Acute Postbronchodilator Changes in Pulmonary Function Parameters in Patients with Chronic Airways Obstruction*

Rolando Berger, M.D., F.C.C.P.; and David Smith, M.D.

Pulmonary function studies were performed before and after one-time administration of an inhaled bronchodilator to ascertain the relative diagnostic value of using FVC, FEF25-75%, static lung volumes, Raw, and/or sGaw measurements, in addition to the FEV1, to assess the reversibility of chronic Airways obstruction in nonasthmatic patients. A total of 517 patients underwent 686 spirometric tests, 264 (38 percent) of which disclosed a significant response to bronchodilators. In 247 (93 percent) studies, this response included a significant change in FEV1, and/or FEF25-75%, while in 17 studies (7 percent), the postbronchodilator improvement was seen exclusively in the FVC measurement. It is concluded that, in the clinical setting, analyzing static lung volumes, Raw, sGaw, and spirometric parameters other than the FEV1, seldom yields meaningful additional information regarding the reversibility of chronic Airways obstruction in nonasthmatic patients. Finally, potentially misleading results can be seen in a relatively small proportion of studies due to errors in the FVC and/or FEF25-75% measurements.

It is common clinical practice to include an assessment of reversibility as part of the diagnostic evaluation of patients with asthma or other obstructive pulmonary diseases. Although specific reversibility criteria have been published by the American College of Chest Physicians,1 controversy regarding their adequacy has persisted for many years.24 Specific criticisms have been directed against the use of postbronchodilator changes in the FVC and/or the FEF25-75% as reliable markers of reversible obstruction, either because these parameters were considered to add little or no additional information in most patients, or because they were felt to be potentially misleading.5-8 Similarly, a study by Light et al9 suggested that, for this purpose and despite their higher sensitivity, Raw and sGaw determinations often do not provide meaningful additional information.

Theoretic considerations notwithstanding, aside from a paper by Ramsdell and Tisi,10 several published studies11-13 have been done on relatively few patients and often including a large proportion of patients known to have asthma. Thus, it is not clear from these data with what frequency the FVC, FEF25-75%, static lung volumes, Raw, and/or sGaw measurements really contribute to the assessment of reversibility of Airways obstruction in nonasthmatic but otherwise unselected patients, or how often potentially misleading postbronchodilator changes in some of these parameters are actually seen in the clinical setting; we designed this study to answer these questions.

Patients and Methods

We reviewed approximately 1,350 pulmonary function studies, randomly selected from among 2,500 tests performed before and after bronchodilation in two clinical laboratories over a period of four years. We eventually accepted for analysis those studies which met the following criteria:

1. The patient was referred for pulmonary function testing because of a clinical diagnosis of chronic obstructive Airways disease.4
2. The patient did not have a pre-established diagnosis of bronchial asthma.4
3. The patient had not used an inhaled bronchodilator within four hours before testing.4
4. The requested tests of pulmonary function were performed before and after supervised one-time administration of inhaled metaproterenol via a commercially available metered-dose inhaler, using a spacer device whenever considered necessary by the technician. The standard dose protocol was to administer one puff every one to two minutes for a total of three doses, with postbronchodilator testing being done five to ten minutes after the last dose.4
5. Studies done before and after long-term therapeutic trials with one or more bronchodilator drugs were not included in this study.4
6. All spirometric tests were performed in accordance with accepted standards for an adequate valid study.14,15 and under the supervision of certified pulmonary function technicians who had a combined experience in pulmonary function testing of over 30 years at the VA laboratory, and of over ten years at the university facility.4

The pulmonary function testing equipment used in both clinical laboratories during the study period met ATS standards. Spirometry was performed at the VA Medical Center with two computerized systems using a water-seal spirometer. At the University Hospital, spirometry was performed with an automated system using a pneumotachograph and X-Y recorder.

For editorial comment see page 452

*From the Division of Pulmonary and Critical Care Medicine, Veterans Administration and University of Kentucky Medical Centers, Lexington, Ky., and the Division of Pulmonary Medicine, University of Tennessee Center of Health Sciences, Memphis. This study was supported in part by the Biomedical Research Support grant RR-00074 from the Biomedical Research Support Branch, Division of Research Facilities and Resources of the National Institutes of Health.

Manuscript received June 4; revision accepted August 17.

Reprint requests: Dr. Berger, VA Medical Center 111-1, Lexington, KY 40511.
Because of the intrinsic variability of repeated spirometry measurements done in patients with chronic obstructive lung disease, Acute 9 and for the purpose of this study, we defined "significant improvement" as a postbronchodilator increase from baseline of more than 15 percent for the FEV₁ and the FVC, and of more than 20 percent for the FEF25-75%. We accepted as indicative of reversible airways obstruction a significant improvement in two of these parameters, or an isolated significant improvement in FEV₁ if the corresponding FVC or FEF25-75% also improved by at least 10 or 15 percent, respectively.

Whenever the FEF25-75% or the FVC improved without a concomitant significant increase in the FEV₁, the FEF25-75% was volume-adjusted for any simultaneous change in the FVC, and flows during the latter portion of the tracing, eg. FEV₁, FERV, FEF25-75% and/or FEV₁ were specifically measured. We accepted an isolated postbronchodilator increase in FVC as representing true improvement if the increase resulted from enhanced flows in the latter portion of the curve, or if the post-bronchodilator FVC maneuver had a longer duration and the shorter predilation effort had been stopped after reaching a plateau of zero airflow. Similarly, a significant improvement in FEF25-75% was accepted if it persisted after volume-adjustment of this measurement was done as previously described, although isolated improvements in this parameter were not considered evidence of reversible airways obstruction.

Static lung volumes, Raw, and sGaw were determined before and after bronchodilatation using the body plethysmography technique. In the VA laboratory, this was done with a variable-pressure body box and an amplifier-recorder system. Similarly, in the University's laboratory, these tests were performed on a variable-pressure body box connected to an amplifier-recorder. For our study, a change of over 15 percent from baseline was considered significant for TLC, FRC, and RV, while a change of over 20 percent was required for the Raw and sGaw measurements.

RESULTS

Of all the studies reviewed, 686 studies done on 517 patients were eventually accepted for analysis in accordance with our selection criteria. Besides a pre-established diagnosis of bronchial asthma, patients were excluded from consideration only if their pulmonary function studies were considered to be unsatisfactory for adequate interpretation, i.e., suboptimal expiratory efforts, one or both FVC maneuvers lasting less than six seconds, or unavailability of the original spirometry tracings), or because the patient had used an inhaled bronchodilator prior to testing.

The average age of our study patients was 59 years, (range 17 to 88), including 403 men (78 percent) and 114 women (22 percent). At the time of testing, 91 percent of the patients were recorded as being smokers or exsmokers, 5 percent as nonsmokers, and in 4 percent, it was not specified.

Table 1 shows the baseline spirometry data from the 686 studies included in the study. Table 2 summarizes the proportion of spirometric test results which showed a positive response to the inhaled bronchodilator, as well as the relative contribution of each specific parameter to the final interpretation of the study. In our series, there was no significant difference in the baseline values of spirometry between the patients who were flow responders, (improved FEV₁ and/or FEF25-75%), and those who were volume responders, (improved FVC only). Responsive studies as a whole, however, did show a more severe degree of baseline obstruction than the nonresponsive ones (Table 1).

In the overwhelming majority of responsive studies, (231 of 264 or 88 percent), a significant increase in the FEV₁ was part of the bronchodilator response. In 99 of the spirometric test results which did not show a significant increase in the FEV₁, a significant but isolated postbronchodilator improvement in FVC, (75 cases) or FEF25-75% (24 cases) was shown on the numerical report of the study. On further analysis of the individual spirometry tracings, however, in 58 (77 percent) cases of isolated FVC improvement and in 22 (92 percent) cases of isolated FEF25-75% improvement, the increase in these parameters was found to be the result of technical differences between the prebronchodilator and postbronchodilator measurements.

As shown in Table 3, more than one prebronchodilator and postbronchodilator study was available for analysis in 86 patients, with a mean interval between consecutive tests of 21 weeks, (range five days to 19 weeks).

Table 2—Baseline (Prebronchodilator) Spirometry Values in 686 Studies*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>FVC</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*All values are given as mean ± SD. The FVC, FEV₁, and FEF25-75% are expressed as the percent of the predicted normal value. "Flow-responsive" refers to a significant postbronchodilator improvement in the FEV₁, and/or the FEF25-75%, and "volume-responsive" to an isolated improvement in the FVC.

Table 3—Results from 517 Patients who had Spirometry Performed Before and After Metaproterenol Inhalation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>FVC</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*See text for explanation of reversibility criteria. The volume-adjusted FEF25-75% was used to assess reversibility in all studies which did not show a concomitant significant increase in FEV₁.

†See text for explanation of "false" and "true" improvement in FVC or FEF25-75%.
Table 3—Results of Repeated Spirometries on 86 Patients

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>No. of Patients with Conflicting Results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>50</td>
<td>12 (24)</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>7 (39)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4 (50)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>3 (75)</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3 (100)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2 (100)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Totals</td>
<td>86</td>
<td>33 (38)</td>
</tr>
</tbody>
</table>

*Repeated testing before and after bronchodilators was always done on different days. “Conflicting results” means that the same patient could be considered responsive to bronchodilators on the basis of one or more of the tests, and nonresponsive on the basis of others. Postbronchodilator conductance, besides

months. Apparently conflicting results (ie, responsive on some tests and nonresponsive on others) were observed in 33 (38 percent) of these patients. If only those patients with four or more studies are considered, 14 of 19 (74 percent) showed this type of results.

Finally, 42 studies done on 34 patients included, besides spirometry, concomitant determinations of static lung volumes, airways resistance, and specific conductance, done before and after one-time bronchodilator treatment. Isolated improvements in Raw and/or sGaw were found in 19 studies with a simultaneous nonresponsive spirometry. Significant postbronchodilator improvement in static lung volumes (TLC, FRC, and/or RV) was seen in only four studies which were nonresponsive by spirometry criteria, and in two of these cases, there also was a concomitant significant improvement in Raw and/or sGaw. The most relevant results from the plethysmographic studies are presented in Table 4.

**DISCUSSION**

The assessment of reversibility in chronic airways obstruction is a somewhat confusing subject and the source of persisting debate.47 The ACCP guidelines for the assessment of reversibility of airways obstruction,1 though certainly helpful, do not address the methodologic aspects5-9 of using the FVC and FEF25-75% measurements for this purpose. Similarly, although the limitations of testing only once are clearly acknowledged, other recommendations in the ACCP document are general statements and thus necessarily vague. Questions about the proper role and clinical usefulness of specific parameters have been raised,4-6,11,15,22 and even the clinical value of one-time testing for reversibility in suspected cases of bronchial asthma has been questioned.44 Finally, although in the clinical setting, the percentage of postbronchodilator change from baseline in various parameters is routinely used to interpret this type of study, the validity of such an approach is not established,4-5 and inconsistencies in interpretation among different clinicians have been reported.45

Potential limitations notwithstanding, and aside from research and epidemiologic studies, the common clinical practice of assessing the degree of reversibility of airways obstruction in individual patients is largely based on the widespread perception (albeit a controversial and unproven one) that establishing marked reversibility does one or more of the following:40-42 (a) supports a diagnosis of asthma; (b) justifies aggressive bronchodilator therapy; (c) may predict a positive response to corticosteroids, and thus, justifies their use in cases with relative contraindications and/or marginal indications for their use; (d) implies a better prognosis than "fixed" obstruction. The latter three points could be particularly relevant for nonasthmatic patients because of the increasing reluctance among some physicians to indiscriminately treat patients with "irreversible" chronic airways obstruction with theophylline and corticosteroids due to the important cost and risk-benefit considerations of such an approach.40-42

The data in Table 2 show that when a significant response to the inhaled bronchodilator was established by spirometric criteria, a significant improvement in FEV1, was present in the overwhelming majority of cases: 231 of 264 studies or 88 percent. Isolated improvements in the FVC were seen in only 17 patients, accounting for 7 percent of the "responsive" spirometric test results or 2 percent of the total number of studies. Furthermore, three of the patients with isolated FVC responses had another similar study done on a different day, and in two patients, this new study showed a significant improvement in FEV1.

In our study, the proportion of patients who showed an isolated volume (FVC) response to bronchodilatation is lower than that previously reported by Ramsdell and Tisi,48 who observed it in 19 percent of their 241 patients. However, as pointed out by Block,49 in that study the FEV1/FVC ratio and the FEF25-75% mea-

---

**Table 4—Additional Diagnostic Contribution of Raw and sGaw Measurements**

<table>
<thead>
<tr>
<th>No. of studies (%)</th>
<th>Raw Improves</th>
<th>sGaw Improves</th>
<th>Both Improves</th>
<th>Neither Improves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsive by</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>spirometry (10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients)</td>
<td>(24)</td>
<td></td>
<td>(10)</td>
<td>(90)</td>
</tr>
<tr>
<td>Nonresponsive by</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>spirometry (28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients)</td>
<td>(76)</td>
<td>(3)</td>
<td>(15)</td>
<td>(41)</td>
</tr>
<tr>
<td>Both types of</td>
<td>1</td>
<td>6</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>study combined</td>
<td>(100)</td>
<td>(2)</td>
<td>(14)</td>
<td>(53)</td>
</tr>
</tbody>
</table>

*Four patients had two separate studies done on different days, one with a responsive and one with a nonresponsive spirometry, and thus, these patients were counted twice, once in each group.
measurement, rather than the FEV\textsubscript{1}, \textit{per se}, were used to determine improvement in expiratory flows. Although these parameters did not change, the mean improvement in FEV\textsubscript{1} in patients considered to be “isolated volume responders” was reported to be 13 percent, which suggests that some of them actually had a greater than 15 percent improvement. Similarly, it is not entirely clear if all postbronchodilator FEF25-75\% measurements were volume-adjusted, nor is it clear if the increases in FVC were due to enhanced flows in the latter portion of the expiratory maneuver or simply due to a longer expiratory effort.

We found 58 spirometry test results which showed an apparently significant postbronchodilator increase in the FVC without a corresponding significant improvement in the FEV\textsubscript{1}. In agreement with Girard and Light’s\textsuperscript{7} recommendation, we elected to consider these findings as having an indeterminate meaning, because in all cases, the increase in FVC was exclusively due to a longer duration of the postbronchodilator maneuver. Although this type of improvement may still reflect true bronchodilatation,\textsuperscript{7,14} we believe that this cannot be stated with certainty unless there also is a measurable improvement of late flows (\textit{i.e.,} FEV\textsubscript{1}, through FEV\textsubscript{4}), or the shorter pretreatment FVC effort is stopped after reaching a plateau of zero airflow.\textsuperscript{7} Nonetheless, if we were to consider these patients as also being truly responsive to bronchodilators, our proportion of “isolated volume responders” would then increase to 14 percent of the total number of patients (75 of 517), a value quite similar to the 19 percent (46 of 241) reported by Ramsdell and Tisi.\textsuperscript{18}

In regard to the FEF25-75\% measurement, Newball,\textsuperscript{10} Stitson et al.,\textsuperscript{13} and others\textsuperscript{6,9,12} have shown that it may often change unpredictably and in a paradoxical direction after the administration of a bronchodilator or bronchonoconstrictor agent, especially when the FVC also changes. Thus, in our study, if the FEV\textsubscript{1} did not improve significantly after bronchodilator but the FEF25-75\% did, we re-measured this latter parameter on a FVC of the same volume as the original pretreatment determination.\textsuperscript{6,9,13} It must be emphasized, however, that we did not volume-adjust all FEF25-75\% measurements by only those which fit the above description. Thus, among 422 spirometry tests which showed no significant postbronchodilatation improvement in either the FVC or the FEV\textsubscript{1}, 24 studies (6 percent) reported a greater than 20 percent improvement in the FEF25-75\%. In 22 of these cases, the volume-adjusted posttreatment FEF25-75\% was no longer significantly different from the predilatation value.

An observation which deserves a special comment is the fact that in our study, almost one third of the spirometry tests which showed a significant postbronchodilator improvement in FVC and FEV\textsubscript{1} reported either no significant improvement in the FEF25-75\% or a posttreatment value which was actually lower. As stated before, paradox postbronchodilator changes in FEF25-75\% have been reported previously\textsuperscript{6,9,12,13} and in our study, they reflect the fact that isovolume measurements of the FEF25-75\% cannot be routinely performed with a computerized spirometry system. However, since these specific patients had already met our criteria for reversible airways obstruction on the basis of their FVC and FEV\textsubscript{1}, improvement, we did not manually volume-adjust their FEF25-75\% measurements.

The ACCP guidelines\textsuperscript{4} clearly state that acute testing with bronchodilators must be done more than once because false-negative results on one test are not uncommon. This is strongly supported by our data, as shown in Table 3, since out of 86 patients with multiple studies, 33 (38 percent) had apparently conflicting results when different studies were compared. If only those patients with four or more studies are considered, this type of result was seen in 14 of 19 cases (74 percent). This finding is not surprising and rather than true “conflicting results,” it probably reflects a normal (bell-shaped) distribution for this type of data, as well as the regression to the mean which is to be expected when the percentage of change from baseline is used to analyze several individual tests. However, in the clinical setting, many patients will be tested only once (83 percent in our series), and thus, the clinician must be aware that drawing negative therapeutic or prognostic conclusions from a one-time no-response test result is unacceptable, even if one accepts that the assumptions regarding the clinical implications of acute testing with bronchodilators are essentially correct.

It must also be pointed out that our failure to differentiate the patients who were FEV\textsubscript{1} responders from those who were volume (FVC) responders on the basis of their baseline spirometry data does not imply that such a characterization is impossible. Because of the particular objective and design of our study, measurements of lung volumes and diffusing capacity were not made in most of our patients, and we had no information on symptoms, values of arterial blood gases, or roentgenographic findings. Thus, although a difference between these groups of patients may indeed exist, it could not be shown from our data. Our finding that patients with a significant acute response to bronchodilator drugs tend to be more severely obstructed than those who show no such a response (Table 1) has been reported before,\textsuperscript{6,29-30} and it simply reflects the fact that using arbitrary percentage changes from baseline to define “significant improvement” will magnify the importance of relatively small absolute changes when the baseline value is very low.

Previous studies\textsuperscript{39-42} have suggested that Raw and
sGaw measurements are more sensitive in detecting changes in airways caliber than simple spirometry. In our series, out of 42 studies, postbronchodilator improvement was seen exclusively in both Raw and sGaw in 13 cases (31 percent), only in Raw in one case (2 percent), and only in sGaw in five instances (12 percent). Isolated improvements in static lung volumes were seen in four studies (9 percent), and in two of these cases, a concomitant improvement in Raw and/or sGaw was also observed. In this regard, it must be emphasized that our selected levels of significance may have been relatively low, and that the clinical relevance of isolated postbronchodilator improvements in these parameters is not known. Furthermore, six of the 19 patients who had isolated improvements in Raw or sGaw had a repeat study on a different day which showed a positive bronchodilator response by standard spirometry criteria. Thus, considering the additional time and cost involved in performing body plethysmography, we believe that our findings do not justify the routine performance of this type of studies to evaluate the degree of reversibility of chronic airways obstruction in the clinical setting.

Three final comments regarding our study design are necessary. First, we have stated that our selected limits for defining "significant change" could be considered low for the FEV₁, the FEF25-75%, and the static lung volumes, and the Raw and sGaw determinations. However, these "low" percentages are based on coefficients of variation reported in the medical literature and using more stringent criteria (eg, 25 or 30 percent change for the FEF25-75%, Raw, and sGaw) would only strengthen our findings since it would decrease further the already small diagnostic contribution of these parameters.

Second, we used the percentage of change from baseline to interpret our studies, rather than using a relatively more sophisticated and probably more accurate approach because this is the type of analysis routinely used in the clinical setting to interpret individual tests. However, it must be re-emphasized that this type of analysis has several potential limitations.

Lastly, the lack of standardization in our equipment and the fact that the pulmonary function tests were performed by different technicians in each laboratory are unlikely to have had any significant impact on our overall results, because in a study such as ours, each patient is his/her own control, and interlaboratory variability for spirometry has been shown to be negligible as long as testing is done by trained personnel using adequate equipment.

Thus, from our data, we conclude that, in the clinical setting, changes in the FEV₁ will identify the overwhelming majority of patients with a significant acute response to bronchodilators, and that drawing conclusions from a one-time no-response test may be erroneous in many cases. Static lung volumes, Raw, sGaw, and spirometry parameters other than the FEV₁ (ie, FVC and FEF25-75%) seldom yield additional diagnostic information regarding the reversibility of chronic airways obstruction in nonasthmatic patients. We also confirmed previous observations indicating that isolated postbronchodilator changes in FVC or FEF25-75% may be potentially misleading in a relatively small proportion of cases.

ACKNOWLEDGMENT: The authors are deeply grateful to Cathy Dent and Jackie McGruder, senior pulmonary function technicians at the Veterans Administration Medical Center, for their valuable and generous help with this project.

REFERENCES

7. Girard WM, Light RW. Should the FVC be considered in evaluating response to bronchodilator? Chest 1983; 84:87-89
18. Cockcroft DW, Berscheid BA. Volume adjustment of maximal midexpiratory flow: importance of changes in total lung capacity.
Fifth Einthoven Meeting: Past and Present Cardiology

This year's theme for the Fifth Einthoven Meeting is "Nonsurgical Interventions in Coronary Artery Disease," to be held May 27-28 at the State University of Leiden, The Netherlands. Co-sponsors are the European Society of Cardiology and the Netherlands Heart Foundation. For information, contact Dr. Albert V. C. Bruschke, University Hospital, C5-33, PO Box 9500, 2300 RC Leiden, the Netherlands.