EDITORIALS

Insights into the Spectrum of Chronic Lower Respiratory Disease
Low Lung Function Is Still Bad

Chronic lower respiratory diseases (CLRDs) are a heterogeneous collection of disorders such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, interstitial lung disease, and others. The pulmonary community has spent a great deal of time and effort over the past 60 years focused on components of this spectrum of illnesses (1). Much of this focus has been on precise definitions of what makes up obstruction (2), restriction (3), bronchitis (4), asthma (5), emphysema (6), and the various degrees of overlap between these components (7).

One of the debates revolves around what we call people with a low vital capacity. The predictive value of the vital capacity goes back to its origins—people with lower values died more quickly (8). This manifestation of CLRD has gone by a number of different names. The term "restrictive lung disease" describes people with low total lung capacity as determined by measuring lung volumes. The challenge with this definition was that measurement of lung volumes is typically limited to clinical scenarios and was only rarely done in population-based studies. Researchers with only spirometric data had to decide what to do with people with evidence of impaired lung function who did not have evidence of obstruction. Although these people were not obstructed (based on their FEV_1 to FVC being above a certain threshold), they did not have "normal" lung function and, longitudinally, died more quickly than did people with normal lung function. This has resulted in new terminology, such as "restricted spirometry" (9), "restricted on spirometry" (10), "restricted spirometric pattern" (3), "nonspecific pattern" (11), and more recently "preserved ratio impaired spirometry" or PRISm (12). The only reason, however, that the ratio is "preserved" is that people with a low FEV_1 also have a low FVC; thus, it seems a "restricted" terminology is more accurate and descriptive.

In this issue of the *Journal*, Marott and colleagues (pp. 910–920) report findings from long-term follow-up of participants in the Copenhagen City Heart Study (13). Only prebronchodilator spirometry was available and restriction was defined using an FEV_1/FVC greater than the lower limit of normal (LLN) with an $FEV_1 < 80\%$. People with obstruction at any point (based on the FEV_1/FVC less than the LLN) were excluded from the analysis. Of note, the spirometers used differed between the initial evaluation in 1976–1978 or 1981–1983 and the follow-up examination in 2001–2003, with the later test establishing which of the four trajectories people were placed into.

Of the 543 people who were restricted at the baseline examination, 227 (41.8%) were seen at the follow-up examination and classified. This can be contrasted with the 933 of 1,727 (54.0%) people who were not restricted at the baseline evaluation. The known deaths were 62% higher (12.2% vs. 7.5%) in the restricted group, and it is likely that some of the other nonresponders, who were also overrepresented in the restricted group (31.7% vs. 26.0%), either had died or were too ill to participate in the follow-up examination. Understanding these numbers is critical to interpreting findings in this paper. For example, although 155 people who were restricted at baseline were no longer restricted at follow-up (and 72 were persistently restricted), the proportion of people who improved is not 155 of 227 (68.3%) but rather some value much closer to 155 of 543 (28.5%). This can be compared with a different cohort, such as the COPDGene trial (14); of those restricted at baseline who participated in the 5-year follow-up, 52.6% remained restricted, 25.1% became obstructed, and 22.2% improved to normal.

So how can one explain the transition from restricted to normal in these 155 people over the 25-year interval between the first and second evaluations? There are some clues in the data to help explain this. First, if one looks at the total change in FEV_1 between the two surveys, it was −622 ml in the persistently normal, −583 ml in the persistently restricted, but +23 ml in those that changed from restricted to normal. In addition, the FEV_1 as a percentage of predicted improved from 74 to 93% in the restricted to normal group, with an improvement in the FVC from 75 to 95% (Table 1). Note that also in Table 1, the normal group had an improvement from 95 to 100% for the FEV_1 and from 93 to 102% for the FVC. One explanation for the physiologically improbable improvement in lung function over 25 years is that people have variability in their lung function measurement that can be as high as 12% in normal people and nearly twice that in people with lung disease (15). Requiring people to be below a threshold to qualify for the restricted group (at baseline) could thus result in a regression to the mean phenomenon at the follow-up examination. Another possibility is a systematic error related to the change in spirometers between the baseline and follow-up visit. Support for this is seen in the percent predicted values being much higher (5% for FEV_1 and 9% for FVC) at the follow-up evaluation in participants who were normal (with neither restriction nor obstruction). My suspicion is that the subgroup of people who "improved" were actually normal at baseline and had either a bad day or a poor effort on spirometry, with this finding amplified by spirometers that underestimated lung function by 5–10%.

The final finding of interest is what happened to people who were restricted at the follow-up examination in the subsequent 15 to 17 years. COPD hospitalizations were higher in the restricted group (20.9% vs. 3.3%), as were total deaths (36.5% vs. 11.6%), as seen in Figures 3 and 4. When this cohort was previously examined in an analysis that focused on COPD (16), 49.3% of the participants with COPD at the follow-up examination had a subsequent COPD hospitalization and 44.4% died. The higher risk of COPD hospitalizations among the restricted group in the present study supports the concept that a restricted spirometry may reflect COPD in some patients, a viewpoint the COPDGene 2019 definition includes (7). In addition, in the sensitivity analysis that used the $FEV_1/FVC < 70\%$ to define obstruction rather than the LLN (Table E1 and Figures E2 and E3), the outcomes were nearly identical, suggesting that using this fixed ratio is a reasonable means of categorizing patients. This analysis also confirms findings from other studies that a low FEV_1, in the presence or absence of obstruction, is predictive of mortality (17).

To conclude, CLRDs include a spectrum of diseases with varying manifestations and clinical and physiologic characteristics. The analysis by Marott and colleagues has highlighted the importance of restricted spirometry in this important subgroup of patients (13). ∎

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