Calculation of Provocative Concentration Causing a 20% Fall in FEV₁*
Comparison of Lowest vs Highest Post-Challenge FEV₁

Beth E. Davis, BSc; and Donald W. Cockcroft, MD, FCCP

Background: Considerable, unexamined controversy exists surrounding the use of the highest vs the lowest FEV₁ for calculating the provocative concentration causing a 20% fall in FEV₁ (PC₂₀) during direct bronchoprovocation challenges.

Objective: To compare the PC₂₀ calculated using the lowest FEV₁ post-diluent and post-histamine/methacholine vs the PC₂₀ calculated using the highest FEV₁ post-diluent and post-histamine/methacholine.

Method: Retrospective analysis of 225 challenges: 75 research methacholine challenges, 75 research histamine challenges, and 75 clinical methacholine challenges. For each test, the PC₂₀ was calculated twice, first using the lowest post-diluent FEV₁ to the lowest post-histamine/methacholine FEV₁, and then using the highest to the highest.

Results: The intraclass correlation coefficients for methacholine research, histamine research, and methacholine clinic challenges were 0.99, 0.98, and 0.95, respectively. The PC₂₀ calculated using the lowest to lowest FEV₁ was slightly and significantly lower in all three groups (paired t test p < 0.0001).

Conclusions: The PC₂₀ values calculated using the highest FEV₁ are almost identical to the PC₂₀ values calculated using the lowest FEV₁. The difference, although clinically irrelevant, holds statistical significance.

(CHEST 2000; 117:881–883)

Key words: airway hyperresponsiveness; FEV₁; methacholine; provocative concentration

Abbreviations: ICC = intraclass correlation coefficient; PC₂₀ = provocative concentration causing a 20% fall in FEV₁

Direct-acting nonselective chemical stimuli such as methacholine and histamine are commonly used to induce bronchoconstriction in both clinical and research settings for the purpose of assessing and investigating airway hyperresponsiveness. The end point of these bronchoprovocation challenges is the provocative concentration causing a 20% fall (PC₂₀) in the FEV₁. The algebraic calculation of the PC₂₀ and the tidal breathing method used to generate the variables required for the calculation are widely accepted and commonly used. There is however disagreement as to which FEV₁, the highest or the lowest, should be used to calculate the PC₂₀. We arbitrarily choose the lowest post-diluent to the lowest post-histamine/methacholine, as do others; however, many investigators prefer to use the highest to the highest. There is little or no evidence in the current literature to support which is right and no data comparing the two methods. This retrospective study was done to compare the PC₂₀ calculated with both the lowest and the highest FEV₁.

Materials and Methods

Collection of Data

We retrospectively collected single, technically acceptable FEV₁ data recorded at 30 s and 90 s after inhalation, from either
methacholine or histamine bronchoprovocation challenges (2 min tidal breathing method) and assigned the data to one of three groups: methacholine challenges conducted in a research laboratory, methacholine challenges conducted in a clinical pulmonary function laboratory, and histamine challenges conducted in a research laboratory. A total of 225 tests were collected, 75 tests per group. Selection criteria consisted of a percent fall in FEV\textsubscript{1} after inhalation of the final concentration of methacholine or histamine of \( >20\% \) and administration of at least two doubling concentrations of methacholine or histamine. For subjects who had multiple tests, we used the first test identified that met the above criteria.

### Data Analysis

We recorded both the lowest FEV\textsubscript{1} and the highest FEV\textsubscript{1} measured at 30 s or 90 s following diluent and following the last two concentrations of histamine or methacholine. Percent fall in FEV\textsubscript{1} was then calculated using both the highest post-diluent to highest post-histamine/methacholine data, and the lowest post-diluent to lowest post-histamine/methacholine data. The PC\textsubscript{20} was then calculated from the standard formula:\textsuperscript{4}

\[
\log \text{PC}_{20} = \log C_1 + \frac{(\log C_2 - \log C_1)(20 - R_1)}{(R_2 - R_1)}
\]

where \( C_1 \) = second-to-last concentration, \( R_1 \) = second-to-last response, \( C_2 \) = last concentration, and \( R_2 \) = last response.

In some instances, the response calculated using the highest FEV\textsubscript{1} was \(<20\%\). In these situations, the PC\textsubscript{20} was calculated by extrapolation using the single point formula.\textsuperscript{7} The geometric mean PC\textsubscript{20} values were compared using a paired \( t \) test, and the reproducibility was examined using the intraclass correlation coefficient (ICC).\textsuperscript{8}

### Results

For all three groups, as illustrated in Figure 1, the PC\textsubscript{20} using the highest FEV\textsubscript{1} is almost identical with the PC\textsubscript{20} using the lowest FEV\textsubscript{1} (methacholine research ICC = 0.99, histamine research ICC = 0.98, and methacholine clinic ICC = 0.95). For all three groups, the geometric mean PC\textsubscript{20} (Table 1) calculated using the lowest to lowest FEV\textsubscript{1} was slightly, but significantly, lower than that calculated using the highest \( (p < 0.0001) \).

### Discussion

The results indicate a high level of reproducibility and reliability for the calculation of PC\textsubscript{20} that is independent of the FEV\textsubscript{1} used. Despite the strong similarity between end points, we prefer the lowest FEV\textsubscript{1} due to the transient and rapid mechanism of action of these types of constricting stimuli, in both their onset and recovery.\textsuperscript{9} The purpose of the test is to constrict the airways and to measure this constriction or hyperresponsiveness by way of a decrease in FEV\textsubscript{1}; therefore, using the lowest FEV\textsubscript{1} would serve to capture the maximal response to the constricting agent. In contrast, tests of bronchodilation or indirect challenges, such as exercise and allergen, commonly use the highest FEV\textsubscript{1} due to the much slower time course in both the onset and recovery of drug efficacy and mediator release.\textsuperscript{10,11} Others choose the highest FEV\textsubscript{1} during direct challenges to avoid an overestimation of the response that could potentially result from recording a falsely low FEV\textsubscript{1}. The likelihood of recording a falsely low FEV\textsubscript{1} should be minimal when the maneuvers are performed in the presence of experienced technicians and by well-trained subjects. As is our practice, any spirogram that does not meet American Thoracic Society guidelines\textsuperscript{12} should be discarded and repeated immediately. Conversely, using the highest FEV\textsubscript{1} may in fact fail to capture the maximal response of these types of

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**Figure 1.** Comparison of PC\textsubscript{20} values calculated using the highest FEV\textsubscript{1} (y axis) with PC\textsubscript{20} values calculated using the lowest FEV\textsubscript{1} (x axis) for each group. Lines represent linear regression (ie best fit).
constricting agents due to the rapid recovery. The importance of well-trained technicians and subjects in recognizing and performing acceptable spiromgrams is again applicable and may, in part, be evidenced by the higher ICCs of the two research groups compared to that of the clinic group.

We used a retrospective approach to avoid any possibility of bias in the selection and retention of FEV₁ values. A study such as this cannot determine which method is "correct" and has in fact provided evidence that either value can be used with no clinical relevance on the outcome. However, enhancement of the level of standardization of bronchoprovocation challenges aside, we believe use of the lowest FEV₁ makes empirical sense, and the slight but highly significant difference in the results warrants a need for consistency in the recording of FEV₁, certainly within a given study and perhaps within a given research setting.

### Table 1—Geometric Mean PC₂₀ *

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Calculated Using Lowest FEV₁</th>
<th>Calculated Using Highest FEV₁</th>
<th>p Value</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine research</td>
<td>0.77</td>
<td>0.84</td>
<td>&lt; 0.0001</td>
<td>0.99</td>
</tr>
<tr>
<td>Histamine research</td>
<td>2.0</td>
<td>2.3</td>
<td>&lt; 0.0001</td>
<td>0.98</td>
</tr>
<tr>
<td>Methacholine clinic</td>
<td>2.2</td>
<td>2.5</td>
<td>&lt; 0.0001</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Data are expressed in milligrams per milliliter unless otherwise indicated.

REFERENCES

4. Juniper EF, Cockcroft DW, Hargrave FE. Histamine and methacholine inhalation tests: tidal breathing method; laboratory procedure and standardisation. 2nd ed. Lund, Sweden: AB Draeco, 1994