CORRESPONDENCE

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Matthieu Schmidt, M.D.*
Marc Pinetonde Chambrun, M.D.
Guillaume Lebretot, M.D.
Guillaume Hékimian, M.D.
Juliette Chommeloux, M.D.
Nicolas Bréchot, M.D.
Petra Barhoum, M.D.
Lucie Lefèvre, M.D.
Juliette Chommeloux, M.D.
Julie Molle, M.D.
Lucie Lefèvre, M.D.
Aïnèl Combes, M.D.
Sorbonne Université
Paris, France

*Corresponding author (e-mail: matthieu.schmidt@aphp.fr).

Correspondence

1. Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D, et al.; Groupe de Recherche Clinique en RÉanimation et Soins intensifs du Patient en Insuffisance Respiratoire aiguë (GRC-RESPIRE) Sorbonne Université; Paris-Sorbonne ECMO-COVID investigators. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med 2020;10:1121–1131.

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FEV1 Minimum Important Difference versus Minimal Detectable Difference? In Search of the Unicorn

To the Editor:

The goals of managing chronic obstructive pulmonary disease (COPD) include optimizing lung function, reducing symptoms, improving health status, and reducing exacerbations. As COPD is multidimensional in nature, composite scores have been proposed to better predict risk of death and assess effects of pharmacological therapies. Regarding the latter, the concept of clinically important deterioration (CID) was proposed using the purported minimum clinically important differences (MCIDs) of health status (St. George’s Respiratory Questionnaire ≥4), moderate–severe exacerbation incidence, and lung function (FEV1 ≥100 ml) (1). This concept of CID has since been used in subsequent clinical trials. However, the lung function criterion of an MCID of 100 ml was initially posited from a literature review (2), which proffered that although a change of 100 ml can be perceived by a patient, several limitations exist, including placebo effect, reproducibility, and variability, leading to the conclusion that “The MCID in FEV1 remains an important but still undetermined issue for patients with COPD” (2). This is important when considering the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force statement on interpretive strategies for lung function testing
that suggests, for an individual patient, only changes that fall outside the coefficient of repeatability (CR) should be considered significant (3). CR determination is recommended because it takes into consideration the measurement variability over a specified interval (i.e., measurement noise) and represents the value below which the absolute difference between two measurements would lie with a 95% probability.

To further explore the robustness and, hence, utility of a 100-ml threshold as gleaned from clinical trials, as the CID was initially proposed using such data, we reviewed data from two clinical studies.
in patients with COPD to assess the short-term variability of change-from-baseline FEV₁. We hypothesized that the FEV₁ CR observed in multicenter trials would exceed the 100-ml threshold currently adopted as the MCID.

**Methods**

We examined data from two COPD trials (HZC102871, NCT01009463; HZC102970, NCT01017952) (4). These were registration studies designed to replicate the efficacy and safety of the inhaled corticosteroid/long-acting β₂-agonist combination fluticasone furoate/vilanterol 100/25 µg. Enrolled patients were ≥40 years old with ATS/ERS-defined COPD history (5), a smoking history of ≥10 pack-years, a post-bronchodilator FEV₁/FVC ratio of ≤0.70, a post-bronchodilator FEV₁ <0.70 predicted, and ≥1 documented moderate or severe COPD exacerbation in the year before screening. These trials were selected for post hoc analysis as they measured spirometry at baseline and 4 weeks later, during which the patients could not have had an exacerbation, a respiratory tract infection, or a change in their inhaled therapy. The patient subgroup selected for this analysis (HZC102871, N = 427; HZC102970, N = 421) was already receiving an inhaled fluticasone propionate/salmeterol 250/50 µg combination product. At baseline, patients received open-label inhaled fluticasone propionate/salmeterol for 4 weeks prior to randomization. The spirometry equipment had to meet or exceed the minimum ATS performance recommendations (6), and external spirometric tracing readings were made to assure acceptability and reproducibility. Variability of FEV₁ measurements over the 4-week interval was assessed using Bland-Altman plots (7).

**Results**

The study design and baseline characteristics of the entire COPD cohort are completely described in the primary publication (4). Patients in this subgroup had a mean age of ~63 years. In studies HZC102970 and HZC102871, respectively, ~45% and 55% were male; mean (±SD) FEV₁ values were 1.26 L (±0.42) and 1.22 L (±0.46); and mean (±SD) predicted post-bronchodilator FEV₁ percentages were 45.8% (±12.8) and 43.9% (±13.6). The Bland-Altman plots are shown in Figures 1 and 2; the CR for both COPD trials exceeded the putative MCID of 100 ml (370 ml and 422 ml, respectively).

**Discussion**

The 4-week CR attained in patients with COPD in multicenter clinical trials exceeds the putative MCID of 100 ml. CR values obtained in both trials are similar to the 3-month CR of 400 ml reported in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study (8). This is notable because in the ECLIPSE report, 37% of the patients with COPD either had an exacerbation or changed their medication during that 3-month window, and the severity of airflow limitation ranged from moderate to very severe. Patients with more severe airflow limitation, and hence lower baseline values, were more likely to demonstrate less variability compared with patients with less impaired airflow and perhaps more demonstrable reversibility. However, the percentage change would likely be of similar magnitude. Conversely, the Figures clearly illustrate the differences in individual variability. According to the ATS/ERS Task Force on interpreting lung function studies, week-to-week FEV₁ variability should exceed 20% (and year-to-year exceed 15%) before considering it as a significant change in patients with COPD (3).

An MCID should not only represent a change in an endpoint detectable to the patient but also one that the patient or clinician deems as clinically beneficial. A patient with severe/very severe airflow limitation may not only perceive but benefit from a specified improvement in FEV₁ compared with a patient with moderate airflow obstruction. For example, when measured on a seven-category scale (“much worse...about the same...much better”), a correlation of FEV₁ with dyspnea at r = 0.29 (95% confidence interval, 0.22–0.35) and a correlation of FEV₁ with overall health of only 0.10 (95% confidence interval, 0.03–0.17) was reported (9). The rating change from “about the same” to a “little bit better/worse” related to an average FEV₁ change of 112 ml (10). Patients or clinicians could debate whether “little bit better/worse” is clinically meaningful. In the noninterventional ECLIPSE trial, a 100-ml FEV₁ decrease was associated with an increased odds ratio of a subsequent exacerbation (9). However, there are no robust data purporting that an FEV₁ increase of 100 ml decreases exacerbation risk (6), and a recent study demonstrated minimal overlap of FEV₁ “responders” with those of several patient-reported outcome instruments (11).

Clearly, identifying an MCID is important in clinical practice. As with the unicorn, it was often sought but difficult to capture. From this analysis, one cannot conclude that 100 ml is not the MCID but rather that FEV₁ data gleaned from multicenter clinical trials do not support the validity of this adopted value. It is probable that spirometry performed at a single center, with highly trained personnel, allows for determination of “abnormality” by demonstrating a CR for FEV₁ with a value <100 ml. However, although such an abnormality might be detectable to patients, it remains to be proven that it is clinically or biologically important. Therefore, we propose that COPD therapy should be guided to improve FEV₁ above the CR determined in one’s pulmonary function laboratory rather than focusing on some “universal” number, while reducing symptoms and exacerbations.

**Author disclosures** are available with the text of this letter at www.atsjournals.org.
To the Editor:

The small airways (those <2 mm internal diameter) offer little resistance to airflow in health; however, the response to repetitive and continual insult by inhaled noxious particles causes them to become the principal site of impedance to airflow in chronic obstructive pulmonary disease (COPD). As disease progresses, several pathophysiological mechanisms collectively lead to emphysema and lung hyperinflation, recognized as significant contributors to the patient’s perception of breathlessness and activity limitation that predicts not only the risk and severity of exacerbations but also all-cause mortality. These observations have stimulated interest in lung volume reduction (LVR) techniques, lung volume reduction surgery (LVRs), and more recently, placement of endobronchial valves (EBVs), which limit air entry but permit unimpeded expulsion of air and mucus, to deflate the lung in an attempt to restore respiratory mechanics. Accruing evidence supports the concept of LVR to improve lung function, exercise capacity, quality of life, and survival. Volume reduction is the key driver of the benefit (1).

Although the small airways are the principal site of disease pathogenesis, the effects of LVR on small airway function are largely unknown. Bilateral LVRs undertaken in 29 patients with severe emphysema has demonstrated more efficient small airway lung ventilation with scintigraphic imaging of regional lung $^{133}$Xe gas washout (2). Oscillometry in 23 patients whose heterogeneous emphysema or emphysematous bullae had been treated with histoacryl gel, an experimental “biological” LVR not clinically approved for routine practice, showed a decreased $R_{5Hz}$, with unaltered $X_{5Hz}$ (3). Here, we study the impact on lung mechanics of EBVs. We hypothesized that EBV’s implanted in the proximal bronchi of the most severely diseased lung lobe(s) would lead to functional improvements in the peripheral lung. Small airway function was assessed using oscillometry and ventilation distribution tests.

**Methods**

In a prospective observational study (ethics reference 14/SC/0193), patients with COPD with severe emphysema and without collateral ventilation underwent EBV placement (Zephyr; PulmonX). During a stable disease state before and 3 months after the procedure, patients underwent clinical phenotyping: symptom scores (modified Medical Research Council dyspnea scale and St. George’s Respiratory Questionnaire [SGRQ]), functional exercise capacity (6-min-walk distance), radiological assessment, and lung function testing. After bronchodilation (400 μg albuterol), routine body plethysmography was followed by impulse oscillometry (Cardinal Health) and multiple-breath nitrogen washout (MBN,W) testing (PK-Morgan), as described previously (4). Wilcoxon signed-rank tests were performed using GraphPad Prism (v8), with significance at $P < 0.05$.

**Results**

Twelve patients with COPD (five female) participated, with a baseline median modified Medical Research Council dyspnea scale score of 2.5 and SGRQ-total score of 50.9 and features of very severe airflow obstruction (FEV$_1$ 28% predicted), hyperinflation (residual volume [RV] 225% predicted), and radiological signs of emphysema (Table 1). Three months after the procedure, with a radiologically verified median volume reduction of 730 ml, significant gains were observed in spirometry, static lung volumes (RV and RV/TLC), exercise capacity, and SGRQ-activity score (Table 1). Distinct improvements were obtained for impulse oscillometry indices of reactance ($X_{5Hz}$, $P = 0.013$; and $X_{\text{in5Hz}} - X_{\text{ex5Hz}} + P = 0.010$) (5, 6), and for MBN,W

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*Corresponding author (e-mail: crim52c@ncrr.com).

**Present address:** University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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