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Research Article

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# Müller's Manoeuvre, an Autonomic Approach to the Treatment of Bronchoconstriction Relevance in Clinical Trials

**Khalid Abou Farha***

*MBChB, M.D., Ph.D., DPM, CPT, MFPM, MBPS Celerion, Clinical Pharmacology Research Centre, Belfast, United Kingdom*

***Corresponding author**
Khalid Abou Farha, MBChB, M.D., Ph.D., DPM, CPT, MFPM, MBPS Celerion, Clinical Pharmacology Research Centre, Belfast, United Kingdom, Tel: +44 2890 55-4059; Fax: +44 2890 55-4141; Mob: +44 7980018586; E-mail: Khalid.aboufarha@celerion.com

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## Abstract

***Background:*** *Many respiratory clinical trials include sputum induction to evaluate airway inflammation and monitor treatment response. This may cause airway autonomic dysregulation and induces bronchoconstriction necessitating discontinuation of the procedure and administration of β2 adrenergic receptor agonists such as salbutamol. Müller's manoeuvre is a technique that has been proposed for the diagnosis of sleep apnoea syndrome. The manoeuvre induces an autonomic response consisting of increased sympathetic flow and withdrawal of parasympathetic activity. It is therefore, conceivable that Müller's manoeuvre may exhibit a bronchodilator effect.*

***Patients and Methods:*** *The potential bronchodilator effect of Müller's manoeuvre has been assessed in 9 healthy subjects and 11 patients with moderate to severe COPD. All patients had undergone sputum induction procedure. Thereafter, patients were asked to perform Müller's manoeuvre. Pre- sputum, post -sputum and post- manoeuvre assessment of 3 spirometry parameters, FVC, FEV1 and FEV1/ FVC ratio, has been performed. In healthy subjects, spirometry testing was done at 2 time points, before and after Müller's manoeuvre.*

***Results:*** *Ten COPD patients out of 11 completed Müller's manoeuvre. The manoeuvre was poorly tolerated in one subject. In the remaining 10 patients, the manoeuvre led to clinically relevant improvement in the declined spirometry parameters and obviated the need to use pharmacological bronchodilator. In healthy subjects, Müller's manoeuvre caused increase in FEV1 and FVC however, less pronounced than in COPD patients.*

***Conclusion:*** *Müller's Manoeuvre showed a potential bronchodilator effect and produced clinically meaningful improvement in post-sputum induction bronchoconstriction. It obviated the requirement to use bronchodilator therapy in all 10 patients. The data in this report suggest that Müller's Manoeuvre might be used as a first aid measure to treat bronchoconstriction and may serve as a potential alternative to B2 agonists in COPD patients participating in clinical trials. Further investigations to confirm this finding are still warranted.*

**Keywords:** Müller's Manoeuvre, Bronchodilator, Obstructive Lung Disease

## Introduction

Sputum induction is a non-invasive procedure commonly used in respiratory clinical trials to evaluate airway inflammation and monitor drug response. The procedure has been used for this purpose in patients with stable bronchial asthma and chronic obstructive pulmonary disease (COPD) [1]. It includes inhalation of isotonic saline or increasing concentrations of hypertonic saline (HS). This can cause bronchoconstrictive response in many patients particularly in subjects with bronchial hyperreactivity [2,3]. HS may provoke bronchoconstriction indirectly via activation of airway inflammatory cells, including mast cells, and sensory nerve endings stimulation ending up in autonomic dysregulation,tipping the balance toward parasympathetic dominance [2,4,5]. This concept might explain the reason why short acting β2 adrenergic receptor agonist (B2A) such as salbutamol may prevent and quickly revert airway hyperresponsiveness (AHR) to HS aerosol inhalation in patients undergoing the procedure. In this regard, it is worth mentioning that, B2A administration does not completely prevent airway constriction in all subjects [2,4,6,7]. In addition, the use of B2A in COPD patients might be associated with high risk of adverse cardiac events [8]. On one hand, COPD is an independent risk for cardiovascular diseases including hypertension, heart failure, ischemic heart disease, myocardial infarction, supraventricular arrhythmias and stroke (9, 10). On the other hand, the use of beta adrenergic receptors agonist in COPD patients has been found to be associated with increasing

the risk of these cardiovascular morbidities [9].

Müller's Manoeuvre (MM), the reverse of Valsalva's manoeuvre, is a technique used in the evaluation of patients with obstructive sleep apnoea [11]. It consists of voluntary forced inspiration against closed mouth and nose.The underlying mechanism of MM involves interplay among 3 mechanistic elements. These are hemodynamic changes due to fall in the intrathoracic pressure and increase in venous return caused by forced inspiration against closed mouth and nose; chemo reflex stimulation due hypoxemia and hypercapnia; and hyperventilation and decrease in baro reflex sensitivity that occur after restart normal breathing. This initiates a complex multistep physiologic process that causes a reversible biphasic autonomic response, an initial fall followed by an ultimate increase in sympathetic flow and withdrawal of parasympathetic activity [12].

Taken all together, it is conceivable to hypothesize that MM through its dual autonomic response might exhibit a bronchodilator effect and therefore, could revert an indirect AHR such as that caused by sputum induction. To the best of my knowledge, this is the first time to explore the potential bronchodilator effect of Müller's Manoeuvre.

## Subjects and Methods

The potential bronchodilator effect of MM was assessed in 9 healthy non-smoking subjects (4 males and 5 females, age range: years after 25-59, BMI: 29 (±9)) kg/ m2), all were employees of Celerion clinical pharmacology unit, Belfast, UK; and eleven (11) patients with moderate to severe COPD (GOLD stages II-III). All individuals participated in this exploratory work had been consented before starting the manoeuvre. All COPD patients had undergone sputum induction procedure to monitor the efficacy of the treatment received for their disease. Post-sputum induction, all patients developed asymptomatic bronchoconstriction and were consequently asked to perform Muller's Manoeuver. Ten (10) out of the 11 COPD patients (9 males and one female, age range: 60-76 years, BMI: 29 ±12 kg/ m2 (mean ± SD)) completed the manoeuvre. One patient with severe COPD poorly tolerated the manoeuvre and was therefore excluded from participation in this exploratory work. Four (4) out of the 10 patients were current smokers. Three (3) patients had controlled hypertension. Otherwise, none of the participants had a past or current history of any clinically relevant active or chronic disease including obstructive sleep apnoea or heart disease.

Sputum induction (SI) procedure has been described elsewhere [13]. In this exploratory work, all COPD patients had received inhalation dose of salbutamol 400 ug. After 20 minutes, they were asked to inhale increasing concentrations, 3%, 4% and 5%, of HS. HS inhalation was allowed for a maximum of 15 minutes (3 x 5 minutes) during the whole procedure.

As a part of SI procedure and before HS inhalation, all COPD patients performed assessment of pulmonary function tests, by means of spirometry, to establish baseline (BL) values. In this context, the following 3 main spirometry parameters were assessed: Forced Vital Capacity (FVC) which reflects the volume of air forcibly exhaled in one breath; Forced Expiratory Volume in 1 second (FEV1) that reflects the volume of air exhaled in the first second of forced expiration; and the FEV1/FVC ratio expressed as a percentage.

The spirometry testing was performed by an experienced respiratory technician in accordance with the ATS guidelines [14]. At least 3 and up to maximum 8 attempt of blows had been made by each patient in order to achieve 3 technically accepted measures of FVC and FEV1where the highest 2 FEV1 and FVC values were ≤150ml of each other. The highest FEV1 and FVC values were then used.

In COPD patients, spirometry testing was performed after salbutamol inhalation (post- bronchodilator BL) and after inhalation of each saline concentration. During the SI procedure, development of symptoms of respiratory distress or fall in post-saline inhalation FEV1 below 20% of post-bronchodilator BL values at any time point necessitated termination of the procedure. As per spirometry guidelines, decline in FEV1 below 20% of BL mandates follow up with spirometry testing until the FEV1 return to ≥ 90% of the BL values. In clinical trial settings, this usually requires administration of a short- acting bronchodilator such as salbutamol.

MM, voluntary forced inspiration against closed mouth and nose, was explained to all participants. Participants were asked to perform the manoeuvre 3 consecutive times in the sitting position, and maintain forced inspiration for a period of at least 20 seconds or as long as tolerated.

In healthy subjects spirometry was performed at 2 time points, before and 5 minutes after MM.

COPD patients were asked to start MM 5 minutes after the last SI spirometry and every 5 minutes thereafter over a period of 20 minutes. Following each manoeuvre spirometry testing was then performed. For descriptive reason, this period has been divided into 4 intervals of 5 minutes, A to D.

During the manoeuvre, oxygen saturation (SpO2) and pulse rate were monitored, by means of pulse oximetry, for any relevant changes, in magnitude or duration.

## Results

In COPD patients, sputum induction resulted in asymptomatic bronchoconstriction with decline in FEV1 and FVCcompared to post- bronchodilator BL, respectively -23% and -29.5% (table 1).

**Table1: Post- MM changes (mean values and %) in FVC, FEV1 and PEF post-BD values in COPD patients, compared to baseline**

| Parameter | Post- BD V | PSI V Δ%*) | A V %*) | B V Δ%*) | C V Δ%*) | D V Δ%*) |
|---|---|---|---|---|---|---|
| FVC (ml) | 2815 | 1986 (-29.5) | 2242 (-20) | 2272 (-19) | 2319 (-18) | 2337 (-17) |
| FEV1 (ml) | 1553 | 1193 (-23) | 1351 (-13) | 1373 (-12) | 1400 (-10) | 1447 (-7) |
| FEV1/ FVC (%) | 55 | 60 | 60 | 60 | 60 | 62 |

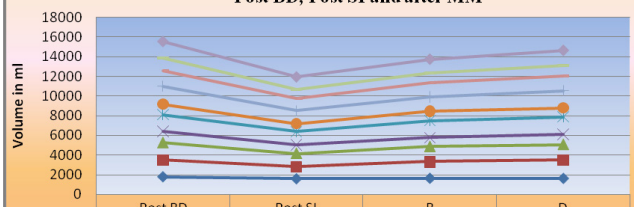
PBD= post bronchodilator administration (BL), PSI= post sputum induction.
A-D denote time window in minutes after MM; A: 05-10 minutes, B: 10-15 minutes, C: 15-20 minutes and D: 20-25 minutes.
V: volume; Δ%* in relation to Pre-BD

At the individual patient level decline in post SI values below post-BD BL levels ranged from 20% to 30% and from 15% to

56% respectively for FEV1 and FVC in 9 out of 10 patients. In one patient the FEV1 and FVC values obtained after 15 minutes of exposure to HS were respectively 12% and 27% below BL. Figures 1 and 2 demonstrate the data.

Based on the decline in FEV1 levels, the SI procedure had been terminated and patients were asked to perform MM. The use of MM led to gradual increase in the means of all declined values. FEV1 of all 10 patients returned within 20 minutes to ≥90% of their BL without the use of pharmacological bronchodilator (Fig.1-3, table 1).

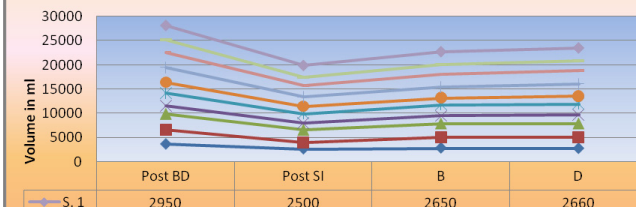
**Fig.1, FEV1 values obtained from 10 COPD patients Post BD, Post SI and after MM**




| FEV1 | Post BD | Post SI | B | D |
|---|---|---|---|---|
| S. 1 | 1630 | 1250 | 1390 | 1490 |
| S. 2 | 1290 | 900 | 960 | 1050 |
| S. 3 | 1610 | 1280 | 1480 | 1530 |
| S. 4 | 1840 | 1300 | 1450 | 1780 |
| S. 5 | 1050 | 820 | 930 | 900 |
| S. 6 | 1700 | 1330 | 1750 | 1750 |
| S. 7 | 1160 | 900 | 920 | 1070 |
| S. 8 | 1790 | 1350 | 1560 | 1590 |
| S. 9 | 1680 | 1230 | 1670 | 1860 |
| S. 10 | 1780 | 1570 | 1620 | 1610 |

B and D denote time window after MM; B: 10-15 minutes post MM; D: 20-25 minutes post MM.

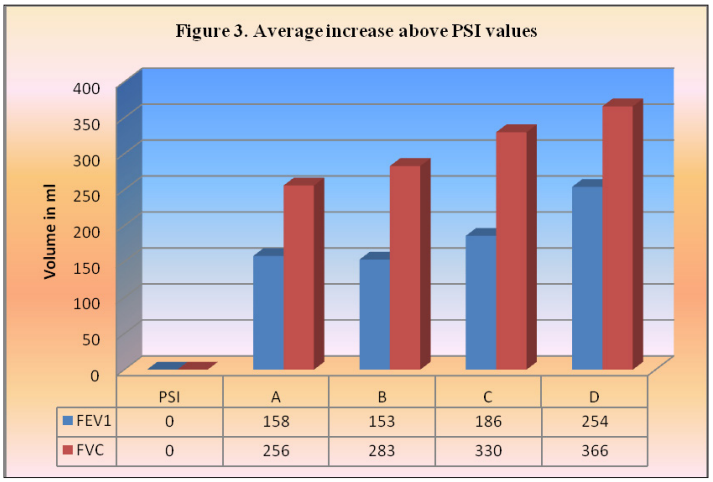
**Fig.2, FVC values obtained from 10 COPD patients, Post BD, Post SI and after MM**




| FVC | Post BD | Post SI | B | D |
|---|---|---|---|---|
| S. 1 | 2950 | 2500 | 2650 | 2660 |
| S. 2 | 2690 | 1610 | 2090 | 2010 |
| S. 3 | 3040 | 2320 | 2570 | 2760 |
| S. 4 | 3110 | 1990 | 2240 | 2530 |
| S. 5 | 2220 | 1530 | 1460 | 1630 |
| S. 6 | 2630 | 1960 | 2272 | 2307 |
| S. 7 | 1640 | 1350 | 1530 | 1680 |
| S. 8 | 3250 | 2670 | 2860 | 2890 |
| S. 9 | 2990 | 1300 | 2230 | 2300 |
| S. 10 | 3630 | 2630 | 2820 | 2730 |

B and D denote time window after MM; B: 10-15 minutes post MM; D: 20-25 minutes post MM.

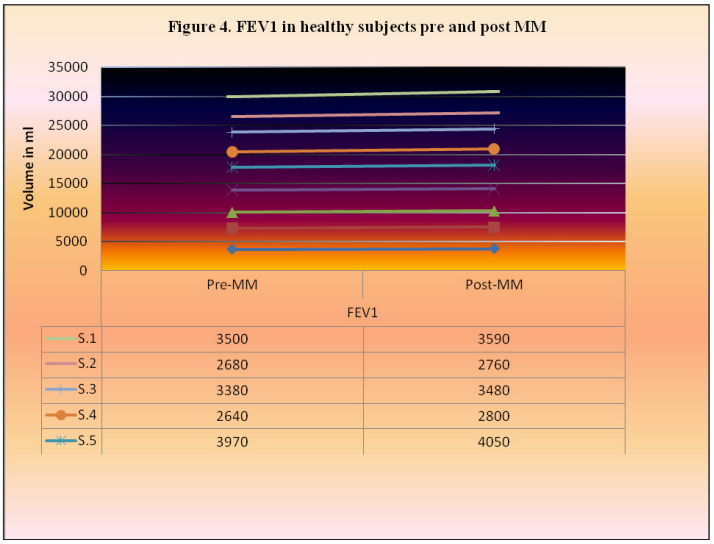
**Figure 3. Average increase above PSI values**




| PSI | A | B | C | D |
|---|---|---|---|---|
| FEV1 | 0 | 158 | 153 | 186 | 254 |
| FVC | 0 | 256 | 283 | 330 | 366 |

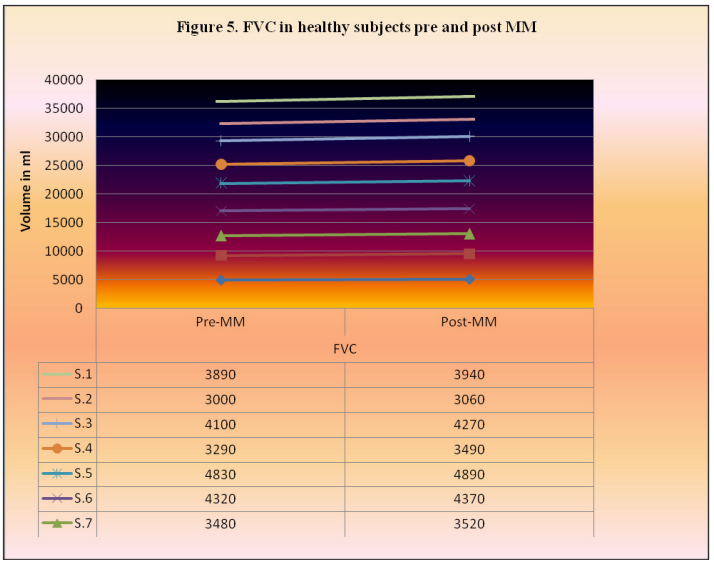
A-D denote time window in minutes after MM; A: 05-10 minutes, B: 10-15 minutes, C: 15-20 minutes and D: 20-25 minutes.

**Figure 4. FEV1 in healthy subjects pre and post MM**




| FEV1 | Pre-MM | Post-MM |
|---|---|---|
| S.1 | 3500 | 3590 |
| S.2 | 2680 | 2760 |
| S.3 | 3380 | 3480 |
| S.4 | 2640 | 2800 |
| S.5 | 3970 | 4050 |

**Figure 5. FVC in healthy subjects pre and post MM**




| FVC | Pre-MM | Post-MM |
|---|---|---|
| S.1 | 3890 | 3940 |
| S.2 | 3000 | 3060 |
| S.3 | 4100 | 4270 |
| S.4 | 3290 | 3490 |
| S.5 | 4830 | 4890 |
| S.6 | 4320 | 4370 |
| S.7 | 3480 | 3520 |

In healthy subjects, the average changes due to MM relative to pre manoeuvre values were + 101 ml (+ 2.5%), + 88 ml (+ 2.6%) respectively in FVC and FEV1 (table 2). The individual values obtained from the healthy subjects for FEV1 and FVC are shown in figures 4 and 5. During the manoeuvre, no relevant changes in SpO2or HR were observed.

**Table2. The effect of MM on 4 assessed spirometry parameters in healthy non-smoking subjects**

| Parameter | Before MM Mean (SD) | After MM Mean (SD) | Δ V (Δ%*) | No. I/T* |
|---|---|---|---|---|
| FVC (ml) | 4017 (669) | 4118 (676) | +101 (2.5) | 9/9 |
| FEV1 (ml) | 3330 (520) | 3418 (508) | +88 (2.6) | 9/9 |
| FEV1/ FVC (%) | 82.9 | 83 | 0.1 % | |

* Number of subject with increased values (N)/ Total (T) number of subjects

## Discussion

In this work, the potential bronchodilator effect of Muller's Manoeuvre, has been explored, in both healthy and COPD patients. Intra-subject changes in FEV1 and FVC have been used to assess the utility of the manoeuvre in this respect. This avoids inter-subjects variability and the known impact of subject's demographic characteristics such as age, gender and height on the FEV1/ FVC ratio. In this regard, FVC, FEV1 and the FEV1/ FVC ratio are 3 important spirometry parameters to assess lung function. FEV1/ FVC ratio determines the presence of airway narrowing and is considered a useful indicator for air trapping in the lungs particularly when combined with low FVC. FEV1 is an effort- independent parameter that determines the severity of obstruction and reflects functional states of small and medium airways.

In healthy volunteers, MM resulted in an increase of 2.6% and 2.5% respectively in FEV1 and FVC without relevant change in FEV1/ FVC ratio. Earlier reports demonstrated a similar, albeit less pronounced effect on FEV1 and FVC 20 minutes after inhalation of salbutamol 400 ug. In this regard, Kainu and associates, 2008 and da Costa et.al, 2014 reported post salbutamol increase of 1.1-1.8% and 1.17% respectively in FEV1 and FVC [15,16]. The difference between the results of this exploratory work and those in earlier reports might be attributed to the dual autonomic action of MM versus the single B adrenergic agonistic effect of salbutamol. However, different sample sizes might play a role in this difference.

The dual autonomic action of MM and results obtained in healthy subjects, parallel changes in FVC and FEV1 without impacting the FEV1/ FVC ratio, persuaded testing MM bronchodilator potential in COPD patients. The results obtained from the COPD group of patients show gradual MM-induced progressive increase in FEV1 starting as early as 5-10 minutes after the manoeuvre. The magnitude of increase in both FEV1 and FVC relative to the PSI levels (16% and 12.5% respectively in FEV1 and FVC) is of clinical relevance. Interestingly, the FEV1/ FVC ratio obtained after MM was 7% higher than that obtained after salbutamol administration indicating less air trapping in the lungs. Also none of the 10 patients received B2A (Salbutamol) to revert the bronchoconstriction induced by SI. In terms of FEV1/ FVC ratio, the data of this report show increase in the FEV1/ FVC ratio in the assessments obtained after SI and during MM, as compared to post BD values. Noteworthy is that the increase in post SI ratio is due to disproportionate drop in FVC compared to FEV1 while, the increase observed during MM is the result of increased FEV1 values.

In this exploratory work BL pre salbutamol assessment of respiratory functions has not been done. AS mentioned before, salbutamol had been administered before start of SI procedure. This is to avoid potential SI- associated severe complications. Therefore, data obtained from this work do not allow comparison between the bronchodilator effect induced by inhalation of Salbutamol 400 ug (i.e. difference between pre and post salbutamol values) and that induced by MM. Nevertheless, earlier reports showed reversibility (from basal condition) in FEV1 and FVC of 110- 210 ml (12-16%) and 260-380 ml (10-15%) after 15 minutes of salbutamol 400 ug inhalation. This is comparable to the results reported in this paper, in spite of the fact that MM was performed post HS- induced bronchoconstriction and not on basal condition [16].

In summary, the data in this report support the bronchodilator potential of Müller's Manoeuvre. The manoeuvre could be useful treatment tool in patients with obstructive lung diseases. The manoeuvre is an autonomic approach that stimulates body physiologic responses to correct provoked autonomic dysregulation. When deemed necessary, such autonomic response can be reversed by Valsalva's manoeuvre. This makes MM an attractive first aid approach and possibly alternative to B2A for the treatment of autonomic dysregulation-induced bronchoconstriction in clinical and clinical trial settings. The usefulness of this manoeuvre might be more obvious in cardiac risk patients with obstructive pulmonary diseases.Further investigations to confirm this finding are still warranted.

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