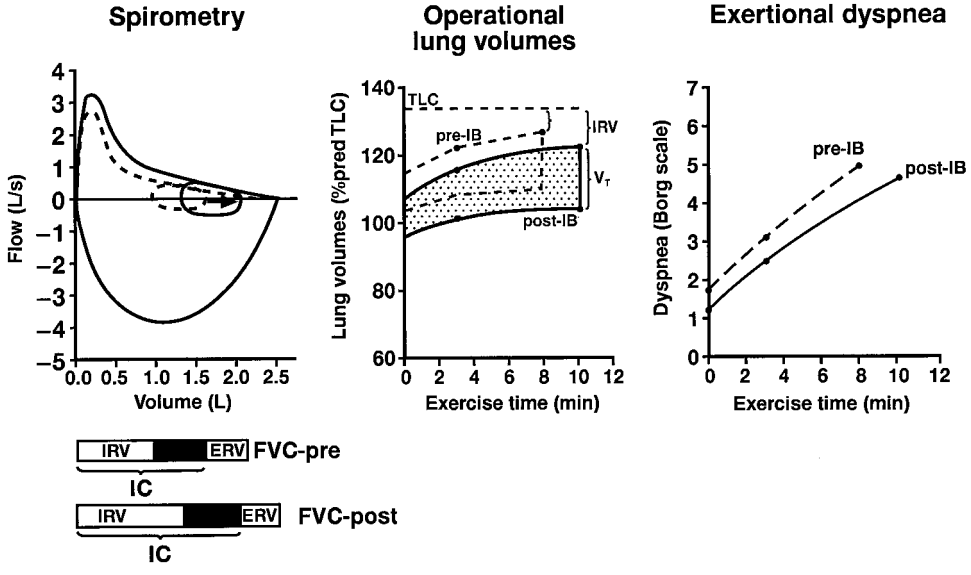

FIGURE 3. Resting spirometry, operational lung volumes during exercise, and exertional dyspnea ratings in COPD patients before (pre-IB) and after (post-IB) the administration of nebulized ipratropium bromide (IB), 500 μg. Note improved volume-matched expiratory flows over the VT range with increased resting IC. There is consequent reduction in operational lung volumes and an increased IRV at the peak of symptom-limited exercise, with less mechanical restriction. These mechanical improvements translated into improved dyspnea and exercise capacity. FVC-pre = FVC before treatment; FVC-post = FVC after treatment; see Figure 1 for abbreviation. Reprinted with permission from O'Donnell et al.[8]

ercise endurance, and quality of life. The future development of a composite index that collectively incorporates these outcome measures may increase our ability to critically evaluate the clinical benefit of combination bronchodilator therapy in symptomatic COPD patients.

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