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Use of a Mucus Clearance Device Enhances the Bronchodilator Response in Patients With Stable COPD*

Norman Wolkove, MD, FCCP; Hany Kamel, MD; Michael Rotaple, MD; and Marc A. Baltzan Jr., MD

**Study objective:** To determine whether the use of a mucus clearance device (MCD) [Flutter; Axcan Scandipharm; Birmingham, AL] could improve the bronchodilator response to inhaled ipratropium and salbutamol delivered by a metered-dose inhaler in patients with stable, severe COPD.

**Patients:** Twenty-three patients with severe COPD were studied. Mean ± SD age was 71.7 ± 6.3 years. Mean FEV1 was 0.74 ± 0.28 L or 34.5 ± 12.7% predicted.

**Methods:** Patients were tested in random order on 2 subsequent days after using an MCD or a sham MCD. A bronchodilator (four puffs; each puff delivering 20 μg of ipratropium bromide and 120 μg of salbutamol sulfate) was administered by metered-dose inhaler with a holding chamber after use of the MCD or sham MCD. Spirometry was performed before and after use of the MCD or sham MCD, and at 30 min, 60 min, and 120 min after the bronchodilator. Six-minute walk distance was tested between 30 min and 60 min; oxygen saturation, pulse, and a dyspnea score were recorded before and after walking.

**Results:** Immediately after use of the MCD, but not the sham MCD, there was a statistically significant (p < 0.05) improvement in FEV1 and FVC (11 ± 24% vs 1 ± 7% and 18 ± 33% vs 6 ± 18%, respectively). Whether patients were pretreated with the MCD or sham MCD, there was a significant improvement in FEV1 and FVC compared to baseline with combined bronchodilator therapy. At 120 min, the change in FEV1 after treatment with the MCD was greater than with the sham MCD (186 ± 110 mL vs 130 ± 120 mL; p < 0.05). When comparing the MCD to the sham MCD, 6-min walk distance was greater (174 ± 92 m vs 162 ± 86 m; p < 0.05), with less dyspnea before and at the end of walking.

**Conclusion:** Patients with severe COPD may demonstrate a significant bronchodilator response to combined ipratropium and salbutamol delivered by metered-dose inhaler. This response may be enhanced and additional functional improvement obtained with the prior use of a bronchial MCD.

**Key words:** bronchodilators; ipratropium; mucus clearance device; obstructive lung disease; physiotherapy; salbutamol

**Abbreviations:** MCD = mucus clearance device; 6MWT = 6-min walk test

*COPD is characterized by airflow obstruction leading to dyspnea, which often limits activity. Bronchodilators most frequently administered by metered-dose inhaler remain the mainstay of pharmacotherapy for these individuals. However, the response to these agents is variable and, even when present, is frequently small in absolute terms. Strategies to improve bronchodilator efficacy have included the use of holding chambers and using combined therapy with a β-agonist and an anticholinergic agent.1–4

The mucus clearance device (MCD) [Flutter; Axcan Scandipharm; Birmingham, AL] is a simple handheld apparatus that promotes the clearance of sputum through the generation of low-frequency pressure waves (Fig 1). It has been used most extensively in patients with cystic fibrosis and bronchiectasis.5–8 However, we postulated that it might also be efficacious in patients with COPD. Specifically, by improving mucus clearance, the MCD may allow inhaled bronchodilators to penetrate airways more completely, thereby optimizing their beneficial effect. Furthermore, the clearance of mucus from

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smaller airways may directly improve diffuse airflow obstruction. Therefore, we studied the effect of combined salbutamol and ipratropium therapy delivered by metered-dose inhaler on maximal bronchodilation. In this study, we sought to determine whether the MCD, when added to therapy with salbutamol and ipratropium, could provide additional improvement in pulmonary function, exercise capacity, and dyspnea compared to combined bronchodilator treatment alone in patients with stable COPD.

**Materials and Methods**

**Patients**

Twenty-three patients with severe COPD were studied (Table 1). All subjects were former cigarette smokers with a clinical history consistent with COPD. Patients were eligible for inclusion if they had an FEV\(_1\) \(\leq 50\%\) predicted and an FEV\(_1\)/FVC ratio < 65\%. All patients were in clinically stable condition and were free of obvious respiratory tract infections. They were studied while hospitalized at Mount Sinai Hospital, Montreal, Canada, for a pulmonary rehabilitation program or for convalescence after a recent exacerbation of COPD. All patients were receiving inhaled β-agonists and/or ipratropium bromide but were asked to refrain from using these medications for 12 h prior to the beginning of each study-day protocol.

The Research and Ethics Committee of Mount Sinai Hospital approved the study. The protocol was explained to all patients, and written informed consent was obtained from all participants.

**Experimental Protocol**

The patients were studied at the same time in the morning on 3 separate days. The first day was considered the “familiarization” or prestudy day. At this time, subjects were asked to complete a brief questionnaire that included demographic data (Table 1). They were asked if they had noticed cough on most days of the week year round. Those who answered in the affirmative were asked whether the cough was dry or productive of significant amounts of visible mucus.

On this day, subjects were introduced to the MCD and taught its correct use. Patients were instructed to breathe through the device and to change the inclination of the MCD slightly, up or down from the horizontal, and to choose the position that resulted in the greatest “fluttering” or vibration sensation within the chest.\(^5\) Optimizing the sensation from the MCD was then to be done in this way on the later MCD study day.

On 2 subsequent days, in random order, the bronchodilator response to inhaled ipratropium and salbutamol was determined after the subject had used either the MCD or a sham MCD (Fig 2). The MCD was used according to the technique described above. The sham MCD was identical to the MCD, but had the stainless steel ball removed in order to remove the infrathoracic oscillations.

Pulmonary function test results were recorded prior to use of the MCD or sham MCD. The MCD or sham MCD were then used for 10 min, and pulmonary function tests were immediately repeated. The latter testing took < 5 min. Four puffs of Combivent (Boehringer Ingelheim; Burlington, ON, Canada), each puff delivering 20 μg of ipratropium bromide and 120 μg salbutamol sulfate (equivalent to 100 μg salbutamol base), were then administered using a metered-dose inhaler with a holding chamber (Aerochamber; Boehringer Ingelheim). Pulmonary function tests were then repeated at 30 min, 60 min, and 120 min after the bronchodilator.

Between the 30-min and 60-min evaluations, a 6-min walk test (6MWT) was done in a marked hospital corridor. No encouragement was given during the test, but individuals were told to walk as fast as comfortably possible. The total distance traversed was noted. Subjects were asked to scale their sensation of dyspnea prior to and immediately after the 6MWT using a 10-point Borg scale.

Pulse rate was measured at the beginning and end of the

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**Table 1—Demographic and Respiratory Characteristics (n = 23)*

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<th>Characteristics</th>
<th>Data</th>
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<tr>
<td>Age, yr</td>
<td>71.7 (6.3)</td>
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<tr>
<td>Male gender, No. (%)</td>
<td>10 (43.5)</td>
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<tr>
<td>Smoking history, No. (%)</td>
<td>23 (100)</td>
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<tr>
<td>Chronic cough, No. (%)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Chronic sputum, No. (%)</td>
<td>15 (65.0)</td>
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<tr>
<td>FEV(_1), L</td>
<td>0.74 (0.28)</td>
</tr>
<tr>
<td>FEV(_1), percent predicted</td>
<td>34.5 (12.7)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.54 (0.53)</td>
</tr>
<tr>
<td>FVC, percent predicted</td>
<td>49.2 (14.7)</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>48.4 (14.3)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated.

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*Figure 1. Schematic description of the Flutter MCD. For use as a sham MCD, the steel ball was removed.*

*Figure 2. Schematic description of the protocol during testing days. Use of MCD (Flutter) or the sham MCD was performed under direct supervision for 10 min. SB = baseline spirometry; S0 = spirometry before the bronchodilator; S30 = spirometry 30 min after the bronchodilator; S60 = spirometry 60 min after the bronchodilator; S120 = spirometry 120 min after the bronchodilator.*
Pulmonary Function Testing

Pulmonary function testing was done by simple spirometry. Spirometry was performed prior to and immediately after use of the MCD or the sham MCD, and 30 min, 60 min, and 120 min after the bronchodilator. The FEV1 and FVC were recorded on the best of three valid expiratory efforts (according to American Thoracic Society standards) using an electronic Spirometer (Vitalograph model 42.000 Type C; Vitalograph Ltd.; Buckingham, UK). Predicted values were those of Crapo et al.9

Statistics

The study design was that of a randomized, crossover placebo or, in this case, sham treatment controlled trial. A priori sample size calculations estimated that 20 patients with this design provided 90% power and 95% confidence to detect a minimal difference of 50 mL in FEV1.

Demographic data are summarized using descriptive statistics with standard deviations. The t test for paired measurements was used for all comparisons. Statistical significance was declared at p < 0.05 for planned comparisons of all spirometric measurements with baseline, and at parallel time points between use of the MCD and sham MCD.

RESULTS

All of the 23 subjects enrolled had severe chronic airway obstruction (Table 1). Figure 3 shows the absolute and percentage change in FEV1 after use of the MCD and sham MCD. Time 0 represents the change immediately after use of the MCD or sham MCD. The 30-min, 60-min, and 120-min values represent changes (compared to baseline) after the bronchodilator had been administered following use of the MCD or sham MCD. When expressed in this way, there was a negligible change immediately after use of the sham MCD. In absolute terms, there was a statistically significant (p < 0.05) improvement immediately after use of the MCD, but this was small, with the mean change of 50 ± 90 mL. At 30 min, 60 min, and 120 min after the bronchodilator, the change in FEV1 compared to baseline improved significantly in the MCD and sham MCD groups. The mean improvement 120 min after the bronchodilator was 186 ± 110 mL in the MCD group, a significantly larger improvement (p < 0.05) than the parallel 130 ± 120 mL mean improvement in the sham MCD group.

When expressed as percentage change in FEV1 compared to baseline, there was a small improvement in FEV1 after use of the MCD of 11 ± 24% (p < 0.05), while the change after the sham MCD was only 1 ± 7%. At 30 min, 60 min, and 120 min after the bronchodilator, the change in FEV1 expressed as percentage change from baseline improved significantly in both groups. Although the improvement in FEV1 expressed as percentage change from baseline was always greater after use of the MCD than the sham MCD, the difference in the magnitude of the improvement, when expressed in this way, was not statistically significant until 120 min, when the mean improvement after use of the MCD (36 ± 23%) was statistically greater (p < 0.05) than the mean improvement after the sham MCD (24 ± 18%).

Figure 4 shows the change in FVC in absolute values and percentage after use of the MCD and sham MCD. The statistically significant mean improvement after use of the MCD was 199 ± 300 mL, while the mean improvement after the sham MCD was only 65 ± 300 mL. The difference in the changes after use of the MCD vs the sham MCD did not reach a statistically significantly level (p = 0.33). In a manner similar to FEV1, changes in FVC improved significantly after the bronchodilator in both groups. At 120 min after the bronchodilator, the mean FVC improved by 435 ± 380 mL in MCD group and 368 ± 360 mL in the sham MCD group.

When expressed as percentage change in FVC
immediately after use of the MCD but not after the sham MCD, there was a significant (p < 0.05) improvement in FVC (18 ± 33% vs 6 ± 18%). After the bronchodilator, the percentage change in FVC at all times was significant in both groups. At 120 min, the change after use of the MCD (36 ± 43%) was greater but not statistically different than the change after the sham MCD (28 ± 30%; p = 0.09).

In general, the changes demonstrated tended to be slightly larger in the patients who reported cough. For the subgroup of 16 patients with cough (15 of whom also reported sputum), the mean percentage change in FEV₁ for the MCD and sham MCD groups at 120 min was 45 ± 22% and 30 ± 38%, respectively (p < 0.05). The corresponding values at 120 min for FVC in the MCD and sham MCD groups was 44 ± 47% and 36 ± 31%, respectively.

The results of the 6MWT are presented in Table 2. As compared to results after use of the sham MCD, following use of the MCD there was a greater distance walked, a lower dyspnea score before and after exercise, and a lower heart rate, with a higher saturation at the end of the walk test.

**Discussion**

In this study, we have shown significant improvement in lung function after inhaled bronchodilator therapy with a combination of ipratropium and salbutamol in patients with severe COPD. Regardless of whether patients had been pretreated with the MCD or sham MCD, the administration of ipratropium and salbutamol resulted in significant improvements in FEV₁ and FVC between 30 min and 120 min later. However, the prior use of the MCD, compared to the sham MCD, improved the subsequent bronchodilator response in these patients. Functional outcomes of exercise capacity and dyspnea were also favorably influenced by the addition of the MCD to combined bronchodilator therapy. Patients with a history of cough and sputum seemed to benefit most from the MCD.

Traditionally, β-agonists have been used to treat patients with chronic lung disease. More recently, attention has been focused on the use of anticholinergic therapy in the treatment of COPD. While adequate doses of either agent alone may result in similar degrees of bronchodilation, it has been shown that the combination of ipratropium and a β-agonist is superior to treatment with single agents. Furthermore, the use of a combination of ipratropium and albuterol is superior to either agent alone in identifying bronchodilator responsiveness in patients with COPD.

In this study, we chose to use higher-than-"standard" doses of salbutamol and ipratropium (four puffs vs two puffs). We did so because we wanted to optimize the bronchodilator response in order to see whether the use of an MCD provided additional benefit. It has been suggested that higher-than-standard doses of these agents may be necessary to promote maximal bronchodilatation and improvement in exercise performance.

Although improvement in lung function is an important end point, functional outcomes may be more relevant to patients themselves. At the time the 6MWT was done, baseline dyspnea was already lower in the MCD group compared to the sham
MCD group (Table 2). After use of the MCD (compared to the sham MCD) and the bronchodilator, subjects were able to walk further, had a better oxygen saturation, and were slightly less dyspneic. Interestingly, at the time the 6MWT was performed (30 to 60 min after bronchodilator), there was no significant difference in FEV$_1$ or FVC between use of the MCD and the sham MCD. This suggests that use of the MCD may have physiologic benefits not adequately measured by FEV$_1$ or FVC alone.

In order to explain any potential benefits of the MCD, one must understand the principles of its design. The Flutter device is a small handheld pipe-like device with a plastic mouthpiece and a conical perforated cover at the opposite end (Fig 1). Located within is a stainless steel ball that can roll up and down repeatedly during each exhalation, producing oscillations in air pressure and flow.$^{15,16}$ The positive expiratory pressure produced is thought to be between 6 cm H$_2$O and 20 cm H$_2$O.$^{15,16}$ By changing the inclination of the MCD, the patient selects the position that results in the greatest resonance, which is perceived as “fluttering” or vibration sensation within the chest. The resultant oscillations loosen mucus and promote expectoration. It has been used primarily as an adjunct to physiotherapy in patients with bronchiectasis and cystic fibrosis.$^5$ In the latter setting, it has been found to be more than three times as effective in increasing sputum expectoration as traditional drainage and chest clapping.$^5$ It has also been shown to be efficacious in small studies of patients with chronic obstructive lung disease.$^{17–19}$ As might be expected, patients who report sputum production may benefit more from the MCD,$^{15}$ a finding also seen in the present study.

In addition to promoting mucus expectoration, and in part perhaps as a result of this, the MCD has been shown to improve pulmonary function in patients with obstructive lung disease.$^{17–19}$ The statistically significant improvement in FEV$_1$ immediately after use of the MCD in this study was small in absolute terms, and probably not clinically significant. However, others$^{17–19}$ have shown a significant increase in lung function parameters (vital capacity, FEV$_1$, forced expiratory flow) after more prolonged use in an outpatient setting. In part, these may relate to the salutary effect of positive expiratory pressure in patients with severe airway obstruction.

The improved bronchodilator response to salbutamol and ipratropium after use of the MCD compared to the sham MCD may have several explanations. Most obvious is improved aerosol penetration distally as a result of mucus mobilization as already described. In addition, by preventing expiratory airway collapse, the total cross-sectional airway caliber may be maintained for better dispersion of inhaled aerosol.

In conclusion, patients with severe COPD may exhibit a significant bronchodilator response to inhaled ipratropium and salbutamol. This response may be enhanced and additional functional improvement obtained with the prior use of an MCD.

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