



# Absence of airflow obstruction on spirometry: can it still be COPD?

José Alberto Neder<sup>1</sup>, Danilo Cortozzi Berton<sup>2</sup>, Denis E O'Donnell<sup>1</sup>

## BACKGROUND

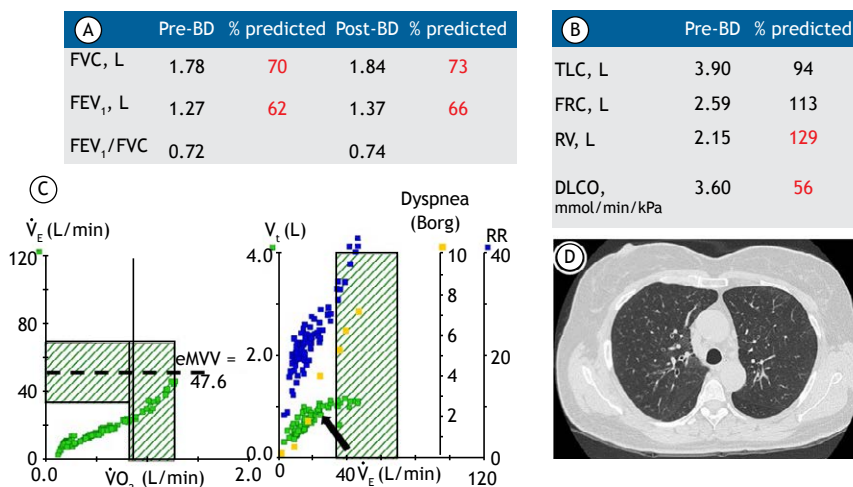
An FEV<sub>1</sub>/FVC ratio < 0.7 has been widely used to define airflow obstruction, because, on average, it correlates well with more sophisticated measurements of expiratory flow limitation. In fact, the cut-off point of 0.7 is at the core of the definition of COPD according to the GOLD.<sup>(1)</sup> It follows that most physicians assume that a post-bronchodilator (BD) FEV<sub>1</sub>/FVC ratio ≥ 0.7 effectively rules out COPD.

## OVERVIEW

A 59-year-old, heavy former smoker (45 pack-years) woman who had complaints of exertional dyspnea (mMRC = 3) received a provisional diagnosis of COPD. Although there was partial improvement with the use of inhaled formoterol (mMRC = 2), she was referred to the pulmonology department for reassessment of diagnosis since her post-BD FEV<sub>1</sub>/FVC ratio had always been ≥ 0.7 (Figure 1A). Additional lung function tests, however, showed mild gas trapping (↑RV) and moderately ↓DLCO (Figure 1B). Considering that the exertional symptoms of the patient could be a mere reflection of severe deconditioning, a cardiopulmonary exercise test was performed to determine whether there was any evidence that “the lungs” could have explained her breathlessness. As shown in Figure 1C, this was indeed the case: a)

dyspnea scores, either as a function of work rate or minute ventilation ( $\dot{V}_E$ ), were typically above the upper limit of normal<sup>(2)</sup>; b) there was evidence of critical constraints to tidal volume expansion (Figure 1C, arrow) as tidal volume prematurely reached ≈70% of the inspiratory capacity and ≈0.5 L of inspiratory reserve volume, that is, the end-inspiratory lung volume was too close to TLC,<sup>(3)</sup> and peak  $\dot{V}_E$  approached the estimated maximal voluntary ventilation. Moreover, a chest CT showed emphysema and thickened bronchial walls (Figure 1D).

Although there is ongoing controversy regarding the best cut-off point to define airflow obstruction (a fixed FEV<sub>1</sub>/FVC ratio < 0.7 or age- and sex-based lower limit of normal), a reduced FEV<sub>1</sub>/FVC ratio has been considered an indispensable criterion for the diagnosis of COPD.<sup>(1)</sup> There is mounting evidence that subjects showing intermediate FEV<sub>1</sub>/FVC ratios (i.e., greater than the lower limit of normal but smaller than 0.7) have higher hospitalization and death rates,<sup>(1)</sup> more cardiovascular comorbidities, and worse exercise tolerance and dyspnea<sup>(4)</sup> than do subjects with no obstruction using both criteria. Occasionally, however, FVC decreases roughly in tandem with FEV<sub>1</sub> as RV increases despite a preserved TLC, reflecting increased small airway collapse/closure at low lung volumes during the forced maneuver.<sup>(5)</sup> In fact, a sizeable number of symptomatic smokers with no spirometric evidence of obstruction may show gas



**Figure 1.** Physiological and structural investigations in a 59-year-old, former heavy smoker woman with complaints of chronic dyspnea. There was a proportional reduction in FEV<sub>1</sub> and FVC, leading to a preserved pre- and post-bronchodilator FEV<sub>1</sub>/FVC ratio (in A), increased RV and reduced DLCO (in B), mechanical ventilatory limitation to exercise (in C; see text for further elaboration), and emphysema plus thickened airway walls on a chest CT (in D) that jointly indicate the presence of COPD. BD: bronchodilator; FRC: functional residual capacity; eMVV: estimated maximal voluntary ventilation;  $\dot{V}_E$ : minute ventilation;  $\dot{V}O_2$ : oxygen uptake; and  $V_T$ : tidal volume.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, Kingston Health Science Center & Queen’s University, Kingston, ON, Canada.  
 2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

trapping and/or  $\downarrow$ DLCO plus structural changes in keeping with COPD.<sup>(1)</sup> Indeed, some such individuals may benefit clinically from a more proactive approach toward early treatment with BDs.<sup>(4)</sup>

### CLINICAL MESSAGE

The key pathophysiological characteristic of the current definition of COPD (a persistently  $\downarrow$ FEV<sub>1</sub>/FVC ratio) is **not** *sine qua non* in smokers showing gas trapping and/or  $\downarrow$ DLCO and/or emphysema on CT. As such,

there is a surge of interest in adding CT variables to the definition of COPD,<sup>(1)</sup> although we strongly believe that the abovementioned physiological variables should also be taken into consideration. The bottom line is that the diagnosis of COPD in subjects with a high pre-test probability of the disease but a preserved FEV<sub>1</sub>/FVC ratio requires a more holistic approach, involving assessment of clinical (dyspnea), physiological (lung volumes and DLCO), and anatomical (emphysema) abnormalities.

---

### REFERENCES

1. Han MK, Agusti A, Celli BR, Criner GJ, Halpin DMG, Roche N, et al. From Gold 0 to Pre-COPD. *Am J Respir Crit Care Med.* 2020;10.1164/rccm.202008-3328PP [published online ahead of print, 2020 Nov 19]. <https://doi.org/10.1164/rccm.202008-3328PP>
2. Neder JA, Berton DC, Nery LE, Tan WC, Bourbeau J, O'Donnell DE, et al. A frame of reference for assessing the intensity of exertional dyspnoea during incremental cycle ergometry. *Eur Respir J.* 2020;56(4):2000191. <https://doi.org/10.1183/13993003.00191-2020>
3. Marillier M, Bernard AC, Gass R, Berton DC, Verges S, O'Donnell DE, et al. Are the "critical" inspiratory constraints actually decisive to limit exercise tolerance in COPD?. *ERJ Open Res.* 2020;6(3):00178-2020. <https://doi.org/10.1183/23120541.00178-2020>
4. Neder JA, Milne KM, Berton DC, de-Torres JP, Jensen D, Tan WC, et al. Exercise Tolerance according to the Definition of Airflow Obstruction in Smokers. *Am J Respir Crit Care Med.* 2020;202(5):760-762. <https://doi.org/10.1164/rccm.202002-0298LE>
5. Berton DC, Neder JA. Measuring slow vital capacity to detect airflow limitation in a woman with dyspnea and a preserved FEV<sub>1</sub>/FVC ratio. *J Bras Pneumol.* 2019;45(2):e20190084. <https://doi.org/10.1590/1806-3713/e20190084>