



Uncovering the beneficial effects of inhaled bronchodilator in COPD: beyond forced spirometry

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BACKGROUND

It is a common clinical observation that many patients with COPD in whom FEV₁ and/or FVC improve less than 200 mL and 12% after the use of inhaled bronchodilator (BD) did report less dyspnea during daily life when exposed to this medication. This state of affairs has shed negative light on the ability of pulmonary function tests to predict a positive clinical response to BDs.

OVERVIEW

A 75-year-old long-term smoker was referred for spirometry with a specific query for diagnosis of COPD—modified Medical Research Council (mMRC) scale score 3. Forced spirometry confirmed moderate-to-severe airflow limitation without a “significant” response to a short-acting BD.^(1,2) Despite these negative results, the patient reported marked improvement in daily exertional symptoms (mMRC scale score 1) after 4 weeks of treatment with a combination of a long-acting β_2 agonist (LABA) and a long-acting antimuscarinic agent (LAMA). He was subsequently enrolled in a cross-over, randomized clinical trial contrasting the effects of the same LABA/LAMA combination against placebo. As shown in Figure 1A, the lack of “significant” changes in FEV₁ and/or FVC after the use of the medication coexisted with a marked decrease in gas trapping (lower RV). As lung hyperinflation— \downarrow functional residual capacity (FRC)—improved to a greater extent than did thoracic hyperinflation (\downarrow TLC), inspiratory capacity (IC) increased significantly. The latter was maintained throughout the exercise test (Figure 1B), being associated with lower dyspnea scores and increased tolerance to physical effort.

Exertional dyspnea arises when the descending motor drive to the inspiratory muscles is increased and the respiratory system fails to meet this increased demand.⁽³⁾ During exercise, the expiratory time becomes too short to fully exhale what has been inspired. Thus, expiratory flow limitation worsens gas trapping, leading to an upward shift in the operational lung volumes (i.e., those theoretically available for breathing). This, in turn, causes tidal volume to become progressively constrained as it approaches the “ceiling” (TLC).⁽³⁾ In this context, BDs fundamentally work as pharmacological deflators: there is more room for tidal volume expansion (IC) when the “floor” (end-expiratory lung volume) drops more than the “ceiling” (Figure 1B).

Why is it possible that forced spirometry may fail to show these beneficial effects on lung volumes? FEV₁ is biased to reflect the function of the larger airways, i.e.

the “fast component” of expiration, which, by definition, empties first.⁽⁴⁾ RV and FRC, in contrast, are strongly influenced by the mechanical properties of the smaller airways which need a longer time to empty (the “slow component”).⁽⁴⁾ Thus, an improvement in the flow rates of the “slow component” might not be detected by the maximal flow parameters from forced spirometry.⁽⁵⁾

CLINICAL MESSAGE

Adding a slow maneuver to forced spirometry to obtain IC (and, if feasible, measurements of static lung volumes) significantly enhances the clinical usefulness of pulmonary function tests in identifying the COPD patients who are poised to benefit from use of inhaled BDs as pertaining to exertional dyspnea and exercise intolerance.

A	LABA + LAMA		Δ , L (%baseline)
	Pre	Post (1 hour)	
FEV ₁ , L (%pred)	1.14 (43)	1.06 (40)	-0.08 (-7)
FVC, L (%pred)	3.50 (88)	3.75 (94)	+0.25 (+7)
FEV ₁ /FVC	0.32	0.28	-0.04
Slow VC	3.75	4.00	+0.25 (+7)
TLC, L (%pred)	6.66 (99)	6.27 (93)	-0.39 (-6)
FRC, L (%pred)	4.54 (126)	3.83 (106)	-0.71 (-16)
RV, L (%pred)	2.91 (118)	2.27 (92)	-0.64 (-22)
IC, L (%pred)	2.12 (67)	2.44 (78)	+0.32 (+15)

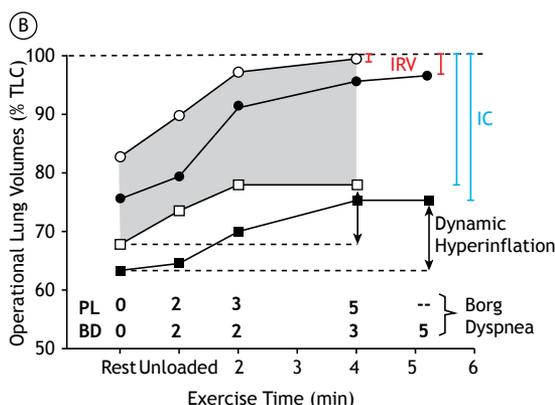


Figure 1. In A, pulmonary function test results (forced and slow expiratory maneuvers and body plethysmography) before and after the administration of a combination of a long-acting β_2 -agonist (LABA) and a long-acting antimuscarinic agent (LAMA). In B, results of endurance cardiopulmonary exercise tests performed after the use of placebo (PL; white symbols) and bronchodilators (BD; black symbols) on different days to determine symptom limitation with serial measurements of inspiratory capacity (IC) in order to track end-expiratory (squares) and end-inspiratory (circles) lung volumes. See text for detailed discussion. FRC: functional residual capacity; IC: inspiratory capacity; and IRV: inspiratory reserve volume.

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