Forced Oscillation Technique vs Spirometry to Assess Bronchodilatation in Patients With Asthma and COPD

Françoise Zerah, MD; Anne-Marie Lorino, PhD; Hubert Lorino, PhD; Alain Harf, MD; and Isabelle Macquin-Mavier, MD

The forced oscillation technique (FOT) is a noninvasive test used to characterize the mechanical impedance of the respiratory system. The aim of the study was to compare the changes in respiratory conductance (Grs) measured with FOT to those in FEV₁ in 22 patients with asthma and 20 patients with chronic obstructive pulmonary diseases (COPD) after salbutamol inhalation. FEV₁ and Grs indexes, computed as the ratio of the difference between postbronchodilator and prebronchodilator values over the predicted value, were used to express reversibility of airway obstruction. After inhalation of salbutamol in cumulative doses up to 1,200 μg in ten patients of each group, FEV₁ and Grs indexes showed parallel changes, and most of the increase was observed after the first dose of 200 μg of salbutamol for the two indexes. In all the 42 patients, we found a linear relationship between the two indexes after inhalation of 200 μg of salbutamol (r=0.7, p<0.0001). We evaluated FEV₁ and Grs indexes in terms of sensitivity and specificity for identifying asthmatics among patients with COPD: using a 10% change as the cut-off value, these indexes proved of similar value (sensitivity, 0.91 and 0.95; specificity, 0.95 and 0.85, respectively). We conclude that the use of FOT can be considered as an alternative to forced expiration for detecting bronchodilatation in asthmatics and patients with COPD.

(CHEST 1995; 108:41-47)

ANOVA=analysis of variance; FEV₁/VC=forced expiratory volume in 1 s/vital capacity; FOT=forced oscillation technique; FRC= functional residual capacity; Grs=respiratory conductance; Rs=respiratory resistance; ROC curves=receiver operating characteristic curves; RV= residual volume; S=slope of the linear relationship of resistive impedance vs frequency; TLC=total lung capacity; VC=vital capacity

Key words: asthma; COPD; FEV₁; respiratory resistance; salbutamol

Over recent years, a number of studies have shown the clinical usefulness of respiratory impedance determination using the random noise forced oscillation technique (FOT) for detecting early airway obstruction and assessing lung function in patients with chronic obstructive lung disease. This method has also been proved useful for evaluating bronchial responsiveness to nonspecific bronchoconstricting agents in both adults and children. In contrast, few studies have evaluated respiratory impedance changes following β-adrenoceptor agonist inhalation in patients with airway obstruction. As a consequence, the value of impedance measurement for assessing responsiveness to bronchodilators in such patients requires further investigations.

The aims of the present study were (1) to compare airway responses to cumulative doses of β₂-agonists in these patients using FOT and spirometric measurements, and therefore determine the dose responsible for the largest response for the two methods, and (2) to assess the sensitivity and specificity of FOT for identifying asthmatics among patients with COPD after inhalation of a dose of β₂-agonist routinely used to test airway obstruction reversibility. To express reversibility of airway obstruction, we chose to use a respiratory conductance (Grs) index computed as the ratio of the difference between postbronchodilator and prebronchodilator values over the predicted Grs value, and an FEV₁ index expressed in the same way, as recommended.

METHODS

Patient Selection

Patients included in this study were ambulatory subjects, presenting to the outpatient clinic, and referred by physicians, to the laboratory for routine pulmonary function testing with a bronchodilator test. The patients had a clinical diagnosis of asthma or COPD. All had airway obstruction due to asthma or COPD. Informed consent was obtained from all subjects before inclusion into the study.

Selection criteria included a clinical diagnosis of asthma or COPD, and evidence of airway obstruction with an FEV₁ of less than 75% of predicted. Exclusion criteria included any history suggestive of exacerbation of airway obstruction in the preceding month and evidence of upper airway obstruction. We defined COPD as cough and sputum production for at least 3 months per year during 2 years or more, with spirometric obstruction and a
history of cigarette smoking. Asthma was clinically diagnosed on the basis of a history of episodic wheezing with dyspnea and a need for medical treatment. Of the asthmatic group, 60% were using inhaled \( \beta \)-agonists, 25% inhaled beclomethasone, and 5% were taking oral bronchodilators such as theophylline. Of the COPD group, 65% were using inhaled \( \beta \)-agonists and inhaled beclomethasone and 25% were taking oral theophylline.

**Study Design**

The study consisted of two parts, separated by at least 48 h in a given patient. In the first part, we studied the bronchodilator response to increasing doses of salbutamol in ten patients, randomly chosen, from each of the two diagnostic groups. Dose-response curves were constructed by administering cumulative doses of inhaled salbutamol via a spacer (Volumatic; Glaxo Pharmaceuticals; Paris, France). Cumulative doses were given every 20 min as follows: (1) the subject inhaled 200 \( \mu \)g of salbutamol and the responses were measured 10 min later; (2) an inhalation of 200 \( \mu \)g of salbutamol was then given yielding a cumulative dose of 400 \( \mu \)g. Further measurements were made at cumulative doses of 800 and 1,200 \( \mu \)g. The FEV\(_1\) and respiratory conductance measured with the FOT (Grs) were measured at baseline and 10 min after inhalation of each dose of salbutamol. During both parts of the study, FEV\(_1\) and Grs measurements were made in random order. Heart rate was monitored and patients were questioned in general terms about side effects, especially tremor, palpitations, headache, and nausea.

In the second part, we studied the bronchodilator response after inhalation of 200 \( \mu \)g of salbutamol in 42 subjects, including 22 asthmatics (9 male, 13 female) and 20 patients with COPD (16 male, 4 female). Following baseline respiratory impedance and spirometric measurements, all patients received 200 \( \mu \)g of salbutamol via a spacer (Volumatic, Glaxo). Impedance measurements and spirometry were performed 10 min after salbutamol inhalation.

Treatment with anticholinergic agents, antihistamine agents, ketotifen, and sodium cromoglycate was withdrawn 3 days before the study day. Treatment with inhaled \( \beta_2 \)-agonists and oral \( \beta_2 \)-agonists was discontinued 6 h and 24 h before testing, respectively. Therapy with theophylline and inhaled or oral corticosteroids was unchanged.

**Spirometry**

Flows and lung volumes were measured in the sitting position, using a closed-circuit spirometer (VG 2000; Mijnhardt BV; Bunnik, Netherlands). Functional residual capacity (FRC) was measured using the helium dilution method, as the mean of two determinations. These values were expressed as the percentage of predicted values.\(^{13}\) Spirometry met international standards.\(^{13}\)

**Forced Oscillation Technique**

The forced oscillation method used has been described previously.\(^{14}\) Briefly, a random noise signal of 4 to 32 Hz was generated by loudspeakers and superimposed on the spontaneous breathing of the subject who was equipped with a mouthpiece and a nose-clip. The subject's cheeks were held firmly. The measurements were performed in the sitting position, with the head in the neutral position. Three technically acceptable measurements were performed. Mouth flow was measured using a screen pneumotachograph (Jaeger; Wurzburg, Germany) connected to a differential pressure transducer (Sensym LX 0600D; Sunnyvale, Calif.). An identical transducer was used to measure mouth pressure. The signals were lowpass-filtered (Butterworth, 8th order, cut-off frequency \( \approx \)32 Hz) to prevent aliasing, \( \nu_c \), to eliminate the possible influence of high on low frequencies, and sampled at a frequency of 128 Hz. The signals were fed into a microcomputer on which spectral analysis was performed using a 512-point fast Fourier transform algorithm. The real component (which is related to the resistive properties of the system) and the imaginary component (which corresponds to inerterance and compliance properties) of respiratory impedance were computed every 0.25 Hz from 4 to 32 Hz and displayed as a function of frequency. For each of these frequencies, a coherence function ranging from 0 to 1, which enables us to evaluate the reproducibility of impedance measurements, was calculated and 0.9 was chosen as the lower limit of data acceptance.\(^{14}\)

The real component of impedance was subjected to linear regression analysis over the frequency range 4 to 16 Hz to obtain the zero- intercept resistance (Rrs) and the slope (S) of the linear relationship of resistive impedance vs frequency that reflects the distribution of flow among intrathoracic parallel inhomogeneities and also the shunt impedance of the upper airway. Respiratory conductance (Grs) was calculated as the reciprocal of Rrs. To assess the quality of the fit, we calculated for each patient in every condition the relative distance between the response of the linear model and that of the patient.\(^{16}\) The relative distance averaged 3.5%, with a standard deviation of 0.8%, which illustrates the adequacy of the linear model to describe resistive impedance over the 4- to 16-Hz frequency range.

**Expression of Results and Statistical Analysis**

The Grs values were expressed as the percentage of predicted values obtained in our laboratory. From a group of 40 healthy nonsmokers (25 male, 15 female) studied with the FOT, we derived the following equation: Grs\(_{\text{pred}}\)=(0.638·H\(_1\)+0.004·A)−0.787, SEE=0.07, where H is the height in meters and A the age in years. We found no influence of body weight on Grs in these normal subjects (body mass index below 25 kg/m\(^2\)). The mean value for Grs was 0.45 L\(_{\text{s−1}}\).cm H\(_2\)O\(^{−1}\) (mean value for Rrs, 2.3 cm H\(_2\)O.s.L\(^{−1}\)).

To evaluate the salbutamol-induced change in FEV\(_1\), we used the FEV\(_1\) index, computed as the ratio of the difference between postbronchodilator and prebronchodilator values over the predicted value.\(^{12,17−19}\) A Grs index was computed in the same way. Sensitivity and specificity of the FEV\(_1\) and Grs indexes for identifying asthmatics among patients with obstructive airway disease after 200 \( \mu \)g of salbutamol were examined by receiver operating characteristic (ROC) curves.\(^{20}\) The ROC curves made it possible to show the true-positive rate (sensitivity) vs the false-positive rate (1-specificity) at various levels of Grs and FEV\(_1\) indexes, and to determine the cut-off value corresponding to the largest number of well-classified patients.

Data are expressed as means±SEM. A paired \( t \) test was used to compare responses to 200 \( \mu \)g of inhaled salbutamol evaluated with the two techniques. Comparisons of the distribution of subjects with indexes above or below the cut-off value were performed in the two groups of patients using a test of paired proportions (McNemar's test).\(^{20}\) Correlations between variables were analyzed using least-square linear regression techniques.

Dose-response curves for salbutamol were evaluated using analysis of variance (ANOVA) for repeated measures in the two groups of patients to test the relationship between dose and effect. When a significant difference was found, we compared individual means using the Scheffé test. Comparisons between groups were made using two-way ANOVA for repeated measures; when significant differences were found, individual means were compared using a modified \( t \) test. Comparisons between methods were made using two-way ANOVA and linear regression with structural covariance matrices for repeated measures (BMDP 5V, statistical software). For all comparisons, \( p \) values under 0.05 were considered significant.
Table 1—Anthropometric Data and Baseline Pulmonary Function Test Results in the Two Groups of Patients.*

<table>
<thead>
<tr>
<th></th>
<th>Asthma (n=22)</th>
<th>COPD (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking history, pack-yr</td>
<td>6±2</td>
<td>47±2</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>51±3</td>
<td>60±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161±2</td>
<td>166±2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69±3</td>
<td>69±4</td>
<td>NS</td>
</tr>
<tr>
<td>TLC, %</td>
<td>99±2</td>
<td>93±3</td>
<td>NS</td>
</tr>
<tr>
<td>FRC, %</td>
<td>102±4</td>
<td>109±4</td>
<td>NS</td>
</tr>
<tr>
<td>RV, %</td>
<td>113±5</td>
<td>126±5</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>60±2</td>
<td>43±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV₁/VC, %</td>
<td>70±2</td>
<td>60±3</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Rs, cm H₂O s L⁻¹</td>
<td>6.9±0.4</td>
<td>7.6±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Grs, L s⁻¹ cm H₂O⁻¹</td>
<td>0.16±0.01</td>
<td>0.14±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>S, 10⁻⁵ cm H₂O S⁻¹ Hz⁻¹</td>
<td>-131±22</td>
<td>-216±24</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Data are expressed as the percentages of predicted values (TLC, FRC, RV, FEV₁, FEV₁/VC). p values <0.05 denote a significant difference between the two groups. NS=not significant. Predicted values (means±SEM) for forced oscillatory parameters: Rs=2.33±0.07, Grs=0.45±0.01, S=7.4±2.1.

RESULTS

Baseline Lung Function

Anthropometric data and pulmonary function variables in the 42 patients who participated in the study are presented in Table 1. Compared with predicted normal values, FEV₁ and FEV₁/VC were significantly reduced (p<0.0001) and residual volume was significantly elevated in the asthmatic group (p<0.0009) and in the COPD group (p<0.0003). In the COPD group, FRC was slightly but significantly higher than predicted normal values (p<0.05).

Respiratory conductance was significantly lower than predicted (p<0.0001) in every subject. A marked frequency dependence of resistance was found, with Rs decreasing as frequency increased. Respiratory conductance did not differ significantly in the two groups, whereas a significant difference in FEV₁ was noted (p<0.0001), with the highest value being observed in the asthma group and the lowest in the COPD group. The negative frequency dependence of Rs (S) was significantly much steeper in the patients with COPD (p<0.05).

Airway Response After Cumulative Doses of Inhaled Salbutamol

No significant change in heart rate was recorded after salbutamol inhalation, and no side effects were reported by the patients. Baseline pulmonary function measurements in these 20 patients were not significantly different from mean values for the entire study population of 42 subjects.

Dose-response curves for bronchodilator responses are shown in Figure 1. The largest increase was seen for the two indexes after 200 μg of salbutamol. Patients with asthma showed significant dose-related increases in the Grs index as well as in the FEV₁ in-
Table 2—Respiratory Parameters at Baseline and After 200 μg of Salbutamol in Patients With Asthma and COPD*

<table>
<thead>
<tr>
<th></th>
<th>Baseline Values</th>
<th>After Salbutamol</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1.64±0.11</td>
<td>2.05±0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>1.20±0.12</td>
<td>1.35±0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rrs, cm H₂O·s·L⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>6.9±0.4</td>
<td>4.2±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>7.6±0.4</td>
<td>6.1±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grs, L·s⁻¹·cm H₂O·L⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0.16±0.01</td>
<td>0.26±0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>0.14±0.01</td>
<td>0.17±0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S, (10⁻⁵ cm H₂O·L⁻¹·s/Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>−131±22</td>
<td>−17±9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>−216±24</td>
<td>−116±15</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Predicted values (means±SEM) for forced oscillatory parameters: Rrs=2.33±0.07, Grs=0.45±0.01, S=7.4±2.1.

dex (ANOVA, p<0.0001), with significant changes after 400, 800, and 1200 μg as compared with the 200-μg dose (p<0.01, p<0.01, p<0.001). By contrast, in patients with COPD, no dose-related variations were found for these indexes after the initial 200-μg response. At each dose and for each parameter, bronchodilator responses in patients with asthma were significantly higher than in the other group (p<0.0005).

We compared the responses to salbutamol analyzed by means of the Grs index and the FEV₁ index: regardless of the group and the dose, there were no significant differences (Fig 1). For both indexes, the largest increase was observed after 200 μg of salbutamol. We therefore selected this dose for the second part of the study.

Airway Response After Inhalation of 200 μg of Salbutamol

Salbutamol caused a statistically significant increase in FEV₁, a significant increase in Grs, and frequency dependence of resistance became significantly less negative in all groups, as shown in Table 2.

The FEV₁ and Grs measurements were made in random order to take in account the delay of each measurement after inhalation of salbutamol. To check that this experimental design was not responsible for an artifact due to the effects of deep inflation on the bronchomotor tone, we analyzed the data considering the order of the two tests: in subgroup A, forced expiration was performed first and followed by FOT, whereas in subgroup B, the reverse order was used. We observed no significant difference in Grs or FEV₁ indexes between the subgroups in any of the groups (asthmatics, COPD).

The FEV₁ and Grs indexes were clearly higher in the asthma group than in the COPD group (Fig 2).

A linear relationship between the FEV₁ index and the Grs index was found in the overall study population (r=0.7, p<0.0001). We evaluated the Grs index and the FEV₁ index in terms of sensitivity and specificity for identifying asthmatics among patients with COPD by means of ROC curves. The cut-off points for these indexes with the largest number of well-classified patients according to the presence or absence of asthma were as follows: (1) for FEV₁ index, a 10% value corresponded to a sensitivity (proportion of true positives [asthmatics] correctly identified by the test) of 0.91 and to a specificity (i.e., proportion of true negatives [nonasthmatics] correctly identified by the test) of 0.95; and (2) for Grs index, a 10% value...
corresponded to a sensitivity of 0.95 and a specificity of 0.85.

In the asthma group, 21 subjects had a Grs index \( \geq 10\% \) and 20 had an FEV\(_1\) index \( \geq 10\% \) (Fig 2); these numbers were not significantly different from each other. Similarly, no significant difference was found in the COPD group (three subjects with a Grs index \( \geq 10\% \) and one with a FEV\(_1\) index \( \geq 10\% \)).

**DISCUSSION**

Therapy with \( \beta_2 \)-agonists is widely used in patients with COPD to decrease airway obstruction. The bronchodilator effect usually is assessed on the basis of changes in FEV\(_1\). However, compared with spirometry, the FOT offers a number of advantages. Due to the little cooperation required from the subject, the technique is applicable in all age groups and particularly in patients where conventional lung function tests are inapplicable, measurements are performed during tidal volume breathing, and forced expiratory maneuvers are not required. Furthermore, the FOT has proved capable of detecting subclinical airway abnormalities.\(^1\) However, despite the advantages offered by this method, it has not achieved routine usage and clinical evaluation is still needed.

The FOT has already been used to evaluate the responses to bronchoconstrictor agents. In normal subjects, Manço et al\(^8\) found increases in resistance and resonance frequency following the administration of bronchoconstricting drugs. Chinet et al\(^9\) showed that the FOT was as efficient as plethysmography in providing information about bronchial sensitivity and reactivity during a challenge with inhaled carbachol and concluded that it could be used for evaluating bronchial responsiveness. In subjects with a history of episodic dyspnea and wheezing consistent with asthma, Van Noord et al\(^5\) concluded that the FOT could be used in clinical practice during bronchial challenge tests as a substitute for spirometry. In asthmatic children, indexes derived from the FOT were found to be correlated to those derived from maximal and partial flow-volume curves obtained during methacholine challenge\(^6\) and a strong linear relationship was found between histamine-induced changes in FEV\(_1\) and Rrs.\(^21\)

As regards bronchodilatation, few studies have examined the value of the FOT for detecting acute changes in respiratory mechanics. The FOT has been proved capable of detecting a decrease in resistance in response to a single dose of a bronchodilator,\(^8\) and in patients with COPD, Wesseling et al\(^10\) demonstrated a significant decrease in resistance after inhalation of fenoterol. In a recent study, Van Noord et al\(^9\) compared the forced oscillation method with the forced expiration to detect minimal bronchodila-

loration. They studied one group of patients with airflow obstruction (asthma or COPD) after inhalation of 40 \( \mu \)g of salbutamol and concluded that, although the forced oscillatory parameters showed larger changes, FOT was less sensitive than forced expiration. However, to our knowledge, studies of the sensitivity and specificity of the FOT to separate asthmas from patients with COPD have not been performed and the FOT response to cumulative doses of \( \beta \)-adrenergic agonists has not been evaluated. We therefore investigated whether the FOT is of value for assessing the respiratory response to bronchodilators in patients with COPD.

We used the FEV\(_1\) index (computed as the ratio of the difference between postbronchodilator and prebronchodilator FEV\(_1\) values over the predicted value) to assess \( \beta_2 \)-agonist effects and to evaluate the value of the FOT for measuring the respiratory response to bronchodilators. This index is standardized for age, height, and sex, and is more suitable than the percent change in FEV\(_1\) for giving an optimal separation between asthmatics and subjects with COPD, and for patients whose initial FEV\(_1\) is very low.\(^11,12\) The Grs changes have been used as a measure of bronchodilator reversibility, and we computed a Grs index as the ratio of the difference between postbronchodilator and prebronchodilator Grs values over the predicted Grs. This method is similar to that used to obtain the FEV\(_1\) index. Reference Grs values were obtained in our laboratory in a group of healthy nonsmokers. In this group of normal subjects, we found a mean Grs value of 0.45 L.s\(^{-1}\).cm H\(_2\)O\(^{-1}\) (mean value for Rrs, 2.3 cm H\(_2\)O.s.L\(^{-1}\)), which is similar to the values for normal subjects reported in the literature.\(^13,22-26\)

At baseline, all our study subjects showed increased Rrs (decreased conductance) with a negative frequency dependence of resistance that was more marked at low frequencies; this pattern has been ascribed to a lack of mechanical homogeneity of the lungs and is commonly observed in airway obstruction.\(^1,2,27-29\) Shunt artifacts resulting from upper airway wall motion during the forced oscillation maneuver have been held responsible for underestimation of resistance values, especially in patients with airway obstruction.\(^27,30,31\) Supporting the cheeks, as was done by our patients, is a way to reduce the error.\(^32\) A comparative study of conventional and head generator techniques did not show the latter technique to be more sensitive for the detection of airway obstruction.\(^33\)

In routine bronchodilatation tests with salbutamol, the dose often administered to the patient is 200 \( \mu \)g: this dose is responsible for a large increase in FEV\(_1\), whereas higher doses of salbutamol appeared to
produce only a small increase in FEV\textsubscript{1}, but also to increase the risk of untoward effects.\textsuperscript{34} Since to our knowledge, no data are available concerning the response to high doses of salbutamol in terms of respiratory impedance, we sought to determine whether a similar behavior would be observed for Grs.

The shape of the dose-response curves using the Grs index was clearly identical to that of the dose-response curves using the FEV\textsubscript{1} index. Indeed, after the increase in the Grs index for 200 \(\mu\)g of salbutamol, nonsignificant changes were observed in the COPD group up to 1,200 \(\mu\)g of salbutamol, whereas a small and significant increase parallel to the FEV\textsubscript{1} curve was noted in the asthma group. We therefore selected the response to a dose of 200 \(\mu\)g of salbutamol to evaluate the sensitivity and specificity of the FEV\textsubscript{1} and Grs indexes.

In asthmatics, we found significant dose-related increases in the FEV\textsubscript{1} index in response to cumulative doses of salbutamol, although the largest response occurred after the first dose of 200 \(\mu\)g. With the highest dose of 1,200 \(\mu\)g of salbutamol, mean increase in FEV\textsubscript{1} was 0.61 ± 0.08 L (52 ± 6% of baseline values). These values are similar to those observed in previous studies. Higgins et al\textsuperscript{35} and Larsson and Svedmyr\textsuperscript{36} found a significant mean increase in FEV\textsubscript{1} of 0.60 L after 1,200 \(\mu\)g of salbutamol, and Marlin et al\textsuperscript{37} demonstrated a significant mean increase of 52% (percent of baseline values) after 1,600 \(\mu\)g of salbutamol. By contrast, in the patients with COPD, we found minor and nonsignificant dose-related increases in FEV\textsubscript{1}, expressed as percentages of predicted values (although FEV\textsubscript{1} variations expressed in the same way as in previous studies—absolute changes—showed a significant mean increase of 0.15 L after 200 \(\mu\)g, and 0.25 L after 1,200 \(\mu\)g). In patients with COPD with an FEV\textsubscript{1} less than 50% of predicted, a mean increase in FEV\textsubscript{1} of 0.2 L in response to salbutamol, whatever the dose, was noted by different authors.\textsuperscript{34,38,39} In a similar group of patients, Lipworth et al\textsuperscript{40} reported a mean increase of about 0.25 L after 1,000 \(\mu\)g of terbutaline. Thus, both in the asthma group and in the COPD group, FEV\textsubscript{1} changes seen in our study were consistent with previous studies.

We found that inhalation of 200 \(\mu\)g of salbutamol in this group of 42 patients with airflow obstruction resulted in an increase in the Grs index, which was significantly correlated to the increase in the FEV\textsubscript{1} index. The clinical value of the Grs index can be evaluated by assessing its sensitivity and specificity for identifying asthmatics among patients with obstructive airway disease. The ROC curves, which simultaneously present the sensitivity and specificity of a diagnostic procedure, can be used to determine the best discrimination of subjects. The threshold of FEV\textsubscript{1} index corresponding to the greatest number of subjects correctly classified was found to be 10%, similarly to previous studies.\textsuperscript{19} The threshold of Grs index was also found at 10%. We found, from the analysis of the data from the 42 subjects, that the Grs and FEV\textsubscript{1} indexes had quite similar sensitivities (0.95 and 0.91, respectively), whereas specificity was slightly lower for the Grs index compared with the FEV\textsubscript{1} index (0.85 and 0.95, respectively). As seen in Figure 2, the Grs index can be considered as sensitive as the FEV\textsubscript{1} index for detecting bronchodilatation and separating asthmatics and patients with COPD.

It has been shown that patients with COPD whose airflow limitation was classified as irreversible on the basis of the acute FEV\textsubscript{1} response to inhaled salbutamol can benefit from bronchodilator therapy. Thomas et al\textsuperscript{41} demonstrated that treatment with theophylline and/or inhaled salbutamol produced significant spirometric improvement in subjects with "irreversible" COPD. Because of the lack of a significant correlation between acute FEV\textsubscript{1} reversibility and ultimate improvement in FEV\textsubscript{1} following 2 weeks of therapy, they concluded that the acute FEV\textsubscript{1} response was not an effective criterion for separating those patients with COPD who are responsive and those who are unresponsive to bronchodilators. Our data suggest that evaluation of reversibility using the Grs index does not give additional information, compared with the acute FEV\textsubscript{1} response to inhaled salbutamol, for predicting the efficacy of bronchodilator therapy in patients with COPD.

In conclusion, this study demonstrates that the FOT is useful for detecting acute bronchodilator-induced changes in airway caliber. We found that the increase in Grs was equivalent to the increase in FEV\textsubscript{1} for detecting bronchodilatation in patients with obstructive conditions, and for identifying asthmatics among patients with obstructive pulmonary diseases. Since the FOT has the major advantage of being a simple method, requiring only the passive cooperation of the subject, such a technique may represent an alternative to the evaluation of airway obstruction reversibility by means of forced expiration.

ACKNOWLEDGMENTS: The authors wish to thank Dr. André Denjean for his helpful comments.

REFERENCES