A Comparison of the Effects of Anticholinergic and β2-Agonist and Combination Therapy on Respiratory Impedance in COPD*

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The effects of three different regimens of inhaled bronchodilators on spirometry and respiratory impedance as measured with the technique of forced oscillations were compared in a double-blind crossover study in 22 patients with stable chronic obstructive pulmonary disease (FEV1 <70 percent predicted). On three trial days, patients inhaled, in random order, 40 µg ipratropium bromide, 200 µg fenoterol hydrobromide, or a combination of 40 µg ipratropium and 100 µg fenoterol from a powder inhaler, followed by a second dose of the same drug after 60 min. The effects were measured at baseline and 20, 40, 60, and 150 min after the first inhalation. No significant decrease in total respiratory resistance at 8 Hz (Rrs) [8] was observed after ipratropium, whereas Rrs (8) decreased significantly 20 min after fenoterol and 40 min after the combination regimen (p<0.05). All three studied drugs resulted in a significant increase in the reactance (p<0.01) and decrease in resonant frequency. Both fenoterol (ΔFEV1, 34 percent, p<0.0001) and the combination regimen (ΔFEV1, 38 percent, p<0.0001) resulted in a significantly larger increase in FEV1 than ipratropium alone (ΔFEV1, 17 percent, p<0.0001). A second dose of fenoterol and of the combination regimen resulted in a further significant increase in FEV1 after 120 min (p<0.05). A second dose of ipratropium did not result in a further significant increase in FEV1. The changes in respiratory impedance were qualitatively similar for all three drug regimens, but larger in absolute terms after fenoterol and the combination regimen than after ipratropium. The similar effect of these drugs on the reactance can be explained by an increase in the capacitance of the respiratory system, and in combination with a decrease in frequency dependence of resistance, by assuming a decrease in peripheral airway resistance.

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FD = frequency dependence of the resistance; fo = frequency at which reactance is 0; R = resistance; Rrs (8) and Rrs [8] = respiratory resistance at 8 and 28 Hz, respectively; Rrs = respiratory system; X = reactance; Xrs (8) = respiratory reactance at 8 Hz; Z = impedance

Inhaled bronchodilators play an important role in the treatment of patients with chronic obstructive pulmonary disease (COPD). Until recently, β2-adrenergic inhalers were by far the most widely used, but since the introduction of anticholinergic drugs as inhaled bronchodilators, these drugs have been increasingly popular, especially in patients with COPD.1

Because decisions on bronchodilating treatment of patients with COPD are often based on the outcome of lung function measurements and reversibility tests, it is important to verify the exact response to bronchodilators. Generally, simple measurements of lung function have been used to assess the therapeutic efficacy of β-adrenergic and anticholinergic drugs.2,3 Occasionally, more complex measurements were used in an attempt to define the site along the airways at which the drugs are effective.4,5

In addition to the standard method of spirometry, impedance measurements of the respiratory system by means of the technique of forced oscillations6 may be useful to assess the effects of bronchodilating agents on the mechanical characteristics of the respiratory system of patients with COPD. This technique allows the determination of the resistance and reactance of the respiratory system over a wide frequency range during spontaneous quiet breathing, and, in contrast with spirometry, does not require forced expiratory maneuvers. This makes this technique very well-suited for serial determinations, since the measurement itself does not modify bronchial smooth muscle tone.7

Additionally, this technique may provide information on the effects of bronchodilating agents, not obtainable with other lung function techniques.8

Numerous studies have been published on the comparative effects of β2-adrenergic and anticholinergic drugs, both in standard and in higher doses, and on the effectiveness of the combination of these drugs.1,2,3,8-15

In the present study, we have used the technique of forced oscillations and spirometry in a study of the effects of the inhalation of standard doses of fenoterol,
a β₂-adrenergic agent and ipratropium bromide, a quaternary isopropyl derivative of atropine and a combination of the two drugs on the impedance of the respiratory system and on FEV₁ in patients with COPD.

Patients and Methods

Patient Selection

Twenty-two male patients with chronic bronchitis and an obstructive ventilatory impairment, with a mean age of 66 years (range, 53 to 78 years), were selected for the study. Inclusion criteria were a clinical diagnosis of COPD and an obstructive lung function impairment as defined by FEV₁ of less than 70 percent of predicted,* with an acute reversibility of less than 15 percent of the baseline value following an administration of an inhaled bronchodilator. All patients had a history of cigarette smoking of at least 20 pack-years. They had no documented upper respiratory tract infections in the two weeks before testing. Patients with documented serious renal, hepatic, endocrine, metabolic, or cardiovascular disease were excluded from the study. All patients were familiar with the use of inhaled bronchodilators.

At entry into the study, patients performed baseline spirometry, and the reversibility of the airflow obstruction was determined on two selection days. Sustained-release theophyllines were continued during the selection days.

On selection day 1, reversibility was determined 30 min after the inhalation of two puffs (40 µg) ipratropium bromide and on selection day 2, it was determined 30 min after the inhalation of two puffs (400 µg) fenoterol hydrobromide, both from metered dose inhalers. These reversibility tests were performed within one week before starting the actual trial. None of the reversibility tests revealed an increase in FEV₁ greater than 15 percent of the baseline value or greater than 7 percent of the predicted value.

The actual studies were performed after abstinence from sustained-release theophyllines for 24 h and inhaled bronchodilators for 8 h. None of the patients used any of the new long-acting sympathicominetics. Treatment with inhaled and oral steroids was continued at the same dose throughout the study period. Five patients used oral corticosteroids (prednisolone, 5 to 10 mg/day), one inhaled beclomethasone 1.6 mg/day. The study was approved by the local ethics committee. Informed consent was obtained from all patients. In Table 1, the characteristics of the subject population are summarized.

Study Design

The study was of double-blind random crossover design. On three separate days, at least 48 h apart, the effects of the inhalation of three different test medications were determined. Following base-

### Table 1—Anthropometric and Spirometric Data of the Patient Group (n = 52)*

<table>
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<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td>Age, yr</td>
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<td>Height, cm</td>
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<tr>
<td>ΔFEV₁, IPR, L</td>
<td>0.068</td>
<td>0.115</td>
</tr>
</tbody>
</table>

*IPR = ipratropium; FEN = fenoterol; Sel = selection day.

Line impedance and spirometric measurements, all patients received either 200 µg fenoterol hydrobromide, 40 µg ipratropium bromide, or a combination of 100 µg fenoterol and 40 µg ipratropium, all from a powder inhaler (Inhalator, Ingelheim).

All medication was administered in the morning between 8 and 10 am by the same investigator.

Impedance measurements and spirometry were performed 20, 40, and 60 min after the inhalation of the drug. After 60 min, a second dose of the test medication was given; 1 h after this second dose, lung function assessments were repeated. Impedance measurements always preceded spirometry.

Patients were asked for side effects and the pulse rate was recorded.

Lung Function Assessment

Spirometry was performed using a wet spirometer (Gould Pulmonet III). Three forced expirations were recorded at each measurement: the highest value of FEV₁ was used for the subsequent calculations. Impedance (Z) of the respiratory system (rs) was determined with the technique of forced oscillations. This technique is extensively described elsewhere.* A complex pseudorandom noise signal consisting of frequencies ranging from 4 to 52 Hz in steps of 4 Hz appearing with random phase shift was used. The signal, generated by an oscillator and amplified and transmitted by a loudspeaker, is superimposed on spontaneous breathing.

This signal is applied at the mouth of the subject who is instructed to support the cheeks and the floor of the mouth with both hands. Mouth pressure relative to atmospheric pressure and air flow; transduced to a pressure signal, is recorded by two identical differential transducers with equal frequency characteristics (Valdyne MP 45). Pressure and flow signals are fed directly without filtering into a Fourier analyzing system, dividing pressure by flow. The system calculated an impedance for each of the investigated frequencies. This impedance is partitioned into a real part or resistance (R) and an imaginary part or reactance (X).

As a criterion for the validity of the measurements, a coherence function was calculated at each frequency. This indicated the amount of noise generated by the subject's breathing, present in the measured signal. Only impedance values with a coherence function ≥0.95 were retained.

All measurements were performed by the same laboratory staff member.

Data Analysis

Three consecutive impedance measurements were performed and the values thus obtained were averaged. To express the results, five sets of impedance parameters were used: the total respiratory resistance at 8 Hz (Rs [8]) and 28 Hz (Rs [28]), respiratory reactance at 8 Hz (Xrs [8]), resonant frequency, ie, the frequency at which reactance is 0 (fo), and the frequency dependence of the resistance (FD) defined as the ratio Rs [28]-Rs [8]/Rs [28], indicating the slope of the resistance versus frequency curve. A negative slope means a decrease in Rs with increasing frequency.

Mean values were compared using students paired t tests and p values <0.05 were retained as statistically significant.

Results

Twenty patients completed the three-day study. Two patients failed to complete the study, one patient because of an upper respiratory tract infection during the study and one patient because he could not be familiarized with the impedance measurements.

Differences in baseline values for FEV₁ and all analyzed impedance data among the three study days
FIGURE 1. Mean values of FEV1 (ml) after 40 μg ipratropium (IPR) bromide, 200 μg fenoterol (FEN) hydrobromide, and a combination (COMB) of 40 μg ipratropium and 100 μg fenoterol. Levels of significance for all figures: n.s. = not significant; * = 0.01 ≤ p < 0.05; ** = 0.001 ≤ p < 0.01; *** = 0.0001 ≤ p < 0.001; and **** = p < 0.0001

FIGURE 2. Values for resistance at 8 Hz (Rrs (8)) in kPa/s/L after 40 μg ipratropium (IPR) bromide, 200 μg fenoterol (FEN) hydrobromide, and a combination (COMB) of 40 μg ipratropium and 100 μg fenoterol.
were not statistically significant. All three study drugs caused a statistically significant increase in FEV₁ at 20, 40, and 60 min after the inhalation (Fig 1). After 20 min the mean increase in FEV₁ after fenoterol was 34 ± 14.2 percent of baseline value, after ipratropium bromide it was 17 ± 9.6 percent, and after the combination therapy it was 38 ± 17.7 percent. After 20 min, no further significant increase in FEV₁ was observed, and significant increases in FEV₁ persisted during the first hour for all three drugs. The second dose of fenoterol and of the combination regimen, but not of ipratropium bromide, resulted in a slight further increase in FEV₁ at 120 min (p<0.05).

The values of Rs at 8 Hz are illustrated in Figure 2. Twenty minutes after the inhalation of fenoterol, the resistance at 8 Hz decreased significantly by 0.043 ± 0.017 kPa/s/L from 0.436 ± 0.154 kPa/s/L to 0.393 ± 0.142 kPa/s/L. Forty minutes after the combination regimen, Rs (8) had decreased significantly by 0.045 ± 0.017 kPa/s/L from 0.421 ± 0.173 kPa/s/L to 0.376 ± 0.157 kPa/s/L. A second dose of the tested drugs did not result in a further significant decrease in Rs values. The changes in Rs (8) after the inhalation of ipratropium bromide did not reach a level of significance at any time of measurement and the changes in Rs (28) were not statistically significant after any drug.

Under baseline conditions, a marked frequency dependence of resistance was found, in that the oscillatory resistance decreased with increasing frequency resulting in negative values for FD as is illustrated in Figure 3. Frequency dependence of resistance became significantly less negative after fenoterol and the combination regimen, at 20 and 40 min. FD increased significantly only at 20 min after the inhalation of ipratropium bromide. Only in the case of fenoterol did a second dose result in a further significant increase in frequency dependence values at 120 min.

Mean baseline reactance values at 8 Hz were highly negative on the three study days (Fig 4). All three medications resulted in a significant increase in the reactance of the respiratory system at 8 Hz. This effect lasted up to 60 min after ipratropium bromide (p<0.0001) and up to 120 min after fenoterol and the combination (p<0.0001).

As a result of the highly negative values for reactance, increased baseline values for resonant frequency, ranging from 18 to 38 Hz, were found. All three study drugs resulted in statistically significant decreases in fo. After ipratropium bromide, the resonant frequency decreased from 28.1 ± 3.4 Hz to 25.1 ± 3.9 Hz at 20 min (p<0.0001), after fenoterol fo decreased from 28.4 ± 3.7 Hz to 24.7 ± 5.4 Hz at 20 min (p<0.001), and finally to 24.1 ± 6.0 Hz at 120 min (p<0.001), and inhalation of the combination resulted in a maximal decrease in fo from 27.8 ± 4.8 Hz to 22.3 ± 5.6 Hz at 60 min (p<0.0001). Decreases in resonant frequency were statistically significant throughout the observation period and only a second dose of fenoterol resulted in a further significant
decrease in \( f_0 \) from 25.3 ± 6.1 Hz to 24.1 ± 6.0 Hz (\( p < 0.05 \)).

No serious side effects were reported by any of the patients throughout the entire study period. No significant differences in pulse rate were found among the three medications.

**Discussion**

In the present study, we have used spirometry and the technique of forced oscillations to assess the effects of three regimens of bronchodilating agents on the lung function and mechanical characteristics of the respiratory system in patients with COPD.

Both 40 \( \mu \)g ipratropium bromide and 200 \( \mu \)g fenoterol and the combination of 40 \( \mu \)g ipratropium + 100 \( \mu \)g fenoterol resulted in a statistically and clinically significant increase in FEV\(_1\), and in the doses used in our study, fenoterol and the combination of fenoterol and ipratropium bromide had a more marked effect on FEV\(_1\) than ipratropium bromide alone. It is observed that the increase in FEV\(_1\) on the study days was larger than on the selection days. An influence of the discontinuation of treatment with the sustained-release theophyllines on the bronchodilator response seems unlikely since baseline FEV\(_1\) differed not significantly between the selection days and the actual study days. A possible explanation is the fact that on the selection days, reversibility was tested after the inhalation of bronchodilating agents from a metered dose inhaler, while on the study days, the bronchodilators were inhaled from a dry powder inhaler. Although several studies have demonstrated no significant differences in efficacy between bronchodilators inhaled from pressure aerosols and dry powder delivery systems, poor hand-lung coordination may have resulted in a smaller increase after the use of the aerosols.

It has been suggested that ipratropium bromide has a slower onset of action than isoproterenol and has a longer duration of action than albuterol. In our study, all three drug regimens resulted in a maximal or near maximal increase in FEV\(_1\) after 20 min, with no further significant increase in FEV\(_1\) throughout the observation period of 2 h. It is not impossible that a longer observation period would have revealed a superiority of ipratropium bromide over fenoterol.

Using the technique of forced oscillations in our patient group, high values for oscillatory resistance at lower frequencies, and frequency dependence of resistance, were demonstrated under baseline conditions. Also, high values for resonant frequency were found as a result of the highly negative values for reactance at lower frequencies. These findings have been described as characteristic for airway obstruction by Clement et al.

The inhalation of all three study drugs resulted in relatively small and for the most part statistically nonsignificant decreases in the real part of the respiratory impedance. On the other hand, the changes in
the imaginary part of impedance were highly significant with all three study drugs. Increases in the reactance values of the respiratory system, resulting from the inhalation of bronchodilators in patients with airway obstruction, have been reported previously.8,22-24

The frequency dependence of Rrs and Xrs data in patients with COPD can satisfactorily be explained by the model of Nagels et al.25 based on the model of Mead.26,27 In that algorithm, reactance is determined by the capacitance of the respiratory system, defined as the sum of lung compliance and airway compliance in series with chest wall compliance and the gaseous inertance, predominantly localized in the central airways. Since inductive reactance or inertance will only decrease by bronchodilation of the central airways,8,25 the increase in the reactance values can be explained by an increase in the capacitance of the respiratory system. Since chest wall compliance will not be influenced by the inhalation of bronchodilating drugs, the finding of an increase in reactance combined with a decrease in frequency dependence of resistance suggests an increase in the capacitance of the respiratory system resulting from a decrease in the resistance of the peripheral airways and/or an increase in the compliance of the airways.25,27,28

De Troyer et al29 have demonstrated a decrease in elastic recoil pressure of the lung following the intravenous administration of atropine and a slight increase in lung compliance, whereas inhalation of ipratropium bromide did not modify the static mechanical properties of the lung.

Since lung compliance is not likely to be of influence in the presence of increased peripheral airway resistance as is the case in patients with COPD, it is thought that the increase in the reactance results mainly from a decrease in peripheral airway resistance and an increase in airway compliance.

Shunt artifacts resulting from upper airway wall motion have been held responsible for errors in the estimation of respiratory impedance and its frequency dependence, especially in patients with airway obstruction.22,25 Supporting the cheeks as was done by our patients does not fully eliminate this error.30 These shunt properties cause an underestimation of the resistance values at lower frequencies in patients with airway obstruction.31 Recently, Ying et al32 confirmed the findings of negative frequency dependence of resistance in reactance in these patients comparing input impedance measured with a head generator to minimize transmural pressure across extrathoracic airway walls to transfer impedance obtained with a pressure input at the chest in patients with COPD.

Our impedance data were not corrected for the influence of lung volume. A possible decrease in lung volume after bronchodilation may result in an increase in Rrs and a decrease in frequency dependence of resistance and in reactance in patients with COPD.25 This increase in Rrs resulting from changes in lung volume may contribute to the discrepancy between spirometric and Rrs changes. On the other hand, the increase in frequency dependence of resistance and reactance values was found despite the possible opposite effects of lung volume changes in these patients.

We have observed a more pronounced effect of the combination therapy on the reactance of the respiratory system and on the resonant frequency, while the immediate effects of ipratropium bromide and feno-terol on both these impedance parameters were qualitatively similar, suggesting equal sites of action of these drugs. Previous studies have provided conflicting information on the comparative effectiveness of standard dose of anticholinergic and β-adrenergic agents in chronic airflow obstruction.9-15

Most studies on the predominant site of action of anticholinergic and β2-sympathomimetic agents have been performed in patients with asthma. Information on this subject in patients with COPD is relatively scarce. In asthma, conflicting results have been reported. Storms et al33 concluded that the major effect of ipratropium appears to be in the larger airways. This finding was later confirmed by Snow et al34 and Ashutosh et al.35 From a study on the effect of ipratropium on maximal midexpiratory flow and FEV1, Gross36 concluded that ipratropium acts on central and peripheral airways. In determining specific airway conductance as well as flow from maximal expiratory flow volume curves, Elwood and Abboud37 could not differentiate between sites of predominant action of fenoterol and ipratropium. In comparing the bronchodilator responses to atropine and terbutaline in asthma, Chick and Jenne38 concluded that atropine exerts its bronchodilation action predominantly in larger airways, as is evidenced by an equal improvement in the plethysmographically determined airway resistance after use of terbutaline and atropine and by a greater increase in flow at 50 percent exhaled volume after use of terbutaline.

Our observation of qualitatively similar bronchodilating effects of β2-sympathomimetic and anticholinergic agents on peripheral airways is in keeping with the identification of muscarinic receptors, especially M3 receptors in airway smooth muscle.39 Based on autoradiographic visualization and selective muscarinic antagonists, Mak and Barnes40 have demonstrated that muscarine receptors are localized in smooth muscle even in peripheral airways.

In our study, no statistically significant additional effect was observed by doubling the dose in the second hour of the observation. This is in keeping with the findings of Le Doux et al40 who observed no objective benefit from doubling the standard dose of ipratropium
bromide in patients with COPD.

In contrast with the findings observed after the inhalation of ipratropium bromide, a second dose of fenoterol did lead to a statistically significant, although clinically probably irrelevant, additional effect in our study. A similar finding has been reported by Larsson and Svedmyr with albuterol. In summary, standard doses of fenoterol and ipratropium bromide and of a combination of these two drugs resulted in qualitatively similar changes in the impedance of the respiratory system, particularly a decrease in frequency dependence of resistance and an increase in reactance. These changes can be explained by an increase in the capacitance of the respiratory system due to an increase in airway compliance and/or a decrease in peripheral airway resistance. The combination of 40 μg ipratropium bromide plus 100 μg fenoterol resulted in a significantly larger increase in FEV1 than did ipratropium bromide alone, and a marginally larger increase in FEV1 than 200 μg fenoterol alone.

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