

# A randomized trial to evaluate the sustained efficacy of a mucus clearance device in ambulatory patients with chronic obstructive pulmonary disease

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N Wolkove, MA Baltzan Jr, H Kamel, M Rotaple. A randomized trial to evaluate the sustained efficacy of a mucus clearance device in ambulatory patients with chronic obstructive pulmonary disease. *Can Respir J* 2004;11(8):567-572.

**OBJECTIVE:** To determine whether a mucus clearance device (MCD) (Flutter; Axcan Scandipharm, USA) could consistently improve the bronchodilator response and exercise performance in patients with chronic obstructive pulmonary disease (COPD) when used in an ambulatory setting over a one-week period.

**SUBJECTS:** Fifteen patients with severe COPD (mean age  $71 \pm 10$  years) were studied.

**METHODS:** A randomized crossover design compared an MCD with a sham MCD (SMCD), in which each were tested for one week. At the beginning and end of each study week, forced expiratory volume in 1 s ( $FEV_1$ ) and forced vital capacity (FVC) were measured before and after MCD or SMCD. A bronchodilator aerosol (ipratropium bromide and salbutamol sulphate) was then given, and  $FEV_1$  and FVC were remeasured 30 min, 60 min and 120 min later. A 6 min walk test (6MWT) was also performed.

**RESULTS:**  $FEV_1$  improved significantly ( $P < 0.05$ ) after bronchodilator administration with both the SMCD and MCD. The improvement was always greater with MCD use than with SMCD. At the baseline measure, 120 min postbronchodilator administration, the mean  $FEV_1$  improved by  $24 \pm 24\%$  with SMCD use and  $60 \pm 28\%$  with MCD use ( $P < 0.05$ ). After one week of use, the corresponding values at 120 min were  $19 \pm 24\%$  and  $43 \pm 26\%$  ( $P < 0.05$ ). Similar findings were obtained for FVC. 6MWT distances increased by  $29 \pm 12$  m ( $P < 0.05$ ) after one week of MCD use, whereas it decreased slightly (by  $16 \pm 18$  m) after SMCD. The decline in saturation with the 6MWT was smaller with MCD use than with SMCD use. After one week, the decline in saturation with MCD use was similar to baseline levels, although patients were walking farther. After one week, dyspnea was lower on walking with MCD use than with SMCD use.

**CONCLUSION:** Patients with COPD had an increased response to bronchodilator therapy after use of the MCD compared with SMCD use. The increase persisted after one week of use, and was associated with improved exercise performance as measured by the 6MWT.

**Key Words:** *Bronchodilators; Dyspnea; Mucus clearance device; Obstructive lung disease; Six-minute walk*

## Un essai aléatoire pour évaluer l'efficacité soutenue d'un dispositif de clairance muqueuse chez les patients ambulatoires atteints d'une maladie pulmonaire obstructive chronique

**OBJECTIF :** Déterminer si un dispositif de clairance muqueuse (DCM) (Flutter; Axcan Scandipharm, États-Unis) pourrait améliorer de manière soutenue la réponse bronchodilatatoire et le rendement à l'exercice chez des patients atteints d'une maladie pulmonaire obstructive chronique (MPOC) pendant une période d'une semaine en milieu ambulatoire.

**SUJETS :** Quinze patients atteints de MPOC grave (âge moyen de  $71 \pm 10$  ans) ont été étudiés.

**MÉTHODOLOGIE :** Une étude croisée aléatoire a permis de comparer un DCM à un pseudo-DCM (PDCM), chacun mis à l'essai pendant une semaine. Au début et à la fin de la semaine d'étude, le volume expiratoire maximal par seconde (VEMS) et la capacité vitale forcée (CVF) ont été mesurés avant et après l'utilisation du DCM ou du PDCM. Un bronchodilatateur en aérosol (ipratropium bromure et sulfate de salbutamol) a ensuite été administré, et le VEMS et la CVF ont été mesurés de nouveau 30 minutes, 60 minutes et 120 minutes plus tard. Un test de marche de six minutes (TMSM) a également été exécuté.

**RÉSULTATS :** Le VEMS s'est considérablement amélioré ( $P < 0,05$ ) après la bronchodilatation, tant avec le DCM qu'avec le PDCM, mais était toujours plus marquée après le DCM. À la première mesure 120 minutes après la bronchodilatation, le VEMS moyen s'améliorait de  $24 \pm 24\%$  après l'utilisation du PDCM et de  $60 \pm 28\%$  après celle du DCM ( $P < 0,05$ ). Après une semaine d'usage, les valeurs correspondantes à 120 minutes étaient de  $19 \pm 24\%$  et de  $43 \pm 26\%$  ( $P < 0,05$ ). Des observations similaires étaient obtenues pour la CVF. Les distances du TMSM augmentaient de  $29 \pm 12$  m ( $P < 0,05$ ) après l'usage du DCM pendant une semaine, tandis qu'il diminuait légèrement ( $16 \pm 18$  m) après l'usage du PDCM. La diminution de la saturation après le TMSM était plus légère après l'utilisation du DCM qu'après celle du PDCM. Au bout d'une semaine, la diminution de la saturation associée à l'usage du DCM était similaire aux taux de base, même si les patients marchaient plus loin. Au bout de la même période, la dyspnée était plus faible à la marche après le recours au DCM qu'au PDCM.

**CONCLUSION :** Les patients atteints d'une MPOC réagissaient davantage à la bronchodilatation après le recours au DCM qu'au PDCM. Cette augmentation perdurait après une semaine d'utilisation et s'associait à une amélioration du rendement à l'exercice démontrée par le TMSM.

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The treatment of patients with chronic obstructive pulmonary disease (COPD) remains challenging. Current available therapy is often of limited efficacy. Bronchodilators, although universally employed by clinicians, frequently yield only modest improvement in lung function and/or symptoms. We have previously shown that the use of a mucus clearing device (MCD) (Flutter; Axcan Scandipharm, USA) can improve the bronchodilator response to combined ipratropium bromide and salbutamol sulphate delivered by a metered dose inhaler in patients with COPD (1). While our initial results were encouraging, they were obtained with the use of an MCD on a single occasion. Therefore, we sought to determine whether more prolonged use would be similarly effective and persistently beneficial. In the present study, we assessed the value of adding an MCD to bronchodilator therapy during a one-week trial in ambulatory patients with stable COPD. We wished to determine whether the previously demonstrated benefits of the MCD would continue to be observed with regular use over this period of time and whether functional benefit, as evidenced by improved exercise performance, would also be seen.

## METHODS

### Subjects

Subjects were recruited from the COPD outpatient clinic of Mount Sinai Hospital (Montreal, Quebec). Patients who had a clinical diagnosis of COPD and who were between 40 and 80 years of age were eligible for inclusion. Patients with clinical or radiological bronchiectasis were excluded. All subjects had at least a 10-pack year history of smoking and a postbronchodilator forced expiratory volume in 1 s to forced vital capacity ratio (FEV<sub>1</sub>:FVC) of 0.7 L or lower. Subjects had stable COPD and had not had an acute exacerbation of COPD for at least two months.

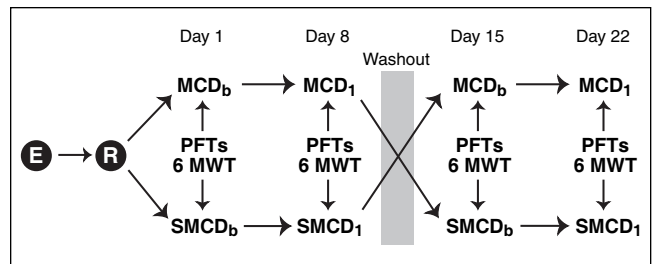
The Research and Ethics Committee of Mount Sinai Hospital approved the study, and written, informed consent was obtained from all participants.

### Experimental protocol

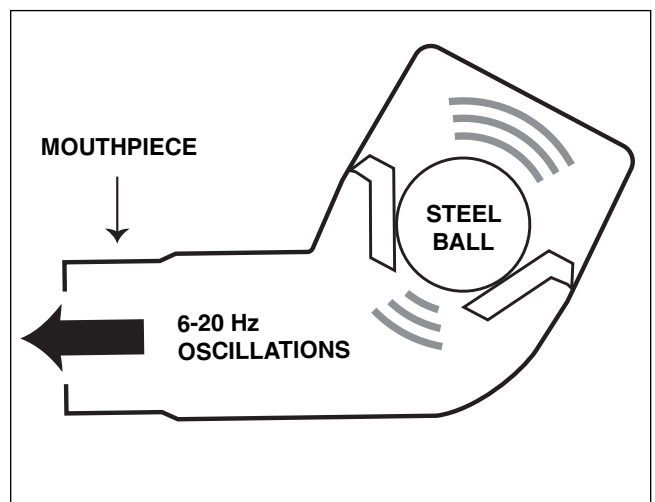
The present study was developed to assess the efficacy of an MCD used at home over a one-week period, using a sham MCD (SMCD) as a control. The design was a randomized crossover trial involving four visits over a three-week period. Visits were scheduled one week apart. Patients were randomized to receive either the MCD or SMCD the first week, and the alternative device the third week. The second week (between each trial) served as the 'washout period' (Figure 1).

The study commenced on day 1 with assessment of eligibility and (if eligible) consent. The patient was then randomized through sealed ordered envelopes to receive either the MCD or SMCD. A return visit was scheduled one week later (day 8), at which time the patient returned the study device. During the next week, patients used their usual therapy and returned for further evaluation (day 15). They were then given the alternative experimental device (MCD or SMCD), which they used for one week, and then returned for the final visit (day 22).

During the active treatment periods (weeks 1 and 3), subjects were to use the MCD or SMCD four times daily for 10 min, just before taking their regular short-acting beta-agonist. For those individuals taking long-acting beta-agonists, the device was to be used before inhaler use, and two additional times during the day at spaced intervals. Beta-agonists were delivered using accepted inhalation techniques and with the use of a holding chamber (Aerochamber; Boehringer Ingelheim, Canada).



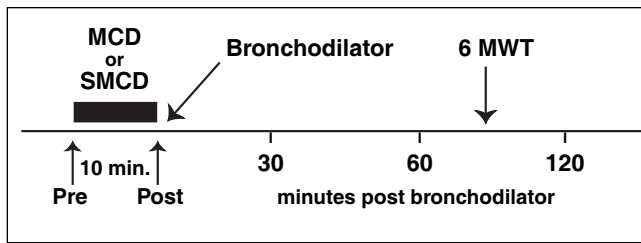
**Figure 1** Experimental protocol. On day 1 patients were enrolled (E) into the study and randomized (R) to receive a mucus clearance device (MCD) or a sham MCD (SMCD). Baseline pulmonary function tests (PFTs) and 6 min walk tests (6MWT) were performed (MCD<sub>b</sub> or SMCD<sub>b</sub>). Patients then used their assigned device at home and returned for repeat testing one week later (MCD<sub>1</sub>, SMCD<sub>1</sub>). They then used their bronchodilators at home in their usual fashion for one week ('washout') and returned to complete the study by using the alternate device for one week with baseline testing on day 15 and, after one week of use, day 22



**Figure 2** Schematic representation of the mucus clearance device (Flutter; Axcan Scandipharm, USA). For use as a sham mucus clearance device, the steel ball was removed

### Experimental devices

The MCD (Flutter; Axcan Scandipharm, USA) has been previously described (1-4). The MCD used in the present study is a pipe-shaped device that contains a stainless steel ball within a central cone (Figure 2). During exhalation, the position of the ball is the result of an equilibrium created by the pressure of exhaled air, the force of gravity on the ball and the angle of the cone. The steel ball rolls up and down on exhalation resulting in oscillation. These oscillations are amplified and, thus, vibration or 'fluttering' is felt by the user. The MCD has also been shown to produce positive expiratory pressure (PEP) between 6 cm H<sub>2</sub>O to 20 cm H<sub>2</sub>O (2-4). At the initial visit beginning MCD use (day 1 or day 15), subjects were instructed in the proper inhalation technique. They were taught to breathe through the device, and to change the inclination of the MCD slightly up or down from the horizontal to choose the position that resulted in the greatest 'fluttering' or vibration sensation within the chest. Optimizing the sensation from the MCD was then to be done whenever it was used during the home trial. The control device was the SMCD, which was identical but had the metal ball, which produces the oscillation, removed. Patients



**Figure 3)** Schematic representation of the protocol during testing days (days 1, 8, 15 and 22). Mucus clearance device (MCD) or sham MCD (SMCD) was employed for 10 min with pulmonary function tests recorded immediately before (pre) and after (post) use. A bronchodilator was then given and pulmonary function tests repeated 30 min, 60 min and 120 min later. A 6 min walk test (6 MWT) was performed between the 60 min and 120 min evaluations

were similarly told to use it for 10 min each time used. They were told to hold it in any mouth position that was comfortable and allowed for unimpeded respiration.

### Measurements

Pulmonary function testing was performed before beginning the use of the MCD or SMCD (days 1 and 15: baseline) and at the completion of each experimental period (days 8 and 22: one week). Measurements were obtained by simple spirometry using an electronic spirometer (Vitalograph model 42.00 Type C; Vitalograph Ltd, United Kingdom). FEV<sub>1</sub> and FVC were recorded from the best of three valid expiratory efforts. Predicted values used were those from Crapo et al (5). Because results for FEV<sub>1</sub> and FVC were similar, the former is presented in detail, while only main findings are shown for the latter. On each test day (days 1, 8, 15 and 22), patients were studied at the same time in the morning. They had been instructed to refrain from using bronchodilators for 12 h before testing. On these visits, pulmonary function test results were recorded before use of the MCD or SMCD (Figure 3). The MCD or SMCD was then used for 10 min and pulmonary function tests were immediately repeated. The latter testing took less than 5 min. Four puffs of Combivent (Boehringer Ingelheim, Canada), each puff delivering 20 µg of ipratropium bromide and 120 µg salbutamol sulphate (equivalent to 100 µg salbutamol base), were then administered using a metered dose inhaler with a holding chamber. Pulmonary function tests were then repeated at 30 min, 60 min and 120 min after bronchodilator administration. A 6 min walk test (6MWT) was performed between the 60 min and 120 min evaluations. The 6MWT was done in a marked hospital corridor. The patients were given no encouragement during the test, but were told to walk as fast as comfortably possible. The total distance walked was recorded. Subjects were asked to scale their sensation of dyspnea before and immediately after the 6MWT using a 10-point Borg scale. The pulse rate was recorded before and immediately after the 6MWT; room air saturation was recorded using a pulse oximeter (Model 71000A1; BCI International, USA) at the same time.

### Statistics

The main outcome variables were FEV<sub>1</sub> and FVC. The authors wished to determine whether there was persistent improvement of postbronchodilator FEV<sub>1</sub> after one week's use of the MCD. Analyses were done comparing the SMCD measurements with those from MCD use. FEV<sub>1</sub> and FVC values were compared within the same patients with a paired Student's *t* test at comparable time

**TABLE 1**  
Patient demographics (n=15)

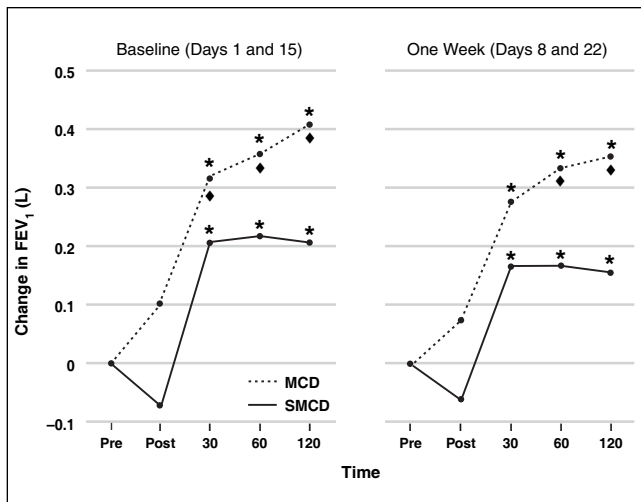
Age, years	71±10
Sex, male:female	9:6
Smoking, pack years	32±29
Currently smoking, n	1
Chronic cough, n	15
Medications, n	
Steroid inhaler	9
Beta-adrenergic	
Short-acting	15
Long-acting	8
Ipratropium bromide	8
Theophylline	3

points throughout the serial spirometric measurements. Results are reported as change in FEV<sub>1</sub> from predevice values (measured before the use of the MCD or SMCD). 6MWT baseline or initial results were compared with measures after one week of MCD or SMCD use. All *P* values are reported as two-tailed with no correction for multiple comparisons.

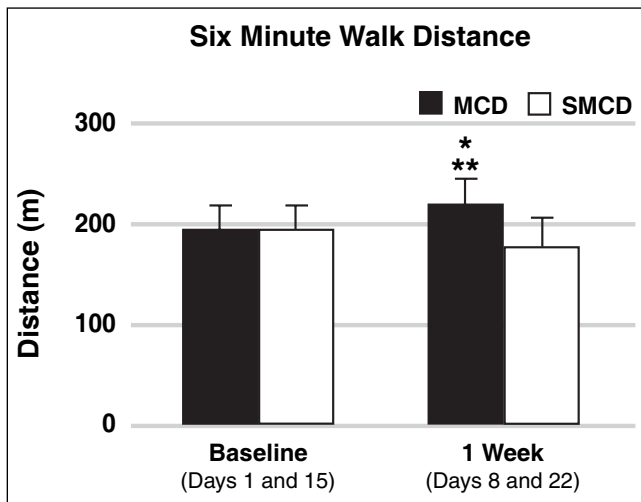
### RESULTS

Fifteen patients with COPD were studied. Demographic information is shown in Table 1. As a group, the subjects manifested severe airway obstruction. The mean FEV<sub>1</sub> was 0.75±0.26 L, 29±9% predicted. All participants had a history of smoking, although only one subject was a current smoker. Patients took one or more of a variety of medications. Pulmonary function testing revealed that before using the MCD or SMCD, FEV<sub>1</sub> was slightly higher at baseline with SMCD use than with MCD use (0.87±0.27 L versus 0.75±0.26 L), as well as after one week of use (0.92±0.28 L versus 0.82±0.21 L). Figure 4 shows the change in FEV<sub>1</sub> with the testing protocol. There was no difference in bronchodilator response between baseline and week 1. All time points between the baseline and week 1 testing were similar within the SMCD condition and MCD condition (all *P*>0.10). With MCD use, but not SMCD use, there was a small improvement in FEV<sub>1</sub> measured immediately after the device was used on both testing days. When the bronchodilator was given immediately after SMCD or MCD use, FEV<sub>1</sub> significantly improved 30 min, 60 min and 120 min later. The improvement was always greater after bronchodilator administration with MCD use than with SMCD use. The greater improvement with MCD use reached statistical significance (*P*<0.05) after 30 min, 60 min and 120 min at the baseline visit, and at 60 min and 120 min at the one-week visit. At the baseline measurement, 120 min after bronchodilator administration, mean FEV<sub>1</sub> improved by 24±24% with SMCD use and 60±28% with MCD use (*P*<0.05). After one week of use, the corresponding 120 min values were 19±24% and 43±26%, respectively (*P*<0.05). Thus, the magnitude of improvement at one week, when expressed as per cent change, was slightly lower than at baseline (but not statistically different), although the greater benefit of MCD use over SMCD use was still seen at that time (*P*<0.05).

At baseline, 120 min after bronchodilator administration, FVC improved from 1.63±0.50 L to 2.22±0.63 L with MCD use, and from 1.91±0.64 L to 2.17±0.61 L with SMCD use. The corresponding changes after one week were 1.77±0.51 L to

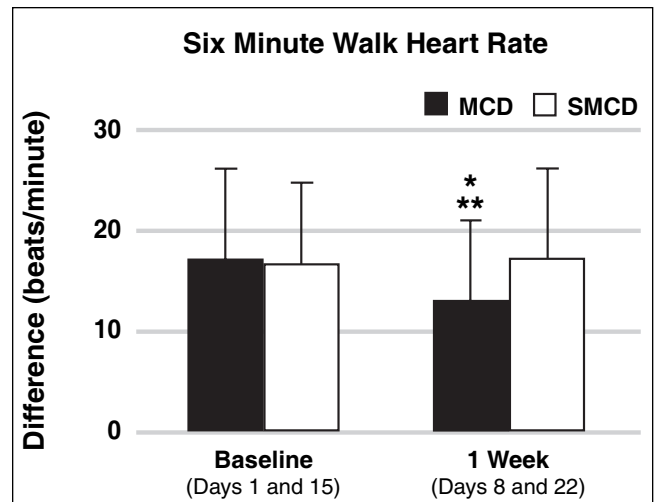


**Figure 4)** Change in forced expiratory volume in 1 s (FEV<sub>1</sub>) after mucus clearance device (MCD) use (dashed lines) or sham MCD (SMCD) use (solid lines). Baseline values were obtained on days 1 and 15 before home device use. One-week values (days 8 and 22) were those after the MCD or SMCD had been used at home for seven days. Pre and post values represent those obtained before and after MCD or SMCD use. \*FEV<sub>1</sub> improved significantly (P<0.05) at 30 min, 60 min and 120 min at baseline and after one week for both MCD and SMCD. \*The improvement with MCD use was significantly greater (P<0.05) at 30 min, 60 min and 120 min at baseline, and at 60 min and 120 min after one week



**Figure 5)** Results of the 6 min walk distance at baseline (days 1 and 15) and after the mucus clearance device (MCD) or sham MCD (SMCD) had been used for one week (days 8 and 22). \*After one week, the walk distance was higher with MCD use than with SMCD use (P<0.05). \*\*The distance walked after one week of use was greater than it had been at baseline for the MCD (P<0.05)

2.37±0.61 L with MCD use and 1.99±0.54 L to 2.19±0.56 L with SMCD use. The greater improvement observed in FVC after MCD use compared with SMCD use was statistically significant (P<0.05) at baseline and one week; however, the magnitude of improvement was similar for both time points. Therefore, the advantage of MCD use over SMCD use was maintained over one week of use, but there was no additional benefit, as measured by FVC, from a week's use at home.



**Figure 6)** The figure shows the change in heart rate with the 6 min walk test. At baseline, the increase in heart rate was similar after mucus clearance device (MCD) use or sham MCD (SMCD) use. At one week, \*the increase in heart rate was smaller after MCD use than after SMCD use (P<0.05) and \*\*also smaller with MCD use than it had been at baseline

**TABLE 2**  
Change in saturation with 6 min walk test

	Saturation start	Saturation end	Difference
Baseline (days 1 and 15),			
MCD	94.5±2.1	93.1±6.5	-1.4±5.6*
SMCD	94.8±1.9	91.7±6.7	-3.1±6.3
One week (days 8 and 22)			
MCD	95.3±1.9	93.9±6.7	-1.4±6.0*
SMCD	94.5±2.1	92.1±6.2	-2.3±6.1

Values reported are per cent saturation by finger pulse oximetry. MCD Mucus clearance device; SMCD Sham MCD. MCD significantly different from corresponding SMCD value (P<0.05)

Figure 5 shows the results of the 6MWT. At baseline, 6MW distances (6MWD) were similar whether MCD or SMCD had been given. After one week, 6MWD after MCD use was significantly greater than the distance after SMCD use (222±75 m versus 176±71 m, respectively; P<0.05). Comparing baseline with one week, the results revealed that the 6MWD increased by 29±12 m for subjects who used the MCD for one week, whereas the 6MWD actually decreased by 16±18 m in those subjects using the SMCD.

At baseline, the increase in heart rate with the 6MWT was of similar magnitude after SMCD and MCD use (Figure 6). After one week of use, the increase in heart rate with the 6MWT was lower after MCD use than after SMCD use (P<0.05). Despite walking farther, the increase in heart rate with this exercise was lower after one week of MCD use than it had been at baseline (P<0.05).

Patients desaturated slightly on walking. The decline in saturation was less after MCD use than after SMCD use at baseline and after one week (Table 2). After one week, the decline in saturation with MCD use was similar to that seen at baseline testing, even though patients were walking farther at that point.

Table 3 shows the Borg scale dyspnea measurements pre- and post-6MWT at baseline and after one week. The change in dyspnea with the 6MWT was similar at baseline after MCD

and SMCD use. At one week, the change in dyspnea scores was slightly lower after MCD use than after SMCD use ( $P < 0.05$ ). Despite walking farther, the Borg dyspnea score was lower at the end of exercise after one week compared with baseline with MCD use,  $2.8 \pm 1.9$  versus  $3.6 \pm 2.1$  ( $P < 0.05$ ), but did not significantly change with SMCD use ( $3.6 \pm 2.2$  versus  $3.6 \pm 2.2$ ).

## DISCUSSION

In the present study, we showed that the use of an MCD could significantly enhance the response to combined bronchodilator therapy in patients with severe COPD. This effect was seen at baseline and after one week of regular use of this device. In addition, after one week of regular use of an MCD, patients were able to walk farther. These observations support and extend those published previously (1), which were obtained using an MCD or equivalent sham on a single occasion.

In the present study, the SMCD data represent the bronchodilator response in our patients with COPD. Although this disease is generally considered one with limited potential for reversibility, our results, and those from previous studies (1,6), suggest that even patients with severe COPD may be capable of a significant response to a bronchodilator. We chose combination therapy to optimize bronchodilator response because previous studies (6,7) have emphasized the advantages of combining a beta-agonist with ipratropium bromide in patients with COPD (6,7).

There was a greater response to the bronchodilator after MCD use than after SMCD use. The improved response to the combined bronchodilator seen with MCD use has at least two possible explanations. First, by promoting mucus clearance, aerosol penetration and, thus, efficacy may be enhanced. In this regard, it has been found that this device is more effective, at least in patients with cystic fibrosis and bronchiectasis, than standard physical therapy including postural drainage and chest clapping (2,8). The second physiological effect of MCD use, that of producing a positive end expiratory pressure may be equally, or even more important, than promoting mucus clearance. It has long been known that pursed lips breathing may be beneficial in patients with severe COPD (9). This breathing strategy has been shown to increase tidal volume, decrease respiratory rate and diminish uneven ventilation (9). Similarly, the use of a PEP device prevents airway collapse and facilitates a more homogeneous distribution of ventilation throughout the lungs (10-12). As a result of these effects, there may be better distribution of the inhaled bronchodilator and, thus, improved efficacy. By retarding expiration, positive end expiratory pressure may also allow more time for retaining medication in the distal airways.

The theoretical benefits of positive end expiratory pressure in improving bronchodilator efficacy have previously been demonstrated in patients with asthma (13). Frischknecht-Christensen et al (13) showed improved bronchodilation in patients with asthma when PEP was combined with inhalation of a beta-agonist than with a beta-agonist alone. Tsai and Tsai (14) found a significant improvement in FEV<sub>1</sub>, FVC and forced expiratory flow rate between 25% and 75% of FVC when a PEP device was used after beta-agonist nebulization therapy in patients with asthma. Subjects in the latter study also claimed to have expectorated more abundantly and to have had less dyspnea after using the PEP device (14).

We used the 6MWT to evaluate functional improvement in the patients. This test is a quick and inexpensive performance

**TABLE 3**  
Borg dyspnea scores pre- and post-6 min walk test

	Pre	Post	Difference
Baseline (days 1 and 15)			
MCD	0.7±1.1	3.6±2.1	2.9±1.8
SMCD	1.1±1.2	3.6±2.2	2.5±1.5
One week (days 8 and 22)			
MCD	0.7±0.9	2.8±1.9*	2.1±1.5**
SMCD	1.0±1.1	3.6±2.2	2.6±1.5

\*Mucus clearance device (MCD) one week value significantly different from corresponding MCD baseline value ( $P < 0.05$ ). \*\*MCD significantly different from corresponding sham MCD (SMCD) value ( $P < 0.05$ )

measurement that correlates with more formal exercise testing, and reflects ability to conduct activities of daily living (15,16). We found that the 6MWD significantly improved after a week of MCD use but not after SMCD use. As well, desaturation and dyspnea with walking appeared to be reduced with MCD use. Although statistically significant, the magnitude of improvement in 6MWD was relatively small (29 m) and, therefore, one can legitimately question the clinical relevance. This value is less than the 54 m minimal difference between walk tests noted by previous authors (17), which is associated with a perceived change in functional status by the patient. However, our patients had severe COPD, with very low baseline walk distances. Therefore, any improvement in walk distance with treatment would be expected to be small. Furthermore, the duration of intervention was short (one week). Severe COPD is a chronic disease with limited potential for improvement. Most longitudinal studies involving intervention, especially trials assessing therapy, are designed to allow potential benefits to manifest over months of continued use. It might be expected that more prolonged use of an MCD would result in even greater functional improvement. Further studies, over longer period of time, are needed to discover the full potential benefit of using an MCD in an ambulatory setting.

A limitation of the present study was that the home use of the MCD and SMCD were unsupervised. However, one investigator (HK) spent considerable time educating patients about the technique of device use and the importance of protocol compliance. Given the frequency of treatments and the home-setting design employed in the present study, it would not have been practical to directly observe every therapeutic intervention in all subjects.

## CONCLUSIONS

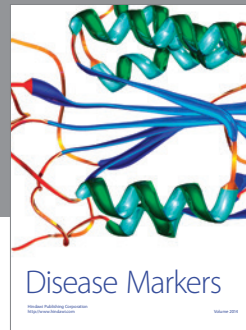
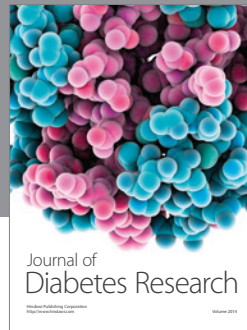
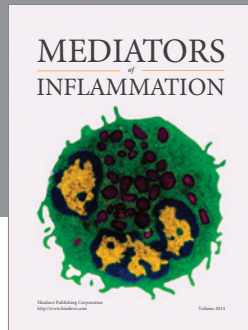
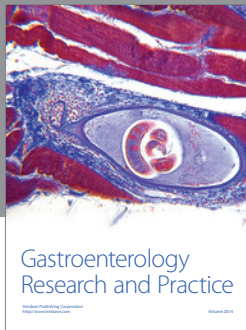
Patients with severe COPD demonstrated an enhanced response to inhaled ipratropium bromide and salbutamol sulphate with the use of an MCD. This effect persisted after one week of use, and was associated with improved exercise performance as measured by the 6MWT.

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