Although the study by McDowell and colleagues is a welcome effort to understand the nature of asthma exacerbations through the T2/non-T2 phenotypic lens, it unfortunately falls short in providing robust data to draw solid conclusions because of several limitations. The limited number of clinically assessed exacerbations introduces potential biases that limit the external validity of the study. Furthermore, the small number of sputum samples analyzed limits the ability to draw meaningful conclusions with regard to the role of the microbiome in exacerbation phenotype. Finally, the concurrent use of OCSs is an important confounder of the study, limiting the ability to fully elucidate the biological basis of the exacerbation phenotype. Although some of these limitations, as pointed out by the authors, are the result of conducting large multicenter asthma exacerbation studies, they do limit the generalizability of their findings.

As outlined by the Lancet Commission on asthma, it is critical to deconstruct airway disease into component parts before planning treatment, with a focus on traits that are identifiable and treatable (10). It is clear that this recommendation should also be applied to the evaluation and treatment of asthma exacerbations. McDowell and colleagues get us closer to this goal but with still lingering important questions, including how much of what we see in patients with exacerbations is truly underlying low T2 biology versus OCS-suppressed T2 inflammation. Additional investigation of asthma exacerbations that incorporates additional biological mechanisms, including a broader interrogation of the microbiome, would be beneficial to further understand the complex pathobiology of exacerbations.

Author disclosures are available with the text of this article at www.atsjournals.org.

Andi Hudler, M.D.
Fernando Holguín, M.D., M.P.H.
Sunita Sharma, M.D., M.P.H.
Pulmonary, Critical Care and Sleep Medicine
University of Colorado
Denver, Colorado

Is It Time to Abandon the Postbronchodilator Requirement in Defining Chronic Obstructive Pulmonary Disease?

Definitions used in clinical medicine are, by nature, dogmatic and somewhat arbitrary. They do, however, serve a useful purpose in helping to determine who may be more likely to benefit from an intervention.

A particular problem with definitions relates to thresholds. Values of any measurement close to a threshold may be within the measurement error for that value, yet one slightly above the threshold is considered “normal” and one slightly below the threshold is considered “abnormal”.

Using spirometry to measure lung function and determine the presence of obstruction presents some of the challenges of these definitions and thresholds. The Global Initiative on Chronic Obstructive Lung Disease (GOLD) recommends classifying

References
1. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet 2018;391:783–800.
2. Holguín F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55:1900588.
3. McDowell PJ, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker S, et al.; MRC Refractory Asthma Stratification Program. Exacerbation profile and risk factors in a type-2–low enriched severe asthma cohort: a clinical trial to assess asthma exacerbation phenotypes. Am J Respir Crit Care Med 2022;206:545–553.
4. Darveau JL, Lemanske RF Jr. Infection-related asthma. J Allergy Clin Immunol Pract 2014;2:658–663.
5. Calmes D, Huynen P, Paulus V, Henkel M, Guissard F, Moermans C, et al. Chronic infection with Chlamydia pneumoniae in asthma: a type-2 low infection related phenotype. Respir Res 2021;22:72.
6. Tsang YP, Marchant J, Li AM, Chang AB. Stability of sputum inflammatory phenotypes in childhood asthma during stable and exacerbation phases. Pediatr Pulmonol 2021;56:1484–1489.
7. Silkoff PE, Laviolette M, Singh D, FitzGerald JM, Kelsen S, Backer V, et al.; ADEPT Investigators. Longitudinal stability of asthma characteristics and biomarkers from the Airways Disease Endotyping for Personalized Therapeutics (ADEPT) study. Respir Res 2016;17:43.
8. Kupczyk M, Dahlén B, Sterk PJ, Nizankowska-Mogilnicka E, Papi A, Bel EH, et al.; BIOAIR investigators. Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma. Allergy 2014;69:1198–1204.
9. Loza MJ, Djukanovic R, Chung KF, Horowitz D, Ma K, Branigan P, et al.; MRC Refractory Asthma Stratification Program. Exacerbation profile and risk factors in a type-2–low enriched severe asthma cohort: a clinical trial to assess asthma exacerbation phenotypes. Am J Respir Crit Care Med 2022;206:545–553.
10. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018;391:350–400.

Copyright © 2022 by the American Thoracic Society
obstruction based on the post-bronchodilator spirometry, and uses a fixed ratio of the FEV$_1$ to the FVC of less than 0.70 to define obstruction (1). Other guidance recommends using the FEV$_1$/FVC below the lower limit of normal to define obstruction but also states that this should be based on a postbronchodilator spirometry (2).

The origins of the requirement for postbronchodilator are not perfectly clear. The initial 2001 GOLD document states, “The presence of a post-bronchodilator FEV$_1$, 80% of the predicted value in combination with an FEV$_1$/FVC < 70% confirms the presence of airflow limitation that is not fully reversible”, without a reference or other justification for this statement (3). In general, measurement of lung function after the administration of a bronchodilator in a population results in a mean improvement of 3–4% in both the FEV$_1$ and the FVC, with a great deal of variability in this change (4). One thought is that the postbronchodilator spirometry is a more accurate and stable measure, although this, to my knowledge, has never really been demonstrated as completely being an actual effect of the bronchodilator as opposed to being a learning effect of doing a difficult set of maneuvers a second time. And although lung function decline based on postbronchodilator spirometry varies from that seen in prebronchodilator spirometry in the context of clinical trials (5), either measurement can be used to assess lung function decline (6). Another thought has been that response to a bronchodilator distinguishes asthma from chronic obstructive pulmonary disease (COPD), although this has also been demonstrated to not be true (7).

An additional complication is the confusing nomenclature used in this space. The terms “reversibility” and “bronchodilator responsiveness” are used interchangeably at times yet describe different things. Bronchodilator responsiveness is the improvement in lung function after administration of a bronchodilator (current American Thoracic Society guidelines say the threshold for this is 12% with a 200-ml minimum for either the FEV$_1$ or the FVC) (8). On the other hand, reversibility describes the change in spirometry from an obstructed pattern (using whatever threshold is desired) to an unobstructed one after the administration of a bronchodilator. This typically happens because of nonsignificant improvement in the FEV$_1$ in a person close to the obstruction threshold (9). For the sake of completeness, another possibility is that of “inverse reversibility”, where a person has a larger improvement in their FVC relative to their FEV$_1$ after a bronchodilator and goes from unobstructed to obstructed (9).

In this issue of the *Journal*, Buhr and colleagues (pp. 554–562) explore reversibility longitudinally in the SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) cohort, using the term “variable obstruction” to describe people who were obstructed before but not after the administration of bronchodilators (in this setting comprising four puffs of both albuterol and ipratropium) (10). Of the 2,982 in the original cohort, 175 (5.9%) met their definition, confirming this was a small but important part of this population. Of interest, though, was the variability of this population over time. As can be seen in the Sankey diagram [Figure 2 in Buhr et al. (10)] there was a great deal of movement into and out of this group through the study. I suspect that had the entire cohort been included in the analysis, including those “obstructed” at baseline, we would have seen a similar movement from that group also. In addition, a large proportion of patients in both the variable-obstruction and never-obstructed group were on therapies consistent with COPD therapy [Table 1 in Buhr et al. (10)], suggesting that clinicians are using metrics other than postbronchodilator spirometry to guide therapy (acknowledging that in this study we do not know what information clinicians had at the time they made their treatment decision).

The COPDGene 2019 definition of COPD expanded the spirometric criteria for possible COPD to include both obstructive and restrictive findings, in addition to including radiology and symptoms in their classification metric (11). Although the spirometric guidance does not specify before or after bronchodilator, one could advocate that abnormal spirometry in either scenario is evidence of abnormality that could support intervention.

To answer the question posed in the title, is there any value in the concept of reversibility in defining the presence of “obstruction” (using whatever metric of obstruction one would like), I would argue that the answer is no. Clinically, if a patient shows up at clinic with respiratory symptoms like dyspnea, wheezing, and cough; has a prebronchodilator spirometry that falls just below the obstructive threshold; has a postbronchodilator spirometry that shows a nonsignificant increase in their lung function that pushes them above the threshold (along with an improvement in some of their symptoms)—is one not going to make a diagnosis and treat them as if they have a chronic lower respiratory disease? Conversely, bronchodilator responsiveness, that significant improvement in lung function that follows a bronchodilator, is an important metric that has the potential to guide therapy (such as the decision to include an inhaled steroid in the treatment). Improving our approach to patients with COPD requires that we refine our approach based on current data that includes clinically meaningful outcomes.

Author disclosures are available with the text of this article at www.atsjournals.org.

David M. Mannino, M.D.
University of Kentucky College of Medicine
Lexington, Kentucky

and

COPD Foundation
Miami, Florida

ORCID ID: 0000-0003-3646-7828 (D.M.M.).

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557–582.

2. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al.; ATS Committee on Proficiency Standards for Pulmonary Function Laboratories. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. *Am J Respir Crit Care Med* 2017;196:1463–1472.

3. Pauwels RA, Buist AS, Jenkins CR, Hurst SD; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–1276.
The Clinical Spectrum of PRISm

Significant heterogeneity in the definitions and nomenclature used for low lung function characterized by proportionate reductions in FEV1 and FVC exists. The most widely used term, "restrictive spirometry," is typically defined by a nonobstructive FEV1:FVC ratio and reduced FVC. Concurrent with the introduction of the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines, which defined obstruction as an FEV1:FVC ratio of less than 0.7, a category known as "unclassified" (GOLD-U) was introduced to capture individuals with an FEV1:FVC ratio of 0.7 or more with FEV1 of <80% predicted on spirometry. The term, "Preserved Ratio Impaired Spirometry" (PRISm) was subsequently proposed (1) as an alternative to GOLD-U as a more informative name that would distinguish the pattern from "restriction" and "nonspecific abnormality," both of which require assessment of total TLC. Although controversy regarding whether fixed or lower limit of normal thresholds should be used in each of these definitions, the body of literature regarding the epidemiology, risk factors, and clinical outcomes associated with symmetrically reduced FEV1 and FVC has increased substantially over the past decade.

The prevalence of PRISm in population-based studies ranges from 7.1% to 20.3% (2–11); although PRISm is enriched for current and former smokers relative to normal spirometry, prevalence estimates in smoking cohorts (12.3%) (1, 12) are similar to those from population-based cohorts. The mean age and cumulative smoking exposure of PRISm as a group tends to be greater than those for normal spirometry and slightly less than that for obstructed spirometry (4–6, 11), and although a prominent and consistent summary statistic associated with PRISm is an increased mean body mass index relative to other spirometry groups (4–6, 11), it is notable that both high and low body mass index are associated with an increased risk for PRISm (13). Given the older age and increased prevalence of obesity and obesity-related comorbidities, including diabetes and hypertension, in PRISm, an increase in crude all-cause mortality associated with PRISm relative to normal spirometry is not unexpected (7); however, the persistence of PRISm as a risk factor for mortality despite adjustment for comorbid conditions and smoking exposure supports that impaired lung function contributes independent information relevant to survival (2–4, 11, 13, 14).

A distinctive feature of PRISm that has recently gained attention is the increased rates of transitions to both normal and obstructed spirometry over time (14). This increased frequency in transitions to other lung function categories has been validated in multiple independent cohorts (3, 9, 11) and emerging data supports that subsets of PRISm with distinct trajectories (e.g., "persistent PRISm" and "PRISm-to-normal") may be differentially associated with mortality (9). Concerns regarding whether the increase in transitions in PRISm represent artifacts owing to measurement variability or imprecision (e.g., noise) exist; however, recent work focusing on transitions associated with substantial changes in lung function (15), which may be more likely to reflect pathological changes, continues to support an enrichment of "significant transitions" among individuals with PRISm.

Despite an increasing body of literature on PRISm, significant knowledge gaps remain. First, the majority of studies examining prospective outcomes, such as mortality and hospitalizations, have been conducted in cohorts primarily comprised of individuals of European descent; data on outcomes associated with PRISm in other races, ethnicities, and societies is modest. Second, the number of studies with longitudinal spirometry data remains limited. Among studies with such data available, the number of spirometry assessments typically ranges between two and three, often with extended periods between assessments. Third, data on anatomical, functional, or genomic variation that may contribute to the development, progression, and clinical outcomes associated with PRISm is also severely limited.

In this issue of the Journal, the study by Washio and colleagues (pp. 563–572), which examines both the cross-sectional features and longitudinal behavior of PRISm within a Japanese population-based...