Re-Defining Lower Limit of Normal for FEV1/FEV6, FEV1/FVC, FEV3/FEV6 and FEV3/FVC to Improve Detection of Airway Obstruction

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Abstract

Background: Spirometric values of 5880 never-smoking black, Latin, and white men and women in the Third National Health and Nutrition Examination Survey (NHANES-3) reference population were reviewed. Good published equations for forced expiratory volume in 1 second (FEV1) over forced expiratory volume in 6 seconds (FEV6) and FEV1 over forced vital capacity (FVC) often significantly mis-identified the lower limit of normal (LLN) targets in both younger and older adults. To improve detection of smaller airways disease in adults, we wished to redefine the LLN for these ratios and develop new ones for forced expiratory volume in 3 seconds (FEV3)/FEV6 and FEV3/FVC.

Methods: In each of 6 ethnic/gender, never-smoking NHANES-3 groups, arranged sequentially by age from 20.0 to 79.9 years, the values of FEV1/FEV6, FEV1/FVC, FEV3/FEV6, and FEV3/FVC were placed in groups of 40 so that the actual lowest second (5%) ratios could be identified. The slopes and intercepts of the resulting 24 linear equations through these lowest 5% ratios were then each adjusted by multiple iterations to best identify equations which actually identified the lowest 5% in both younger and older adults.

Results: In all never-smokers, the new equations were closer to the 5% LLN targets than were those of Hankinson for FEV1/FEV6 and FEV1/FVC and Quanjer for FEV1/FVC. In 3508 NHANES-3 current smokers, the FEV3/FEV6 and FEV3/FVC identified significantly more values below LLN than the FEV1/FEV6 and FEV1/FVC.

Conclusion: New simple linear iterative equations for FEV1/FEV6, FEV1/FVC, FEV3/FEV6, and FEV3/FVC to identify LLN are offered. None require exponents or logarithms. The latter 2 detected more abnormalities in current-smokers and likely better identify small airways disease in adults.

Abbreviations: forced expiratory volume in 1 second, FEV1; forced expiratory volume in 3 seconds, FEV3; forced expiratory volume in 6 seconds, FEV6; forced vital capacity, FVC; lower limit of normal, LLN; Third National Health and Nutrition Examination Survey, NHANES-3; forced expiratory flow at 25%-75% of the forced vital capacity, FEF25-75%; forced expiratory flow at 25% of the forced vital capacity, FEF25%; forced expiratory flow at 50% of the forced vital capacity, FEF50%; forced expiratory flow at 75% of the forced vital capacity, FEF75%

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Introduction

After the introduction of spirometry by Hutchinson in 1846 and forced expiratory maneuvers by Tiffeneau in 1947, the ratios of FEV₁/FVC became the standard criterion for establishing the presence of airway obstruction. Because the ranges of absolute forced expiratory timed-volumes found in apparently normal individuals of the same gender, age, height, and ethnicity are so high, less-variable ratios of these same time-volumes are advantageous. The more recently introduced FEV₁/FEV₆ has the major advantage of avoiding the variability of the FVC duration inherent in the FEV₁/FVC. The extremely high inherent variability of the forced expiratory flow at 25%-75% (FEF₂₅-₇₅%), (and to a lesser extent the forced expiratory flow at 25% [FEF₂₅%] forced expiratory flow at 50% [FEF₅₀%] and forced expiratory flow at 75% [FEF₇₅%]) because both time and flow vary, has limited their utility. The FEV₁/ FVC has been less studied and the FEV₃/FEV₆ apparently not at all. Could the latter ratios be more specific and sensitive than the FEV₁/FEV₆ and FEV₁/FVC in detecting airway obstruction?

Traditionally, lower 95% confidence intervals calculated from mean values and their variability have been used to define the lower limits of normal (LLN) of the FEV₁/FVC. Because the distribution of abnormalities has usually been considered normal, these LLN have been calculated from age-declining FEV₁/FVC predicted mean values less 1.645 times the standard deviation (SD) of reference populations (apparently healthy and never-smoking) to define the 5% likelihood of airway obstruction in other individuals of the same age, gender, and ethnicity. Recently, Quanjer and colleagues, in a major advance, took into account the asymmetry of distribution of several spirometric values plus the differences between ethnicities. Their published equations (each with approximately 20 coefficients) assess many spirometric values, but, unfortunately, do not include any important ratios other than FEV₁/FVC.

Therefore, suspecting that these older ratios might not optimally target borderline individuals across the full adult age span and that FEV₃/FEV₆ and FEV₃/FVC might better define slower emptying airways, we wished to define the LLN for the FEV₁/FEV₆, FEV₁/FVC, FEV₃/FEV₆, and FEV₃/FVC ratios so that those ratios could be better utilized to validly compare the sensitivity and specificity of these spirometric ratios. Finally, we realized that multiple iterative techniques (changing the slope and intercept values) allowed us to best define LLN spirometric ratio equations as close as possible to 5% for each age, ethnicity, and gender.

Initially, using the original values of the best FEV₁, FEV₃, FEV₆, and FVC from the Third National Health and Nutrition Examination Survey (NHANES-3) databases of apparently healthy never-smokers, we were able to calculate, graph, tabulate, and identify the exact number of lowest 5% of values of the ratios of FEV₁/FEV₆, FEV₁/FVC, FEV₃/FEV₆ and FEV₃/FVC for each ethnic/gender group by age. Then, multiple iterations identified new LLN ratio equations to target, by age, -5% of the never-smoking reference population of each equation as abnormal. We hypothesized that these new equations might better identify airway obstruction in individuals and populations.

Methods

Study population: De-identified digital records of the informed-consent volunteers of NHANES-3 were obtained which included age, ethnicity, gender, height, weight, smoking and other history, measurements relating to their health and diet, and spirometric values of highest peak flow, FEV₁, FEV₃, FEV₆, and FVC. As can be seen in Table 1, the number of individuals in ethnic/gender/age groups differed widely. The spirometric values of the 6 groups, identified as black, white or Latin men or women had been used in 2 Hankinson and co-authors articles and our prior publications. Because selection criteria for normalcy may have differed minimally, the 5880 apparently healthy, never-smoking reference individuals selected in this study differed slightly from those selected in the Hankinson publications. Since the results of the 2 Hankinson publications for LLN values for FEV₁/FEV₆ were nearly identical (see below); the original ratio equations were ultimately used. For comparisons with current-smokers, spirometric measures from 3508 NHANES-3 current-smokers without other identifiable diseases were
Table 1. Number of Adult Reference Never-smokers in Each Group of the Third National Health and Nutrition Examination Survey

<table>
<thead>
<tr>
<th>Decade of Age</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>7th</th>
<th>8th</th>
<th>SUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Men</td>
<td>285</td>
<td>144</td>
<td>90</td>
<td>34</td>
<td>50</td>
<td>24</td>
<td>627</td>
</tr>
<tr>
<td>Black Women</td>
<td>370</td>
<td>304</td>
<td>191</td>
<td>97</td>
<td>103</td>
<td>76</td>
<td>1141</td>
</tr>
<tr>
<td>White Men</td>
<td>181</td>
<td>178</td>
<td>113</td>
<td>83</td>
<td>119</td>
<td>90</td>
<td>764</td>
</tr>
<tr>
<td>White Women</td>
<td>224</td>
<td>272</td>
<td>209</td>
<td>220</td>
<td>201</td>
<td>288</td>
<td>1414</td>
</tr>
<tr>
<td>Latin Men</td>
<td>303</td>
<td>165</td>
<td>95</td>
<td>46</td>
<td>70</td>
<td>18</td>
<td>697</td>
</tr>
<tr>
<td>Latin Women</td>
<td>426</td>
<td>312</td>
<td>199</td>
<td>85</td>
<td>158</td>
<td>57</td>
<td>1237</td>
</tr>
<tr>
<td>SUM</td>
<td>1789</td>
<td>1375</td>
<td>897</td>
<td>565</td>
<td>701</td>
<td>553</td>
<td>5880</td>
</tr>
</tbody>
</table>

Comparing equations for individuals in the ethnic/gender groups:
The original Hankinson, Odenkrantz, and Feder equations for FEV\(_1/\text{FEV}_6\), FEV\(_1/FVC\), FEV\(_3/\text{FEV}_6\), or FEV\(_3/FVC\) were used, since results from the FEV\(_1/\text{FEV}_6\) equations were nearly identical to those of the Hankinson, Crapo, Jensen equations and visually overlaid them graphically. Similarly, the FEV\(_1/FVC\), mean and LLN values from the Quanjer equations were calculated for each individual. Comparisons were then made using: 1) all new iterative equations for LLN values for younger and older individuals in the 6 ethnic/gender groups; 2) the Hankinson equations for the mean and LLN FEV\(_1/\text{FEV}_6\) and FEV\(_1/FVC\); 3) the Quanjer equations for mean and LLN FEV\(_1/FVC\); and 4) the Hansen, Sun, and Wasserman equations for mean FEV\(_1/FVC\), to detect abnormal ratios in never-smoking versus current-smoking populations.

Statistical analyses: \(\chi^2\) analyses were used to compare the number of abnormal ratios between groups with a \(p<0.05\) considered significant.

Results

Population and repeated iterative equations: Table 1 reveals the wide spread in the number of never-smokers in each NHANES-3 ethnic/gender/decade cell and the relative paucity of older individuals in the black and Latin groups. Table 2 shows the 24 equations developed by multiple iterations which best delineated approximately 5.0% of each group as <LLN for that group.

Comparing FEV\(_1/\text{FEV}_6\) equations: As an example, Figure 1 shows the FEV\(_1/\text{FEV}_6\) data for never-smoked, white women in groups of 40. The regression lines for the LLN as calculated by Hankinson et al. equations graphically overlap and differ visually from our iterative...
Table 2. Twenty-Four New Adult Iterative Equations Developed Using NHANES-3 Never-Smoking, Apparently Healthy Individuals

<table>
<thead>
<tr>
<th>Ethnic/Gender</th>
<th>n</th>
<th>%FEV₁/FEV₆</th>
<th>%FEV₁/FVC</th>
<th>%FEV₃/FEV₆</th>
<th>%FEV₃/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black, Men</td>
<td>627</td>
<td>76.15</td>
<td>76.8</td>
<td>96.65</td>
<td>98.0</td>
</tr>
<tr>
<td>Black, Women</td>
<td>1141</td>
<td>81.5</td>
<td>84.6</td>
<td>97.8</td>
<td>100.7</td>
</tr>
<tr>
<td>White, Men</td>
<td>764</td>
<td>73.8</td>
<td>74.5</td>
<td>96.45</td>
<td>95.5</td>
</tr>
<tr>
<td>White, Women</td>
<td>1414</td>
<td>78.0</td>
<td>80.2</td>
<td>98.15</td>
<td>101.5</td>
</tr>
<tr>
<td>Latin, Men</td>
<td>697</td>
<td>78.9</td>
<td>80.0</td>
<td>97.6</td>
<td>98.7</td>
</tr>
<tr>
<td>Latin, Women</td>
<td>1237</td>
<td>82.2</td>
<td>85.0</td>
<td>98.4</td>
<td>101.5</td>
</tr>
</tbody>
</table>

Regression equation: \( Y = mx + b \), where \( x \) is age (years), \( m \) is the slope (lower cells), and \( b \) is the Y intercept (upper cells).

NHANES-3 = Third National Health and Nutrition Examination Survey

Comparison of FEV₁/FVC equations: Overall, Table 4 indicates that younger versus older adults frequently have significant LLN differences using either the Hankinson (4 of 6) or Quanjer (3 of 6) equations. As an example of a group with lesser differences, Figure 2 shows the individual FEV₁/FVC values in never- and current-smoking Latin men plus the predicted means and LLN for the Hankinson and, Quanjer equations and the Hansen, Sun, Wasserman equation for mean and the new iterative equations for LLN. It is noteworthy that, though all equations show a decline in the ratio with age, the Quanjer mean equation (which includes height as a variable) is mildly concave upwards while the Quanjer LLN equation is mildly concave downwards. Thus, in this group, the differences between mean and LLN values are not constant but clearly increase with advancing age. The Hankinson LLN equation values for Latin men are consistently higher than those of the
intermediately positioned iterative equation. Further, in all 6 groups, but not shown, at ages 25, 35, 45, 55, 65, and 75 years, the Hankinson equations have the highest LLN values of the times, the Quanjer et al. equations have the lowest LLN values of the times, while the iterative equations give intermediate LLN values of the times, suggesting that the iterative equations are the best available to compare spirometric ratios.

**Comparing all iterative ratio equations:** Table 5. Assessing current-smokers, not surprisingly, the numbers (and percentages) of smoking-individuals below the LLN is much higher in the older (24.5% to 28.5%) than younger (8.5% to 10.5%) age groups (p<0.001). Importantly, there are significantly higher numbers and percentages of smokers below the LLN for the FEV$_3$/FEV$_6$ and FEV$_3$/FVC ratios, respectively, than for the FEV$_1$/FEV$_6$ (14.4%, $\chi^2=5.53$, p<0.05) and FEV$_1$/FVC (18.6%, $\chi^2=9.12$, p<0.01).

**Discussion**

**Summary of the challenge:** Admittedly, if the LLN of a population is set at exactly 5.0%, it is impossible to
Figure 2. FEV<sub>1</sub>/FVC Values of Never-smoking and Current-smoking Latin Men by Age

The green open circles are never-smokers, the solid red diamonds are current-smokers. Shown in upper part of figure are the means of predicted FEV<sub>1</sub>/FVC by Quanjer<sup>15</sup> (wavy red), Hansen<sup>10</sup> (solid black), and Hankinson<sup>4</sup> (dashed lavender), and lower in figure, with the same colors, the LLNs predicted by Hankinson, iterative process, and Quanjer. As years of age increase, the Quanjer mean equation is concave upward while Quanjer LLN equation is concave downward. The Hankinson equations are parallel. The iterative mean and LLN equations are located between the Quanjer and Hankinson equations.

The variability of absolute values of FEV<sub>1</sub>, FEV<sub>3</sub>, FEV<sub>6</sub>, and FVC in individuals of a specific height, gender, ethnicity, and age is high, higher than the variability of the ratios of these values.<sup>3</sup> Thus ratios became important in identifying obstructive airways disease.

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For decades, the FEV₁/FVC has been the favored ratio to evaluate obstruction. The more recently introduced FEV₁/FEV₆, though still infrequently used, has high sensitivity and specificity by meta-analysis, has advantages over the FEV₁/FVC in that the latter has a shifting denominator from test to test and laboratory to laboratory - because breath duration times vary - while the FEV₁/FEV₆ has a fixed denominator, is less stressful for patients, and appears to evaluate airway obstruction as well as or better than the FEV₁/FVC when normality and abnormality are defined according to the bottom 5% as detailed in this paper.

Ratios derived later in forced exhalations have rarely been used, although FEV₃/FVC has been asserted to be of value. Many authorities have accepted the assumption that the exponential-like curves seen when expiratory volumes are plotted against time are adequately defined by the FEV₁/FEV₆ or FEV₁/FVC ratios. The possible additional value of FEV₃/FEV₆ and/or FEV₃/FVC has largely been ignored. Because data from large reference or diseased populations for other time points in the exhalation were not available,
our decision was to evaluate FEV3/FEV6 and FEV3/FVC ratios. In the NHANES-3 population, it appears that in the detection of abnormal airway obstruction in current-smokers, the FEV3/FEV6 is superior to the FEV1/FEV6 (18.6% more, \textit{p}<0.01) and the FEV3/FVC is superior to the FEV1/FVC (14.4%, \textit{p}<0.05) (Table 5). With further evaluations, we suspect the FVC ratios may be less discriminating than the FEV6 ratios because of the uniform denominators of the latter.

\textbf{Limitations:} Testing the new equations in other populations would be advantageous. It would be helpful to have larger numbers of healthy older individuals in a reference population. Perhaps an age other than 45 years would be preferable for separating younger from older smokers. That age was selected since \textit{a}) age 45, rather than later ages, helps equalize the group sizes and \textit{b}) the severity of airway obstruction in surviving current-smokers increases significantly in the 5\textsuperscript{th} decade of life.\textsuperscript{17} Although the effect of changing the LLN value of ratios a few percentage points away from 5% remains uncertain, it seems likely that in comparing the sensitivity of different spirometric ratios, it is best to use ratios with approximately the same percentage (presumably ~5%) of LLN in the reference population. The evaluation of specificity should be more relevant when the available ratios are compared with nonspirometric evidence of airways disease, such as inspiratory and expiratory chest imaging.

\textbf{Conclusion:} To compare the value of different spirometric ratios in detecting airway disease, the ratios should identify approximately 5% of apparently normal reference individuals as below the LLN throughout the age span being considered. New simple linear iterative equations which do that for FEV1/FEV6, FEV1/FVC, FEV3/FEV6, and FEV3/FVC are offered. The latter 2 likely better identify small airways disease in adults. We suggest that these equations be further tested in routine spirometric evaluation of airway obstruction in adults and that consideration should be given to using FEV3 ratios as well as FEV1 ratios.

\textbf{Acknowledgments}

We appreciate the high quality participation of the many volunteer participants, health professionals, and others who assembled and organized these data and the U.S. Department of Health and Human Services which made these data available for us to use. \textbf{Author comments regarding prior publications:} Some of the NHANES-3 data used in this manuscript have been used for other purposes (i.e. LLN = mean $-1.645\ \text{times SD}$) in the following publications:


\textbf{Declaration of Interest}

JP has received consulting fees from Boehringer Ingelheim.


References


