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Postbronchodilator Reference Values: Should They Be the Norm?

When spirometry is used to identify the presence and severity of chronic obstructive pulmonary disease (COPD), pre- and postbronchodilator testing is typically performed. In normal populations, there is at most only a small bronchodilator response (1). As a result, prebronchodilator reference values have been used and compared with postbronchodilator results. The Global Lung Function Initiative (GLI) noted that lung function test results can be interpreted using only robust, relevant, and reliable reference values (2). Using data from nearly 100,000 nonsmokers (55% female subjects) aged 3–95 years from 72 centers and 33 countries, the GLI study showed that the FEV_1:FVC ratio is essentially independent of ethnic group and serves as a reliable, although imperfect, indicator of lung function. However, 9-year follow-up of another multicenter study, PLATINO (Projeto Latino-Americano de Investigação em Obstrução Pulmonar), which used prebronchodilator reference values, identified a substantial underdiagnosis of COPD (3). The subjects in that study who did not receive diagnoses of COPD until they returned after 9 years presented with similar clinical characteristics as those who were not diagnosed in the initial phase. For some time, there has been debate as to whether postbronchodilator reference values would be better than prebronchodilator reference values to identify individuals with COPD or at risk for developing COPD. The landmark GLI study did not explore the effect of using postbronchodilator reference values for interpreting spirometry results. Furthermore, there is limited information as to whether the use of postbronchodilator reference values has a significant impact in the clinical interpretation of spirometry results (4, 5).

In this issue of the *Journal*, Malinovschi and colleagues (pp. 461–471) report the results of the study (6). They set out to determine whether postbronchodilator reference values were more successful than prebronchodilator reference values to identify individuals with mild COPD. To do this, they used pre- and postbronchodilator reference values generated from SCAPIS (Swedish Cardiopulmonary Bioimage Study) (7) and assessed the value of using postbronchodilator reference values as opposed to prebronchodilator reference values in a random population sample. The authors also compared pre- and postbronchodilator reference values from SCAPIS with reference values from the GLI and PLATINO studies.

The study included 30,154 middle-aged adults, 50–64 years of age, evenly distributed between men and women, at six academic medical centers in Sweden. The SCAPIS postbronchodilator reference values were obtained from 10,156 nonsmokers without respiratory symptoms or respiratory disease, after inhaling 400 μg of salbutamol. The SCAPIS prebronchodilator reference values were derived from 1,498 individuals at one of the six centers. In addition to pulmonary function testing, participants underwent high-resolution computed tomography to identify emphysema and completed several questionnaires. Participants were divided into three groups: *1*) postbronchodilator FEV_1:FVC ratio greater than the lower limit of normal (LLN) using both the prebronchodilator and postbronchodilator reference values; *2*) postbronchodilator FEV_1:FVC ratio greater than the LLN using the prebronchodilator reference value but lower than the LLN using the postbronchodilator reference values; and *3*) postbronchodilator FEV_1:FVC ratio less than the LLN using both pre- and postbronchodilator reference values.

The authors report that using postbronchodilator reference values resulted in higher predicted median values and LLN values for the FEV_1:FVC ratio. When the higher predicted median and LLN values were used, the prevalence of postbronchodilator FEV_1:FVC ratio less than the prebronchodilator LLN was 4.8%, while that of postbronchodilator FEV_1:FVC ratio less than the postbronchodilator LLN was 9.9% in this general population. Importantly, the additional 5.1% of participants who had abnormal postbronchodilator FEV_1:FVC ratios only when using postbronchodilator reference values had more respiratory symptoms, more computed tomography–diagnosed emphysema (13.5% vs. 4.1%; $P < 0.001$), and more instances of self-reported physician-diagnosed COPD (2.8% vs. 0.5%; $P < 0.001$) than subjects with postbronchodilator FEV_1:FVC ratio greater than the LLN for both pre- and postbronchodilator reference values. Similar results were seen for FEV_1, but not for FVC.

The study has both strengths and weaknesses. Strengths include the large number of individuals recruited from SCAPIS, the age range of 50–64 years (a population most likely to have early or mild COPD), the even distribution of men and women, and the accompanying clinical data, including respiratory symptoms, diagnosis of emphysema, and physician diagnosis of COPD. These clinical findings demonstrate the clinical relevance of postbronchodilator reference values in this population. Weaknesses include the relatively homogeneous population regarding race, ethnicity, and geographic location (although this may also be a strength by increasing the ability to identify an effect in this population) and the fact that prebronchodilator reference values were obtained from only one of the six research sites. In addition, there were some differences with data compared with other studies, such as PLATINO. However, as noted by the authors, the lower dose of salbutamol (200 μg) used

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for postbronchodilator testing (8), or the different geographic location (South America), may explain some of the differences.

Overall, this study provides valuable new information, as well as the opportunity for the authors and others to initiate additional studies to examine diverse populations and settings and to determine if the findings in this study are relevant beyond Sweden. Then we will know with greater certainty whether postbronchodilator reference values should be the new norm. ■

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Unraveling the Distal Lung Destruction in Emphysema

The landmark study by Booth and colleagues (pp. 472–486) in this issue of the *Journal* hones our understanding of the loss of the terminal conducting airways and gas exchange areas in chronic obstructive pulmonary disease (COPD) by applying single-cell analyses of lung tissue from well-phenotyped individuals (1). The investigation builds on this group's previous discovery (2) that the terminal bronchioles, the smallest conducting airways, are the early battlegrounds of tissue destruction in COPD.

The study's ambitious objective was to create a comprehensive blueprint that sheds light on the structural, cellular, and extracellular matrix changes underpinning terminal bronchiole loss in COPD. The cross-sectional evaluation of more than 200 terminal bronchioles from 109 lungs of individuals with mild to moderate COPD and 24 with severe COPD, as gauged by Global Initiative for Chronic Obstructive Lung Disease criteria, compared with 82 lungs from ex-smokers without lung dysfunction used a multifaceted approach that included stereology, micro-computed tomography, nonlinear optical microscopy, imaging mass cytometry, and transcriptomics. Their findings unveiled that in addition to a net loss, the terminal bronchioles progressively narrow as COPD severity increases, a phenomenon marked by the loss of elastin fibers within alveolar attachments. The pathology of alveolar untethering was noticeable even in the early stages of the disease in the absence of emphysematous alveolar loss, suggesting that this step is one of the first events in the hallmark distal lung destruction of emphysema. Although the concept of matrix elastin and collagen fiber degradation has been the forefront paradigm of protease–antiprotease imbalance of emphysema pathogenesis for decades (3, 4), this report refines our understanding of its spatial and temporal association with centrilobular distal lung destruction.

Furthermore, the single-cell atlas identified inflammatory and immune cells concentrated in this region of interest, with proinflammatory M1-like macrophages and neutrophils being located within disrupted alveolar attachments, whereas adaptive immune cells such as naive T cells, CD4 and CD8 T cells, and B cells were adjacent to terminal bronchiole wall remodeling. The genetic landscape was also consistent with upregulation of genes involved in both innate and adaptive immune responses, IFN response, and neutrophil degranulation. The proximity of macrophages and degranulating neutrophils to areas of matrix disruption is consistent with the mechanistic involvement of matrix metalloproteinases and neutrophil elastase and other proteinases in distal lung destruction (5–7). With our increased appreciation of the lung macrophage heterogeneity, future studies will have to build on expanding on the phenotyping of macrophages associated with disruption of alveolar tethers. Potential candidates are $CD206^{+}/CD43^{-}$ interstitial

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