

# Bronchodilator responsiveness or reversibility in asthma and COPD – a need for clarity

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Asthma and COPD present with multiple overlapping phenotypes,<sup>1–3</sup> making a simplified diagnostic separation between the two disease states difficult. From a practical standpoint, the difficulty in differentiating between asthma and COPD has been a limitation and a foundation for criticism of large prospective trials.<sup>4</sup> Multiple attempts to better define the population of patients with features of both diseases have been made,<sup>5,6</sup> yet a common consensus about the best way to approach this problem is missing. Part of this problem relates to our reliance on oversimplified and relatively crude spirometric definitions of asthma and COPD<sup>7</sup> and an incomplete understanding of how to interpret changes after bronchodilator administration. Imprecise definitions of the terms “bronchodilator responsiveness” and “reversibility” add to the confusion in the attempts to distinguish between COPD and asthma. Although the two terms are often used interchangeably in the published literature,<sup>8</sup> and their difference may seem to be an issue of semantics, appropriately defining “bronchodilator responsiveness” and “reversibility” is essential for understanding the role of bronchodilator administration in the diagnostic workup of obstructive lung disease.

A diagnosis of COPD is currently defined by demonstrating the presence of persistent airflow obstruction postbronchodilator, which implies the lack of “reversibility” of the airflow obstruction following administration of the bronchodilator. Thus, based on their definitions, reversibility of airflow obstruction and COPD are mutually exclusive terms.<sup>7</sup> In the narrowest sense, “reversibility” implies that the abnormality, in this case, airflow obstruction, returns to normal after bronchodilator administration. Clearly, this determination depends on the accepted definition of “abnormal,” with Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines<sup>9</sup> choosing a fixed ratio of  $FEV_1/FVC < 70\%$ , a subject that has generated much debate.<sup>10</sup> Individuals with “reversible” obstruction are at higher risk of future development of COPD.<sup>11,12</sup> The latest GOLD guidelines recommend the need to retest symptomatic subjects at risk of COPD with an  $FEV_1/FVC$  ratio between 60% and 80% to account for variability of this measurement on repeated spirometry as “reversible” airflow obstruction on postbronchodilator spirometry may turn into a persistent airflow obstruction on follow-up testing. At the same time, the same subject with a reduced  $FEV_1/FVC$  ratio of  $< 70\%$  which normalizes after bronchodilator administration may have asthma. Nevertheless, “reversibility” is neither necessary nor sufficient for an asthma diagnosis. Spirometry in asthma may be completely normal between exacerbations, yet persistent, uncontrolled asthma may lead to “irreversible” airflow obstruction, where

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the degree of obstruction may be a function of the duration and severity of the disease.<sup>13</sup>

By contrast, “bronchodilator responsiveness” can be defined in multiple ways,<sup>8</sup> but it is inevitably based on measuring volume changes after bronchodilator administration. The American Thoracic Society (ATS) and European Respiratory Society (ERS) have adopted a definition of bronchodilator responsiveness as being an increase following bronchodilator of either FEV<sub>1</sub> or FVC of  $\geq 12\%$  and  $\geq 200$  mL.<sup>14,15</sup> Bronchodilator administration can also affect FEV<sub>1</sub>/FVC ratio, but the presence or absence of a change from  $< 70\%$  to  $\geq 70\%$  is not used to categorize the bronchodilator response into positive or negative. While “reversibility” is occasionally used as a criterion distinguishing between COPD and asthma-COPD overlap, often what is meant is “bronchodilator responsiveness.”<sup>6,16</sup> Such references may relate to the definition of the term “reversibility” in the seminal paper by Miller et al,<sup>14</sup> on the standardization of spirometry. However, it is important to emphasize that lack of clarification of this term has a significant impact on our interpretation of multiple published studies. A majority of patients with COPD (52%) demonstrate bronchodilator responsiveness, depending on its definition (FEV<sub>1</sub> vs FVC) and disease stage.<sup>8</sup> However, in the study by Prentice et al,<sup>17</sup> among those with reversibility of airflow obstruction, only 28.1% had bronchodilator responsiveness. The repeatability of bronchodilator responsiveness is modest, with about 50% of patients with moderate to severe COPD changing their bronchodilator responsiveness status on a follow-up testing.<sup>18</sup> In addition, oversimplified analysis of bronchodilator responsiveness as present or absent, based on defined ATS/ERS criteria of  $\geq 200$  mL and  $\geq 12\%$ ,<sup>14</sup> further diminishes the clinical usefulness of this spirometric measure in the evaluation of obstructive lung disease. In reality, bronchodilator responsiveness in COPD and asthma differ both quantitatively<sup>8</sup> and in the pattern that reflects pathophysiological processes.<sup>19</sup> In COPD, especially in advanced disease, FVC responsiveness dominates, likely implicating the effect of bronchodilator on reduction of hyperinflation and air trapping, as opposed to the FEV<sub>1</sub> responsiveness, which is usually seen as a marker of bronchoreactivity in larger airways.

What should we do then, in order to derive the best value from spirometry and to help us better understand airway pathophysiology? First, we need to recognize its limitations. Currently used metrics such as FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are not sufficiently sensitive to diagnose early or mild airway disease,<sup>20–22</sup> and, while spirometric staging can be helpful with regard to prognosis, it is well accepted that spirometry alone does not fully characterize the many clinical manifestations of

COPD.<sup>9</sup> What spirometry does reflect well is the physiology of respiratory system and the dynamic changes that occur over time. While the forced expiratory and inspiratory maneuver is an artificial concept and sometimes difficult for patients to perform, the maximal flow volume curves do provide a rich source of physiological data. Large observational studies,<sup>23,24</sup> along with digital technology and machine learning, offer the opportunity to explore novel spirometric indices of airway disease and to compare these indices with early structural abnormalities (eg, parametric response mapping) noted on high-resolution computed tomography scans.

“Reversibility” and “bronchodilator responsiveness” are important spirometric features of a patient with obstructive airway disease, and they may provide useful information about the underlying pathobiology in a given patient. Nevertheless, distinguishing the two terms and better understanding of the limitations derived by their current and widely accepted definitions is of crucial importance as we try to use spirometry as a reference for building more sophisticated diagnostic models.<sup>6,25</sup> In this regard, it is worth noting that uncertainty as to whether a patient has an overlap of asthma and COPD is unlikely to be resolved on the basis of spirometric criteria alone. We believe the term “reversibility” should be dropped from position statements and guidelines in the future. On the other hand, bronchodilator responsiveness, linked to evidence-based minimum clinically important differences, is a distinct clinical feature in comparison to reversibility and it occurs frequently in both asthma and COPD.

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