Response of Lung Volumes to Inhaled Salbutamol in a Large Population of Patients With Severe Hyperinflation*

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Objectives: Current criteria use FEV\(_1\) to assess bronchodilator responsiveness, despite its insensitivity and inability to predict improvement in symptoms or exercise tolerance. Response in lung volumes remains largely unexplored even though volume parameters, such as inspiratory capacity (IC), closely correlate with functional improvements. Therefore, we assessed the response of lung volumes (ie, by IC, total lung capacity [TLC], functional residual capacity [FRC], residual volume [RV], and FVC) to salbutamol and the relationship of these changes to improvements in the spirometry in these patients.

Design: A retrospective review of data extracted from a large database of patients who were undergoing spirometry and static lung volume measurements before and after the administration of 200 \(\mu\)g salbutamol.

Patients: Patients with an FEV\(_1\)/FVC ratio of < 85% of predicted values were defined as being severely hyperinflated (SH) if TLC was > 133% of predicted and as being moderately hyperinflated (MH) if TLC was 115 to 133% of predicted.

Results: Two hundred eighty-one SH patients and 676 MH patients were identified. Salbutamol significantly reduced the mean (\(\pm\) SEM) TLC (SH patients, 222 \(\pm\) 23 mL; MH patients, 150 \(\pm\) 10 mL; \(p < 0.001\)), FRC (SH patients, 442 \(\pm\) 26 mL; MH patients, 260 \(\pm\) 39 mL; \(p < 0.001\)), and RV (SH patients, 510 \(\pm\) 28 mL; MH patients, 300 \(\pm\) 14 mL; \(p < 0.001\)) and increased both the IC (SH patients, 220 \(\pm\) 15 mL; MH patients, 110 \(\pm\) 11 mL; \(p < 0.001\)) and FVC (SH patients, 336 \(\pm\) 21 mL; MH patients, 204 \(\pm\) 13 mL; \(p < 0.001\)). FEV\(_1\) improved in a minority of patients (SH patients, 33%; MH patients, 26%), but if lung volume measurements are also considered, the overall bronchodilator response may improve to up to 76% of the SH group and up to 62% of the MH group. Changes in volumes correlated poorly with changes in maximal airflows.

Conclusions: Bronchodilators reduce hyperinflation. Measurements of lung volumes before and after bronchodilators add sensitivity when examining for bronchodilator responsiveness.

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Key words: bronchodilator agents; lung volume measurements; obstructive lung diseases; pulmonary emphysema

Abbreviations: ATS = American Thoracic Society; DL\(_{CO}\) = diffusing capacity of the lung for carbon monoxide; FRC = functional residual capacity; IC = inspiratory capacity; MH = moderately hyperinflated; NH = not hyperinflated; RV = residual volume; SH = severely hyperinflated; SVC = slow vital capacity; TLC = total lung capacity

The effectiveness of inhaled bronchodilators in individual patients with COPD may be assessed by the comparisons of measurements from pulmonary function tests made before and after the administration of an inhaled bronchodilator. The general practice is to use the FEV\(_1\) as the marker for assessing responsiveness. On the other hand, other measures of lung function, such as lung volumes, are not routinely assessed before and after the administration of a bronchodilator agent in most centers.

The FEV\(_1\), along with other measures derived from maximal forced expiratory maneuvers may, however, be an insensitive marker for responsiveness. The inspiratory capacity (IC), as well as measurements made during a partial flow-volume loop, may be more sensitive for detecting bronchodilator responses.\(^1\) Moreover, an increase in IC is predictive of an improvement in exercise tolerance and dyspnea,\(^2\)\(^\text{-}5\)\(^\text{,}6\) but this is not true for FEV\(_1\).\(^2\)\(^\text{-}5\)\(^\text{,}6\)
To date, the responses of static lung volumes to inhaled bronchodilators, including the IC, have not been well-defined in a large population of patients with chronic hyperinflation. Existing data from small or inhomogeneous sets indicate that the administration of a short-acting β-agonist agent, anticholinergic agent, or long-acting β-agonist agent results in a reduction of the functional residual capacity (FRC) and residual volume (RV), while total lung capacity (TLC) remains unchanged. On the other hand, one small series of asthmatic subjects demonstrated a reduction of TLC after bronchodilator administration. An understanding of the effects of bronchodilators on lung volumes is important, as hyperinflation is responsible for much of the increased work of breathing and dyspnea seen in patients with obstructive lung diseases.

In this study, our aim was to determine the response patterns of lung volumes, (ie, FRC, RV, FVC, and IC) in patients with moderate and severe hyperinflation due primarily to COPD.

**Materials and Methods**

**Patients**

A retrospective analysis was performed, deriving subjects from a large (ie, > 20,000 patients) database of patients who had undergone pulmonary function testing at the pulmonary function laboratory at Kingston General Hospital between 1982 and 1998. To be eligible, the patient was required to have undergone spirometry testing and a determination of static lung volumes before and after the administration of 200 μg salbutamol. All patients with a baseline TLC of > 115% of predicted, and airways obstruction defined as an FEV₁/FVC ratio of < 85% of predicted were included in the study. The analysis also was limited to patients aged ≥ 55 years to reduce the likelihood of including asthmatic patients. Because many subjects have undergone repeated pulmonary function testing for reasons of medical follow-up, it was decided that each patient could be entered into the study on only one occasion and that the patient’s first visit to the laboratory during which all requirements for the study were met would be the visit from which information for the study would be included.

Detailed clinical information for each subject was not available for the purpose of the analysis. We wished, however, to evaluate patients with hyperinflation secondary to COPD. TLC was used to define eligibility. For the analysis, patients were stratified to either a severely hyperinflated (SH) group or moderately hyperinflated (MH) group. The MH group was defined as those patients with a TLC of between 115% and 133% of predicted values. It is likely that this group contained some asthmatic patients. With specific normative values for lung volumes from Goldman and Becklake and for diffusing capacity of the lung for carbon monoxide (DLCO) from Burrows et al., Salbutamol (200 μg) then was administered, and the spirometry and lung volume determinations were repeated after a wait of 20 min.

**Criteria for Reversibility**

Current ATS criteria require an increase in FEV₁ of at least 200 mL and 12% from baseline values, and a similar change in FVC of 200 mL and 12%, to indicate a response to a bronchodilator. We used these criteria in our study.

In the analysis, the magnitude of increase in IC that represents a significant response must be defined. Work by O’Donnell et al. has indicated that an increase of 10% of predicted IC results in a 25% increase in exercise endurance time. Moreover, the 95% confidence interval for variability on repeated measurements in patients with airways obstruction (mostly asthmatic patients) has been demonstrated to be 220 mL or 9% of the predicted value. Finally, the bronchodilator change in IC in the not-hyperinflated (NH) group was 30 mL (0.8%). Therefore, we determined that a significant increase in IC would be 200 mL and 10% of predicted.

Little guidance is available in the literature to help define what level of reduction in baseline hyperinflation or gas trapping constitutes an important response. We arbitrarily chose a reduction in RV of 20% of the predicted value as representing a significant improvement. For normative reference values, we also examined the bronchodilator-induced changes in airflow and lung volumes in NH individuals, with normal pulmonary function testing, which were derived from the same database (TLC, between 85% and 115% of predicted; FEV₁, > 80% predicted; and DLCO, > 80% of predicted). Ninety-five percent confidence limits were computed for changes in maximal flows and lung volumes in this NH group.

**Pulmonary Function Testing**

Patients were required to abstain from using short-acting inhaled bronchodilators for at least 4 h prior to testing (12 h in the case of long-acting bronchodilators). Patients were tested (after 1992: model 2130 spirometer with Autobox model V6200; Sensormedics; Yorba Linda, CA; or prior to 1992: Spiroflow dry rolling seal spirometer; Morgan; Haverhill, MA; with constant volume plethysmograph; Collins; Braintree, MA) in the seated position in a comfortable chair. Measurements of FEV₁, FVC, and slow vital capacity (SVC) were made according to American Thoracic Society (ATS) recommendations.

Plethysmographic determination of FRC was made in standard fashion, using slow panting maneuvers, according to the method of Dubois et al. Patients were asked to perform the panting maneuvers with their cheeks held, with a panting frequency of 1 to 2 Hz. Following the panting maneuvers, a slow inspiration, followed by a slow expiration were performed to determine IC, RV, and SVC. Normative values were obtained from Morris with specific normative values for lung volumes from Goldman and Becklake and for diffusing capacity of the lung for carbon monoxide (DLCO) from Burrows et al.

Salbutamol (200 μg) then was administered, and the spirometry and lung volume determinations were repeated after a wait of 20 min.

**Statistical Analysis**

Data storage and extraction were performed using appropriate software (Excel 97; Microsoft; Redmond, WA). Data are expressed as the mean ± SEM. For comparisons before and after intervention and between groups, the Wilcoxon signed-rank test or Student’s t test was used. All statistics, including linear regressions, descriptive statistics, and confidence intervals were computed using appropriate software (Signmastat, version 2.03; SPSS; Chicago, IL).
RESULTS

Patient Characteristics

Nine hundred fifty-seven individual patients who had been evaluated at the pulmonary function laboratory were included in the study. Of these, 534 were men and 423 were women. The mean age was 64.7 ± 0.37 years.

Of the 957 patients, 281 were classified as SH (ie, TLC, > 133% of predicted; FEV1/FVC ratio, < 85% of predicted), and the remaining 676 patients were classified as MH. The baseline characteristics of both groups are depicted in Figure 1.

The patients in the SH group had significant baseline obstruction with a mean FVC of 72.6 ± 1.2% of predicted, mean FEV1 of 52.4 ± 1.3% of predicted, and mean FEV1/FVC ratio of 48.8 ± 0.6%. They also had significant hyperinflation with a mean TLC of 144.8 ± 0.7% of predicted and a mean FRC of 187.4 ± 1.6% of predicted. This group also demonstrated significant gas trapping (mean RV, 236.4 ± 2.6% of predicted). Baseline IC was reduced to 87.1 ± 1.5% of predicted, with the predicted IC value defined as the predicted TLC value minus the predicted FRC value, as no reference values exist. Single-breath DLCO was low, with an average value of 66.1 ± 1.5% of predicted.

The patients in the MH group had a lesser degree of abnormality. Obstruction was still evident with an FVC of 84.9 ± 0.8% of predicted, an FEV1 of 78.1 ± 1.1% of predicted, and a mean FEV1/FVC ratio of 63.4 ± 0.5%. They also had significant hyperinflation (mean TLC, 123.1 ± 0.2% of predicted; mean FRC, 146.9 ± 1.2% of predicted) and gas trapping (mean RV, 170.2 ± 1.3% of predicted). The baseline IC, at 94.9 ± 1.2% of predicted, remained in the normal range. DLCO was low, with an average value of 77.7 ± 0.9% of predicted.

An additional 252 subjects in the NH group also were examined. These patients were younger (mean age, 36.3 ± 14.7 years) and had no airflow obstruction (mean FEV1, 107.1 ± 0.7% of predicted). Static lung volumes were also normal with a mean TLC of 100.1 ± 0.5% of predicted, a mean FRC of 95.4 ± 1.2% of predicted, and a mean RV of 100.6 ± 1.2% of predicted. DLCO was also preserved with a mean value of 101.8 ± 0.7% of predicted.

Bronchodilator Administration

All 957 patients received 200 µg salbutamol and had full pulmonary function test determinations before and after salbutamol administration. This medication resulted in a significant increase in FEV1 and FVC, and a significant reduction in TLC, FRC, and RV. An increase also was seen in the IC. Parallel changes were evident in the SH and MH groups, as is shown in Figure 2. The magnitude of changes was greater in the SH group, both in terms of absolute change and the percentage of change from baseline (Fig 2).

Airflow obstruction was significantly relieved in both groups. In the SH group, FEV1 increased by 0.16 ± 0.01 L (14.9 ± 0.9%); and in the MH group, by 0.15 ± 0.01 L (11.0 ± 0.7%). Both groups also showed an improvement in FVC, which is consistent with volume recruitment. The change was more striking in the SH group (mean increase, 0.34 ± 0.02 L; 15.6 ± 0.9% of baseline value) than in the MH group with an increase of 0.20 ± 0.01 L (9.1 ± 0.6%).

Unlike previous studies, we observed a small, but significant, reduction in TLC after bronchodilator administration. This effect was seen in both the SH group (mean reduction, 0.22 ± 0.023 L [2.9 ± 0.3%]) and the MH group (mean reduction, 0.15 ± 0.01 L [2.3 ± 0.2%]). The reduction in FRC was greater, with mean decreases of 0.44 ± 0.03 L (7.7 ± 0.5%) in the SH group and 0.26 ± 0.01 L (6.2 ± 0.3%) in the MH group. This resulted in mean increases in IC of 0.22 ± 0.02 L (11.5 ± 1.1%) in the SH group and 0.11 ± 0.01 L (5.7 ± 2.2%) in the MH group. A net reduction in RV was seen in both groups, (SH group, 0.51 ± 0.03 L [10.1 ± 0.6%]; MH group, 0.30 ± 0.02 L [8.4 ± 0.5%]). All of these changes were highly significant (p < 0.001). Changes in SVC, as the difference between TLC and RV, were not significantly different from those in FVC.

In the NH group, there were no significant changes either in airflow or lung volumes. The FEV1 decreased on average by 0.034 ± 0.28 L (0.29 ± 0.5%). There were also only small changes in static lung volumes, with FRC increasing by 0.029 ± 0.03 L (0.66 ± 1.0%) and RV decreasing by 0.012 ± 0.20 L (0.26 ± 1.1%). The inclusion range of 5 to 95% was −14 to 11% of the

![Figure 1. Baseline pulmonary function parameters for the NH group, the MH group, and the SH group. Data are expressed as the mean ± SEM.](http://journal.publications.chestnet.org/pdifaxx.ashx?url=/data/journals/chest/21976/)
baseline value. Segregating NH patients into one group that was < 55 years of age and another that was > 55 years of age revealed no significant differences in bronchodilator response between the two age groups.

**Pattern of Bronchodilator Responses**

We characterized bronchodilator effect in terms of flow and volume response. Flow response was determined according to changes in FEV₁. The volume response was ascertained by examining the bronchodilator effect on IC, RV, and FVC. Overall, flow response occurred in 33% of patients in the SH group and in 26% of patients in the MH group, and volume response occurred in up to 76% of patients in the SH group and in 62% of patients in the MH group.

A large proportion of the patients (MH group, 57%; SH group, 41%) did not demonstrate a response to bronchodilators, as determined either with FEV₁ or IC. Both groups had an isolated improvement in FEV₁ of 11%, while 17% in the MH group and 26% in the SH group improved IC only. Improvement in both FEV₁ and IC was seen in 15% of the MH group and 22% of the SH group (Fig 3).

In contrast to FEV₁ or IC, no criteria exist to define a significant response in static lung volumes. Therefore, we defined a significant reduction as a drop in the RV by at least 20% of the predicted value. This requires a reduction of approximately 300 to 500 mL in most patients, which is much greater than the mean change seen in our NH group of patients with normal baseline lung function. Using these criteria, a full 65% of patients in the SH group and 51% of those in the MH group demonstrated either an improvement in IC and/or RV. In contrast, only 11% of patients in the SH group and 11% of those in the MH group improved in FEV₁ without an improvement in either lung volume measurement (Fig 4). There was little correlation between changes in RV and IC (SH group, \( r^2 = 0.05 \); MH group, \( r^2 = 0.005 \)). Although the correlation between IC and FRC was better, it remained nevertheless only modest (SH group, \( r^2 = 0.302 \) \( p < 0.001 \); MH group, \( r^2 = 0.28 \) \( p < 0.001 \)).

Volume response also was assessed with FVC, using the ATS criteria for reversibility. FVC was chosen over SVC, since the differences between changes in FVC and SVC were not significant for the SH group (\( p = 0.43 \)) and, numerically, were only very small for the MH group (FVC, 204 mL; SVC, 164 mL; \( p = 0.04 \)). Because FEV₁ is intimately related to FVC, a rise in FVC should be accompanied by a tandem rise in FEV₁. We reasoned that if the increase in FEV₁ was proportionate but smaller...
than that of FVC, the improvement was primarily a volume effect, whereas an increase in FEV$_1$ in excess of that of the FVC was primarily a flow effect. A flow effect should be reflected in a commensurate increase in FEV$_1$/FVC, whereas in the case of a volume effect the FEV$_1$/FVC ratio should remain unchanged or be reduced. A volume response was categorized by FVC values of $>12\%$ and $\geq 200$ mL$^{21}$ and by FEV$_1$ values of $<12\%$ and $<200$ mL. A flow response was categorized by FEV$_1$ values of $>12\%$ and $\geq 200$ mL, and by FVC values of $<12\%$ < $200$ mL. No response was categorized by FEV$_1$ and FVC values of $<12\%$ and $<200$ mL, and the effect was confirmed by using the FEV$_1$/FVC ratio. According to these criteria, $36\%$ of patients in the SH group showed no response (Fig 5), which was also reflected by similar values of the FEV$_1$/FVC ratio ($53\%$) both before and after salbutamol administration. In the $11\%$ of patients with a flow response, the FEV$_1$/FVC ratio improved significantly from $47$ to $54\%$ ($p < 0.02$). On the other hand, the $53\%$ of patients with a volume response exhibited no difference in the FEV$_1$/FVC ratio (before bronchodilator administration, $46\%$; after bronchodilator administration, $47\%$). Sixty percent of the MH group had neither flow responses nor volume responses (FEV$_1$/FVC ratio before and after bronchodilator administration, $67\%$). Similar to patients in the SH group, in the $11\%$ of patients in the MH group with a flow response the FEV$_1$/FVC ratio also improved significantly (improvement, $57$ to $64\%$; $p < 0.001$), whereas in the $29\%$ of patients with a volume response there was no significant change in FEV$_1$/FVC ratio (before bronchodilator administration, $58\%$; after bronchodilator administration, $59\%$).

The specific contribution of individual flow and volume parameters to bronchodilator response without overlap combinations is shown in Table 1. In both the MH and SH groups, each of the volume parameters improved in more patients than did FEV$_1$.

The three approaches for assessing volume response are compared in Figure 6. Although the largest changes from baseline in static lung volumes were evident when combining IC plus RV, overall, the bronchodilator changes were quantitatively similar.

To assess the specific utility of static volumes as markers of bronchodilator responsiveness, patients who showed no improvement in spirometry were assessed for improvement in RV and IC. Thirty-five percent of MH patients and $63\%$ of SH patients improved their static volumes. Individual values are shown in Table 2.

**Table 1—Bronchodilator Responsiveness of Individual Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MH Group (n = 676)</th>
<th>SH Group (n = 281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>FVC</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>RV</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>IC</td>
<td>17</td>
<td>26</td>
</tr>
</tbody>
</table>

*Bronchodilator responsiveness of individual parameters is expressed as a percent of the total number of patients in each group. Overlap combinations of parameters are not included.*
Relationships Between Lung Volumes and Flow Responses

The relationship between volume response and flow response for the SH group is shown on Table 3. Changes in IC and RV correlated poorly with those in FEV1. A similar correlation between ΔFEV1 and ΔFVC is not shown in Table 3, because it is not meaningful, given their inherent interdependence. To determine whether volume changes correlated with maximal expiratory flow rates prevalent at mid to low vital capacity, ΔIC, ΔRV, and ΔFVC also were correlated with the change in the midexpiratory phase of forced expiratory flow and with the change in forced expiratory flow at 75% of vital capacity. All of these correlations were very poor and suggest independence between volume response and flow response. These correlations remain poor within the groups of volume responders, flow responders, and nonresponders. A similar lack of relationships pertained to the MH group.

TABLE 3—Relationship Between Flow and Volume Changes in SH Patients*

<table>
<thead>
<tr>
<th>Volume Changes</th>
<th>Flow Changes</th>
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</thead>
<tbody>
<tr>
<td>ΔIC</td>
<td>ΔFEV1,ΔFEF75-75</td>
</tr>
<tr>
<td>ΔRV</td>
<td>ΔFVC</td>
</tr>
<tr>
<td>ΔFVC</td>
<td></td>
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<table>
<thead>
<tr>
<th>Volume Changes</th>
<th>Flow Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔIC 0.13</td>
<td>ΔFEV1,ΔFEF75-75</td>
</tr>
<tr>
<td>ΔRV 0.08</td>
<td>ΔFVC</td>
</tr>
<tr>
<td>ΔFVC †</td>
<td></td>
</tr>
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<table>
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<tr>
<th>Volume Changes</th>
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<td>ΔIC 0.13</td>
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<tr>
<td>ΔRV 0.08</td>
<td>ΔFVC</td>
</tr>
<tr>
<td>ΔFVC †</td>
<td></td>
</tr>
</tbody>
</table>

*Values given as coefficient of predictability. FEF75-75 = midexpiratory phase of forced expiratory flow; FEF75 = forced expiratory flow at 75% of vital capacity.
†No correlation is shown in view of the inherent dependency of FEV1 on FVC (please refer to the “Results” section for further discussion).

RV, or FVC before and after bronchodilator administration identifies a response that may not be uncovered by the standard measurement of FEV1. Indeed, the inclusion of IC, RV, or FVC with FEV1 suggests that up to three quarters of these patients improve with bronchodilator therapy. The improvements in lung volumes are largely independent of changes in maximal expiratory flow rates.

This was a retrospective analysis of patients undergoing standard pulmonary function testing. We wished to examine the effects of a bronchodilator on lung volumes in patients with COPD, but, as described earlier, secure clinical information was not available for each patient. Nonetheless, it is highly likely that the vast majority of the patients in the SH group were affected by COPD for the following reasons. Dykstra et al15 found that elderly asthmatic patients are unlikely to have the degree of baseline hyperinflation shown in our patients. The baseline reduction in diffusion capacity also suggests that these patients primarily have COPD, because asthma is usually associated with a normal or elevated DLCO level.22 It is also likely that the MH group consisted of patients with COPD, because the response patterns are similar to those of the SH group, if lesser in magnitude. It is possible that some asthmatic patients were included in the latter group, but, nonetheless, the conclusions pertaining to the effects of bronchodilators on lung volume compartments remain clinically relevant.

Although traditionally used as the marker of reversibility, FEV1 has been demonstrated to lack sensitivity in some cases1 and is generally a poor predictor of improvement (or lack thereof) in exercise tolerance in patients with advanced COPD.2,3 Several factors may limit the utility of FEV1. Bronchodilator responsiveness may be masked during maximal forced expiration due to airway and gas compression, especially if elastic recoil is reduced.1,2 As a result, partial expiratory flow measurements

Discussion

The relevant findings of this study are as follows. In hyperinflated patients, the measurement of IC,
may be more sensitive to improvements by made by therapy with bronchodilators than are maximal expiratory flow rate measurements. In our analysis, maximal forced expiration, from which FEV1 is derived, consistently underestimated improvements after bronchodilator administration.

Our findings indicate that by not examining lung volumes after bronchodilator administration, an important bronchodilator effect is missed. This effect is demonstrable when assessing a dynamic lung volume such as FVC, a static volume reflecting gas trapping such as RV, or a volume such as IC that has been shown previously to reflect symptom improvement.1

In both the SH and MH groups, an IC response alone occurred in 19% of patients and a combined response occurred in an additional 17% of patients. Stated another way, sole reliance on FEV1 would result in the exclusion of 50% of those patients who achieve a significant improvement in IC. The improvement in IC (SH group, 0.22 ± 0.02 L; MH group, 0.11 ± 0.01 L) is seen with bronchodilator administration as a result of a decrease in the FRC (SH group, 0.44 ± 0.03 L; MH group, 0.26 ± 0.01 L). TLC decreased less than FRC (SH group, 0.22 ± 0.023 L; MH group, 0.11 ± 0.01 L). The FRC is not necessarily determined by a simple balance between equal and opposite recoil pressures of the chest wall and lung. In obstructive diseases, FRC is dynamically determined, and it depends on ventilation level and the extent of flow limitation.23 The administration of a bronchodilator, which improves gas trapping, causes a decreased FRC with an attendant increase in IC. In our study, however, the correlation between the increase in IC and the decrease in FRC is likely to be limited by the small decrease in the TLC. In other words, the measurement of the IC alone after bronchodilator administration, without plethysmographic determination of the static lung volumes, is not a good reflection of the underlying changes in those volumes. Furthermore, given the modest correlation between changes in FRC and IC, measuring the IC before and after bronchodilators is not a useful surrogate for the behavior of FRC.

We also assessed volume effects in terms of concurrent changes in IC and RV. The rationale for choosing IC is presented above. The inclusion of RV is based on the fact that among the volume changes, the improvement in RV was quantitatively the largest. However, the two parameters are functionally independent, since there was little correlation between them.

Vital capacity was utilized as an additional volume parameter. Since the differences between SVC and FVC were insubstantial and FVC is available from spirometry, particularly if lung volume measurements are not available, FVC was chosen as the volume parameter. Volume and flow response according to changes in FVC and FEV1 (Fig 5) were confirmed utilizing the FEV1/FVC ratio. Patients with a flow response had a significant improvement in this ratio, whereas those with a volume response or no response had no significant difference between values for the FEV1/FVC ratio before and after bronchodilator administration. A similar behavior was seen in patients in the MH group.

A comparison of the responsiveness of individual volume parameters with FEV1 indicates that for both MH and SH patients, FVC, RV, and IC each improved in more patients than did FEV1 (Table 1). Thus, any of the individual volume parameters is at least as good a marker of bronchodilator responsiveness as is FEV1 in these patients.

Bronchodilator effects according to the three volume parameters were quantitatively quite similar (Fig 6). The somewhat larger changes in static volumes with the measurement of IC plus RV are likely reflective of the selection criteria for RV, which include patients with larger changes in RV. Regardless of whether the choice for a volume response is governed by the convenience of using a spirometric index such as FVC or by the intent of maximizing the effect by adding IC and RV, the volume effects are relatively similar.

Perhaps the most unexpected finding was a reduction in TLC, which was demonstrated in both the SH and MH groups. TLC has been considered as a simple balance between the respiratory muscles and the recoil of the respiratory system.6,23 For a bronchodilator agent to effect a reduction in TLC, it would need either to reduce respiratory muscle strength (extremely unlikely) or to increase lung recoil. This is somewhat at odds with information in the existing literature, which suggests that therapy with bronchodilators may decrease lung recoil, at least in asthmatic subjects.13 In our study, however, TLC exhibited a small, but significant (175 mL and 2.5%) decrease after bronchodilator administration. In both the SH and MH groups, the reduction in TLC was closely linked to the reduction in both the FRC and RV.

To achieve a reduction in TLC, FRC, and RV with secondary changes in IC and FVC, bronchodilatation likely relieves gas trapping, especially in particularly overdistended areas of the lungs. The resultant changes in lung volumes are similar, if not as profound, as those seen in patients after lung volume reduction surgery and
bullectomy. In the one other study in which a substantial reduction in TLC (mostly among asthmatic patients) was observed, the reduction of FRC was thought to lead to a decrease in the stretch-relaxation of the airways and lung parenchyma, and this may thereby increase lung recoil.

Why is there almost no correlation between the flow response and the volume response (Table 3)? We hypothesize that this reflects a functional difference that can be likened to a functional fast space and slow space. The slow space with very long time constants has flow rates too low for detection by the maximal flow parameters utilized, but it may affect the RV. Improvement in flows of the slow space would thereby permit further emptying and a reduction in RV. To the extent that the largest improvement occurred in RV, the volume effect may have been mediated primarily through this volume, with secondary improvements in the other volumes.

As has been previously observed, the response to therapy with bronchodilators in the same patient at different times varies, and the spirometric response is not predictive of the clinical result. What then is the utility of measuring any of the pulmonary function parameters before and after a bronchodilator? Certainly, the present data may help to explain this disparity between spirometric and clinical improvement. Moreover, it may be inferred that relief of hyperinflation and gas trapping, in the absence of an improvement in maximal flows, may still result in symptomatic benefit.

The utility of incorporating lung volume measurements into the assessment of bronchodilator responsiveness is illustrated by Table 2. Our data indicate that in those patients with no bronchodilator responsiveness in spirometry (FEV₁ and FVC), RV and IC improve in about one third of MH patients and in about two thirds of SH patients. Whereas lung volume measurements are part of the standard armamentarium of assessing lung function, their use in determining bronchodilator responsiveness in patients with baseline hyperinflation is not predictive of the clinical result. What then is the utility of measuring any of the pulmonary function parameters before and after a bronchodilator?

In summary, a relatively low dose of inhaled salbutamol reduces hyperinflation and gas trapping in patients with significant baseline hyperinflation, often to a remarkable degree, even in patients with advanced disease. In fact, the patients with the most severe disease had the most impressive volume responses. Given the observation that up to one half of potentially responsive patients experience important improvements in lung volumes without an identifiable increase in FEV₁, we suggest that lung volumes along with the standard spirometric indexes be measured when determining bronchodilator responsiveness in patients with baseline hyperinflation. Studies examining the efficacy of new treatments also should pay closer attention to the effect on lung volumes. Further prospective studies examining the behavior of lung volumes after bronchodilator administration in patients with definite clinical diagnoses of COPD are required.

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