Grading the Severity of Obstruction in Mixed Obstructive-Restrictive Lung Disease

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Funding/Support: This work was supported by the Vermont Lung Center. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (http://www.chestpubs.org/site/misc/reprints.xhtml).

Background

The severity of obstructive pulmonary disease is determined by the FEV1 % predicted based on the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. In patients with coexisting restrictive lung disease, the decrease in FEV1 can overestimate the degree of obstruction. We hypothesize that adjusting the FEV1 for the decrease in total lung capacity (TLC) results in a more appropriate grading of the severity of obstruction.

Methods

We examined a large pulmonary function test database and identified patients with both restrictive (TLC < 80% predicted) and obstructive (FEV1/FVC < the lower limit of normal) lung disease. FEV1 % predicted was adjusted for the degree of restriction by dividing it by TLC % predicted. We compared the distribution of severity grading between adjusted and unadjusted values according to ATS/ERS criteria and determined how the distribution of severity would change based on asthma and COPD guidelines.

Results

We identified 199 patients with coexisting restrictive and obstructive lung disease. By ATS/ERS grading, the unadjusted data categorized 76% of patients as having severe or very severe obstruction and 11% as having mild or moderate obstruction. The adjusted data classified 33% with severe or very severe obstruction and 44% with mild or moderate obstruction. Of the corrected values, 83% resulted in a change to less severe obstruction by ATS/ERS guidelines, and 44% and 70% of patients, respectively, would be reclassified as having less severe obstruction by current asthma and COPD guidelines.

Conclusions


This method results in a more appropriate distribution of severity of obstruction, which should lead to more accurate treatment of obstruction in these patients.

**Abbreviations**

- **ATS**: American Thoracic Society
- **ERS**: European Respiratory Society
- **IPF**: idiopathic pulmonary fibrosis
- **ITS**: Intermountain Thoracic Society
- **PFT**: pulmonary function test
- **RV**: residual volume
- **TLC**: total lung capacity

Grading the severity of lung function impairment is currently based on American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, which determine severity based on FEV1 % predicted. The guidelines specifically recommend using the FEV1 % predicted to grade the severity of obstructive, restrictive, and mixed pulmonary disorders. The rationale for choosing the FEV1 as the measure of severity is based on epidemiologic data that strongly support FEV1 as a global measure of health. Although this makes sense as a measure of overall lung function impairment, using FEV1 to gauge the degree of obstruction in mixed disorders would be expected to overestimate the degree of obstruction because FEV1 is reduced from both the obstructive and the restrictive components of the underlying disease. Understanding this limitation is important clinically because the health-care provider may mistakenly use this estimate of the degree of obstruction to select therapy for the obstructive component based on current treatment guidelines for obstructive lung disease.

To address the issue of grading obstruction in the presence of restriction, Balfe and colleagues based the degree of obstruction on the FEV1/FVC ratio, as recommended by the Intermountain Thoracic Society (ITS). These authors theorized that the ratio would be a more accurate measure of the severity of obstruction in the presence of restriction. They compared their results to the severity of obstruction that would be suggested by the ATS guidelines in use at the time, which were essentially similar to the updated 2005 ATS/ERS guidelines. Both sets of guidelines were meant to help categorize the severity of any spirometric abnormality based on % predicted alone, but this approach was not necessarily meant to apply to the situation of obstruction in the presence of restriction, so called mixed disorder. Nevertheless, clinicians commonly use these guidelines to grade the severity of obstruction in any situation of obstruction, restriction, or mixed disorder. The results of the study by Balfe and colleagues showed a significant decrease in severity grades and, in fact, a complete reversal of the distribution of severity when compared with the ATS guidelines. In particular, the distribution of severity based on the ATS criteria was heavily weighted toward severe disease, whereas the ITS grading resulted in predominantly mild disease. Because restrictive lung disease commonly is associated with improved airflow (elevated FEV1/FVC ratio) due to increased radial traction of airways, it is not surprising that using the FEV1/FVC ratio to grade obstruction in the presence of restriction would skew the results toward more mild obstruction. In addition, assuming that the patients studied were chosen at random, we would have expected to see a more even distribution of severity, suggesting that neither the ATS/ERS nor the ITS guidelines are wholly accurate in evaluating the severity of obstruction in patients with mixed disorder.

We have taken a simple approach to address this issue by considering what would happen to the FEV1 in the setting of a pure parenchymal restrictive process. Theoretically, the FEV1, as a subdivision of the FVC, should be reduced in proportion to the total lung capacity (TLC),...
like all lung volumes. However, because the FEV1/FVC ratio is commonly increased in restrictive parenchymal disorders, [8] . [9] . [10] . [11] . [12] . [13] the true decrement in the FEV1 is actually slightly less than the decrement in TLC. To determine how FEV1 is altered in restrictive parenchymal lung disease, we examined lung function data published in studies of idiopathic pulmonary fibrosis (IPF) [8] . [9] . [10] . [11] . [12] . [13] and indeed found that the reduction in FEV1 was slightly less than the reduction in TLC (mean ΔFEV1/ΔTLC = 0.93). In the setting of concomitant obstruction (low FEV1/FVC ratio), we theorized that if we adjust the FEV1 for the proportional loss of TLC, the remaining decrement in FEV1 should be due to the obstructive component of disease. The resulting FEV1 % predicted would then be the measure by which to grade the degree of obstruction. We propose that this simple mathematical correction will result in a significant change in severity grading and will more accurately reflect the true degree of obstruction than either the current ATS/ERS or the ITS guidelines for severity grading.

Materials and Methods

We analyzed a large database of pulmonary function tests (PFTs) collected at St. Louis University Hospital. Equipment and techniques were unchanged throughout the study period and strictly conformed to ATS/ERS criteria for quality. [14] . [15] The study received exempt status approval from the St. Louis University Biomedical Institutional Review Board (#16311) and the University of Vermont Committees on Human Research (#10-055) because all data were deidentified at the time of analysis.

We identified all patients tested between 2003 and 2009 who had both restrictive lung disease, defined as TLC < 80% predicted, [16] and obstructive lung disease, defined as FEV1/FVC less than the lower limit of normal. [17] All tests met ATS/ERS criteria for acceptability and repeatability, and all predicted values were race corrected, as appropriate. [1] Although the ATS/ERS guidelines define restriction based on TLC less than the fifth percentile, we chose to define restriction based on TLC < 80% predicted because this allowed a simple formula for adjustment of FEV1 that would correspond to the ATS/ERS suggestions for grading severity using FEV1 % predicted. [1] Based on these guidelines, we graded the severity of obstruction using the unadjusted FEV1. We then adjusted the FEV1 for the degree of restriction by dividing FEV1 % predicted by TLC % predicted (or 1.07 × TLC % predicted) (e-Appendix 1), and all patients were again graded for severity using the adjusted value. To determine whether the adjusted value more accurately reflected the degree of obstruction, we compared the correlation between the unadjusted FEV1 and adjusted FEV1 vs the degree of air trapping as indicated by the residual volume (RV)/TLC ratio. To determine how the proposed strategy changed the severity grading, we compared the ATS/ERS grading of the adjusted value with the grading of the unadjusted value. We also compared the severity grading based on the adjusted values using the ATS/ERS system with the ITS grading system. [6] Finally, to determine any potential effect on therapy, we compared the severity grading of the adjusted and unadjusted values using the asthma [5] and COPD [4] severity grading guidelines because these guidelines are commonly used to recommend therapy based on the severity of obstruction.

All data were tabulated in a spreadsheet and analyzed for distribution using standard statistical software (JMP, version 8.0.2; SAS Institute Inc; Cary, North Carolina). All data are expressed as mean ± SD, unless otherwise specified. We calculated whether the coefficients of determination between the unadjusted and adjusted FEV1 and RV/TLC were significantly different by the method of Kleinbaum and colleagues. [18] In order to determine whether the distribution of severity grades was significantly different between the different grading systems, we used the Bowker test for symmetry. [19]

Results

We identified a total of 199 patients with coexisting restrictive and obstructive lung disease. Of these patients, 37% were women and 74% were white (Table 1). The mean age was 56 ± 14 years; the mean FEV1, 1.5 ± 0.6 L (42 ± 14% predicted); mean FEV1/FVC, 0.61 ± 0.06; and mean TLC, 4.5 ± 1 L (71 ± 7% predicted). Based on referral requests, patients had a variety of lung diseases, which were categorized into obstructive diseases (eg, asthma, COPD, bronchiectasis), interstitial lung diseases (eg, IPF, pulmonary edema), and extrapulmonary restriction (eg, kyphoscoliosis, obesity). Other categories included lung cancer; evaluation for heart, lung, liver, or kidney transplantation; and unexplained dyspnea. More than one-half were current or former smokers, and many such smokers presented with airflow obstruction (and restriction) diagnosed based on PFTs without having had a previous diagnosis of asthma, COPD, or other obstructive lung disease. The correlation between FEV1 and RV/TLC was significantly greater when using the adjusted than when using the unadjusted FEV1 (r² = 0.42 vs r² = 0.36, respectively; P = .01) (Fig 1), suggesting that the adjusted value more accurately reflects the degree of obstruction. By ATS/ERS grading, the unadjusted data categorized 76% of the patients as having severe or very severe obstructive disease, with 11% having mild or moderate disease (the remainder having moderately severe disease). The adjusted data set rated 33% with severe or very severe disease (the remainder having moderately severe disease). The adjusted data set rated 33% with severe or very severe disease and 45% with mild or moderate disease; this distribution was significantly different from that using the unadjusted values (P < .0001) (Fig 2). In comparison, by ITS guidelines, 98% were graded in the mild to moderate range, with < 1% in the severe category. Among the adjusted values, 83% of patients had a change in grading to less severe obstruction by ATS/ERS guidelines, and 44% and 70%, respectively, had a change to less severe obstruction based on the asthma and COPD severity grading systems (Fig 3). See e-Appendix 1 for the results based on adjusting the FEV1 by the more accurate factor of 0.93.
<table>
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<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age, y</td>
<td>56 ± 14</td>
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<tr>
<td>Sex, male (female)</td>
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<tr>
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<tr>
<td>White</td>
<td>74</td>
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<td>Black</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>Tobacco use</td>
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<tr>
<td>Current or former smoker, %</td>
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</tr>
<tr>
<td>Pack-years smoked</td>
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<td>Other[a]</td>
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<td>FEV₁, L (% predicted)[b]</td>
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<tr>
<td>FEV₁/FVC</td>
<td>0.61 ± 0.06</td>
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<tr>
<td>TLC, L (% predicted)[c]</td>
<td>4.5 ± 1.0 (71 ± 7)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or %, unless otherwise indicated. EPR = extrapulmonary restriction; ILD = interstitial lung disease; TLC = total lung capacity.

a See “Results” section for examples.

b National Health and Nutrition Examination Survey 3 data.[17]

c Goldman et al. [16]
Figure 1  Relationship between RV/TLC and FEV₁ % predicted. A, Unadjusted FEV₁ % predicted. B, Adjusted FEV₁ % predicted. The coefficients of determination (R² values) are statistically significantly different (P = .01). RV/TLC = residual volume/total lung capacity.

Figure 2  Comparison of ATS/ERS severity grading for adjusted and unadjusted FEV₁ % predicted. P value indicates significance of difference in distribution between the adjusted and unadjusted values. ATS/ERS = American Thoracic Society/European Respiratory Society.
Expert Panel Report 3 guidelines for grading the severity of airflow obstruction in asthma for adjusted and unadjusted FEV₁ % predicted. B, GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines for grading the severity of obstruction in COPD for adjusted and unadjusted FEV₁ % predicted. P values indicate significance of difference in distribution between the adjusted and unadjusted values.

Discussion

Current ATS/ERS guidelines recommend using the FEV₁ % predicted to grade the severity of lung disease in the presence of obstruction, restriction, or mixed disorders. Because FEV₁ is such a strong, independent predictor of health status, this recommendation is sensible. However, in the presence of mixed disorders, the severity of the obstructive component alone also might be assessed on the basis of FEV₁, an approach that would be expected to overestimate the degree of obstruction because the reduction in FEV₁ would reflect the combined effects of both the obstructive and the restrictive components. Based on our clinical observations and those of colleagues during informal discussions, we believe that this is commonly the case. This impression is supported clinically by the shape of the flow-volume and volume-time curves in such patients (Fig 4) because for the same FEV₁ % predicted, patients with mixed obstruction and restriction often have curves that suggest markedly less obstruction compared with curves from patients with pure obstruction. Despite apparent agreement that overestimation of the degree of obstruction occurs in the presence of restriction, no consensus has emerged on how to better grade the severity of obstruction in these patients.

Flow-volume and volume-time tracings for a patient with pure obstructive disease (COPD) and for a patient with combined obstructive and restrictive lung disease (COPD + idiopathic pulmonary fibrosis), roughly matched for age, sex, and FEV₁ % predicted. A, A 63-year-old man with COPD and an FEV₁ = 38% predicted. B, A 75-year-old man with both COPD and idiopathic pulmonary fibrosis.
with an FEV₁ = 43% predicted. Notice the obvious differences in signs of obstruction, with the patient in A having a more severely concave upward expiratory limb of the flow-volume loop and prolonged emptying on the volume-time tracing.

The approach presented by Balfe and colleagues [3] proposed using ITS criteria [6] to grade obstruction based on the FEV₁/FVC ratio, and indeed, this approach lowered the severity grade in most subjects. In fact, it showed a complete reversal in the distribution of severity grades to predominantly mild obstruction, which perhaps went too far and underestimated the true degree of obstruction. To correct this, Balfe and colleagues [3] recommended using the ITS grading in these patients but with modified CIs to normalize the distribution of severity grades. However, this strategy was not adopted in the current ATS/ERS guidelines possibly because the proposed grading system involved CIs, which may have been perceived as too complex and not in accord with current ATS/ERS guidelines based on the use of percentage of predicted values.

In the present study, we propose a simple adjustment to the currently used measure of severity (FEV₁) that is physiologically based and results in a more even distribution of severity grades. The higher coefficient of determination between the adjusted FEV₁ and the RV/TLC ratio compared with that of the unadjusted FEV₁ and the RV/TLC ratio is consistent with the concept that the adjusted value more closely reflects the obstructive component of disease. The more realistic even distribution of severity also supports the validity of this methodology. We believe that our method could be easily implemented into current ATS/ERS guidelines and would result in grading that better reflects the true degree of obstruction. Our results show that there would be a significant downgrading of obstruction by all guidelines, [1] , [4] , [5] Although it might appear that this change was greater for the ATS/ERS guidelines (83%) than the asthma or COPD guidelines (44% and 70%, respectively), it is difficult to interpret the importance of these differences because of the different grading intervals used in each guideline. However, we believe that any substantial downgrading of the severity of the obstructive component of a mixed disorder is clinically significant because such a change would be expected to lead to different treatment recommendations.

Medications used to treat more severe obstructive lung disease are expensive and can expose patients to unwanted or adverse side effects. If we can better diagnose the severity of obstruction, we can avoid using medications that are not indicated and incurring the costs and risks associated with their use.

We appreciate that there are some limitations to our findings. First, we based our analysis on a discrete set of PFTs from a single institution. The results, therefore, may not be applicable to other sets of data involving different patients. However, we believe that our data are likely representative of a broad range of patients because they came from a large urban hospital over a long period of time. Given the relative rarity of this combination of mixed obstructive and restrictive disease, [20] , [21] , [22] such a large data set was necessary in order to achieve adequate numbers of patients for analysis.

Second, we assumed that FEV₁ should be adjusted in direct proportion to TLC, but as noted previously, the actual adjustment factor is slightly less, so our current findings are skewed toward less severe obstruction (e-Appendix 1). However, the fact remains that these more accurately adjusted values still result in a distribution of severity ratings that is significantly less severe than not adjusting the FEV₁ at all. Given this result, and our intention to keep the adjustment as simple as possible for ease of use in the clinical setting, we advocate using the simpler one-to-one adjustment in the FEV₁ relative to the TLC in mixed disorders. However, one must be cautious in extrapolating any adjustment derived from data in patients with IPF to restrictive lung disease in general. Although all restrictive lung diseases result in decreases in TLC, not all do so in the same way relative to FEV₁ as does IPF. For example, restrictive disorders associated with changes in chest wall compliance [23] or muscle weakness [24] will affect FEV₁ and TLC differently than diseases that affect lung tissue compliance such as IPF. Slightly different correction formulas might be more accurate for these different patient populations; however, we maintain that our results are qualitatively robust because any type of correction that takes into account a proportional change in FEV₁ and TLC will reduce the severity grading of the obstruction, moving it closer to the true degree of obstruction.

Third, although we believe that the current method is more physiologically accurate in grading the severity of obstruction, we only have correlative data between the adjusted FEV₁ and RV/TLC, observations on the shape of the flow-volume and volume-time relationships, and clinical impressions to confirm this assumption. Further evidence that this approach is more valid would need to come from assessment of clinical response and outcomes in patients whose treatment was modified based on this new severity grading method.

In conclusion, we have demonstrated that grading the severity of obstruction in mixed obstructive-restrictive lung disease, based on adjusting FEV₁ for the degree of restriction, results in a more realistic distribution of the severity of the obstructive component that is no longer heavily weighted toward severe obstruction. This approach should result in more accurate treatment of patients based on the obstructive component of their mixed disorder.

Acknowledgments

Author contributions: Dr Kaminsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Gardner: contributed to the study design; data collection, analysis, and interpretation; and writing of the manuscript.

Mr Ruppel: contributed to the data collection and interpretation and review of the manuscript.
Dr Kaminsky: contributed to the study design; data collection, analysis, and interpretation; and writing of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Kaminsky receives research grant support from the National Institutes of Health, National Cancer Institute, and the University of Vermont and honoraria related to teaching from Medical Graphics Corporation and speaking from Merck & Co. Mr Ruppel has received honoraria as a speaker for Medical Graphics Corporation and has consulted with GlaxoSmithKline for quality assurance of pulmonary function studies. Dr Gardner has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: Data were collected at St Louis University Hospital and analyzed at the University of Vermont. We thank Peter Callas, PhD, University of Vermont, for his help with the statistical analysis.

Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/140/3/598/suppl/DC1.

Web Extra Material

Online Supplement

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