

## Spirometry with bronchodilator test: effect that the use of large-volume spacers with antistatic treatment has on test response\*

Prova broncodilatadora na espirometria: efeito do uso de espaçador de grande volume com tratamento antiestático na resposta ao broncodilatador

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### Abstract

**Objective:** To evaluate whether the use of inhaled albuterol via a metered-dose inhaler with a large-volume spacer with antistatic treatment modifies the bronchodilator test results when compared with the usual technique (no spacer). **Methods:** A prospective study involving 24 patients, 18-45 years of age, clinically suspected of having asthma, and under treatment at the Outpatient Pulmonary Clinic of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. All of the patients underwent two bronchodilator tests: one with and one without the use of a large-volume spacer. **Results:** There was no significant difference in the variation of FEV<sub>1</sub> prior to and after bronchodilator use between the two techniques (mean  $\Delta$ FEV<sub>1</sub> = 0.01 L; 95% CI: -0.05 to 0.06; p = 0.824). No statistically significant difference was found between the two techniques regarding the qualitative results on the bronchodilator test (p = 1.00). There was concordance between the techniques in terms of the bronchodilator test results (kappa coefficient = 0.909; p < 0.005). **Conclusions:** According to the results of this study, the use of large-volume spacers does not significantly modify bronchodilator test results.

**Keywords:** Asthma; Spirometry; Inhalation spacers.

### Resumo

**Objetivo:** Avaliar se o uso de salbutamol inalatório através de inalador dosimetrado acoplado a espaçadores de grande volume com tratamento antiestático na espirometria com prova broncodilatadora modifica os resultados do teste quando comparado à técnica usual (sem espaçador). **Métodos:** Estudo prospectivo envolvendo 24 pacientes, com idades entre 18 e 45 anos e suspeita clínica de asma, atendidos no Ambulatório de Pneumologia do Hospital das Clínicas da Universidade Federal de Minas Gerais, em Belo Horizonte (MG). Os pacientes foram submetidos a duas espirometrias com prova broncodilatadora realizadas com e sem o uso de espaçador de grande volume. **Resultados:** Não houve diferença significativa na variação do VEF<sub>1</sub> antes e após o uso de broncodilatador entre as duas técnicas ( $\Delta$ VEF<sub>1</sub> média = 0,01 L; IC95%: -0,05 a 0,06; p = 0,824). Não houve diferença estatisticamente significativa entre as duas técnicas em relação ao resultado qualitativo da prova broncodilatadora (p = 1,00). Houve concordância dos resultados da prova broncodilatadora entre as técnicas (coeficiente kappa = 0,909; p < 0,005). **Conclusões:** De acordo com os resultados deste estudo, a utilização de espaçadores de grande volume não modificou de forma significativa os resultados da prova broncodilatadora.

**Descritores:** Asma; Espirometria; Espaçadores de inalação.

\* Study carried out at the Department of Clinical Medicine, *Universidade Federal de Minas Gerais* – UFMG, Federal University of Minas Gerais – School of Medicine, Belo Horizonte, Brazil, as part of the Master's thesis presented by Flávia de Barros Araújo under the auspices of the UFMG Graduate Program in Applied Health Sciences.

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Financial support: Flávia de Barros Araújo is the recipient of a fellowship from the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education). Nilton A. Rezende is a researcher for the *Instituto Nacional de Ciência e Tecnologia-Instituto para Avaliação de Tecnologia em Saúde* (INCT-IATS, National Institute of Science and Technology-Institute for Health Technology Assessment). The spacers were donated by the GlaxoSmithKline Brasil laboratory.

Submitted: 10 August 2011. Accepted, after review: 19 September 2011.

## Introduction

Spirometry with bronchodilator test is habitually performed with the use of four 100- $\mu$ g puffs of fenoterol or albuterol, preferably with spacers, after patients have received the appropriate instructions, and the response is measured after 15–20 min.<sup>(1)</sup> Although at most health care facilities the bronchodilator test is performed with no spacer (the usual technique), there is no consistent evidence of the superiority of one technique over the other.

The technique for using a metered dose inhaler (MDI) is difficult because it requires that patients coordinate the triggering of the device simultaneously with inhalation.<sup>(2,3)</sup> Previous reports have demonstrated that 51% of patients have difficulty in coordinating the triggering of the device with inhalation; in addition, the aerosol released in the oral cavity interrupted inhalation in 36% of patients.<sup>(3)</sup> Even when MDIs are used correctly, approximately 10% of the drug is deposited in the lungs, whereas nearly 80% is deposited in the oropharynx.<sup>(4–6)</sup>

Spacers facilitate the use of MDIs, mostly because spacers eliminate the problem of having to coordinate the triggering of the device with inhalation. Previous studies have confirmed the efficacy of large-volume spacers, which have been shown to increase lung deposition of aerosol particles, reduce oropharyngeal deposition, and improve the functional parameters in patients with obstructive lung disease.<sup>(7–10)</sup> However, we found no studies evaluating the efficacy of using spacers in spirometry, especially in comparison with that of the usual technique for performing the bronchodilator test.

The effect of electrostatic charge on plastic spacers and its relationship with bronchodilator test results should also be highlighted. Plastic spacers have an internal electrostatic charge that attracts aerosols to their walls; this reduces pulmonary deposition of drugs. The elimination of the electrostatic charge of plastic spacers can increase the availability of particles that are smaller than 5  $\mu$ m, which are considered to be the respirable particles of aerosol.<sup>(11,12)</sup> Studies have reported that static can be eliminated by simple procedures.<sup>(13–15)</sup>

The objective of the present study was to determine whether the use of inhaled albuterol via an MDI with a large-volume spacer with antistatic treatment modified the bronchodilator

test results in patients clinically suspected of having asthma when compared with the usual technique (no spacer).

## Methods

This was a prospective, matched, noncrossover study. Patients who were in the 18–45 year age bracket and who, because of clinical suspicion of asthma, had been referred to the Outpatient Pulmonary Clinic of the Pulmonology and Thoracic Surgery Department of the *Hospital das Clínicas da Universidade Federal de Minas Gerais* (HC-UFGM, Federal University of Minas Gerais *Hospital das Clínicas*), located in the city of Belo Horizonte, Brazil, were invited to participate in the present study.

We excluded patients with symptoms that were consistent with severe asthma, those who presented with acute exacerbation or who had experienced acute exacerbation in the four weeks preceding the study outset, those who had used oral corticosteroids in the four weeks preceding the study outset or who had used maintenance medication for asthma in the three months preceding the study outset, those who had used beta blockers, those who were current smokers, those who had quit smoking less than one month prior, those with a smoking history of more than 10 pack-years, those with severe decompensated chronic comorbidities, and those who were unable to report to the pulmonary function laboratory. All of the demographic and clinical data were registered in a form designed specifically for the present study.

The patients underwent two tests. Although each test was performed on a different day, the second test was performed at the same time of day as was the first (i.e., in the morning or in the afternoon), the maximum interval between the tests being three days. For each patient, the technique employed on the first test was defined by random sampling. The patients performed the following procedures: inhalation of four 100- $\mu$ g puffs of albuterol via an MDI without a spacer (the usual technique); and inhalation of four 100- $\mu$ g puffs of albuterol via an MDI with a large-volume spacer (650 mL).

The patients were instructed on to how to use the MDI correctly during the bronchodilator test, with and without the spacer. They were also instructed not to use inhaled medication for at least 8 h before the test, in accordance with the

protocol that is routinely used in the HC-UFMG Pulmonary Function Laboratory.

For the tests performed without the spacer, the MDI with medication was placed 4 cm from the mouth, which was kept open. The device was triggered at the beginning of a slow, deep inhalation (after a normal exhalation), followed by an inspiratory pause of at least 10 s. Between puffs, the MDI was shaken. For the tests performed with the spacer, the MDI with medication was shaken and then attached to the spacer. The patients were then instructed to perform the aforementioned maneuvers with their mouths attached to the spacer. Within 20 min after bronchodilator use, spirometry was performed again. On both tests, the drug was administered by the examiner.

All of the spacers received antistatic treatment, which was performed in accordance with a previously described technique.<sup>(13,14)</sup> In brief, the spacers were immersed in a solution of two drops of neutral detergent in one liter of water. After 30 min, the devices were left to dry for 24 h in room air, without having previously been rinsed. The antistatic treatment of the spacers was performed by one of the authors. For each patient, we used a new, Flumax® plastic valve spacer (Flumax Equipamentos Médicos Ltda., Belo Horizonte, Brazil).

For each case, the tests were performed by the same technician, who used a 92494 Koko spirometer (PDS Instrumentation Inc., Louisville, CO, USA).

The principal evaluation parameter was the variation in FEV<sub>1</sub>, expressed by the absolute variation in FEV<sub>1</sub> in relation to the predicted value (post-bronchodilator FEV<sub>1</sub> – pre-bronchodilator FEV<sub>1</sub> × 100/predicted FEV<sub>1</sub>). The bronchodilator test was considered positive when the variation was ≥ 200 mL and > 7% of predicted in patients with airflow obstruction or ≥ 10% of predicted in those with normal spirometry results, in accordance with the Brazilian guidelines for pulmonary function tests.<sup>(1)</sup>

For calculating the sample size, we performed a random, preliminary analysis of spirometric tests performed in the HC-UFMG Pulmonary Function Laboratory on patients who would have met the criteria for inclusion in the present study. This was done in order to determine the mean variation in FEV<sub>1</sub> prior to and after bronchodilator use. On 17 of the tests performed,

the mean FEV<sub>1</sub> prior to bronchodilator use was found to be 2.83 L, whereas the mean FEV<sub>1</sub> after bronchodilator use was found to be 3.05 L. A previous study evaluated the equivalence between two devices for the administration of albuterol to asthma patients, and the weighted mean difference was estimated to be ± 0.25 L.<sup>(16)</sup> Assuming those values, a type I error of 0.05, a type II error of 0.20, and a minimum detectable difference of 0.125 L between the groups for a two-tailed test, we estimated that the number of patients needed for the study was 24.

In order to compare the two techniques in terms of the bronchodilator test results (positive or negative), we used McNemar's test. The kappa statistic was used in order to determine the level of agreement between the two diagnostic tests. In order to determine the difference between the two techniques in terms of the pre- and post-bronchodilator FEV<sub>1</sub> values, we used the Student's t-test. For all analyses, we used the Statistical Package for the Social Sciences, version 10 (SPSS Inc., Chicago, IL, USA).

The study project was approved by the UFMG Research Ethics Committee (ETIC Ruling no. 179/07) on June 20, 2007. All of the participants gave written informed consent.

## Results

The tests were performed between August 31, 2007 and August 5, 2009 in the Pulmonary Function Laboratory of the HC-UFMG Department of Pulmonology. We selected 25 patients. One patient did not return for the second test and was therefore excluded. The mean age was 27 years (range, 18-41 years). Of the 24 patients, 16 (67%) were female and 8 (33%) were male (Table 1).

Regarding the bronchodilator test results (positive or negative), there were no statistically significant differences between the usual technique and the technique with a spacer ( $p = 1.00$ ).

There was significant concordance between the techniques in terms of the bronchodilator test results (kappa statistic = 0.909;  $p < 0.005$ ), meaning that the results obtained with the usual technique did not differ from those obtained with the use of spacers. There was no concordance between the techniques in terms of the bronchodilator test results in only 1 patient. For that patient, the bronchodilator test with the

**Tabela 1** - Demographic characteristics of the 24 patients under study.<sup>a</sup>

Characteristics	Values
Age, years <sup>b</sup>	27 (18-41)
Height, cm <sup>b</sup>	164 (145-189)
Gender (M/F)	8/16
Dyspnea (No/Yes)	6/18
Wheezing (No/Yes)	1/23
Persistent cough (No/Yes)	11/13
Nocturnal symptoms (No/Yes)	14/10

<sup>a</sup>Values expressed as n/n, except where otherwise indicated.

<sup>b</sup>Values expressed as mean (range).

usual technique was positive (variation, 270 mL and 8%), whereas the bronchodilator test with the spacer was negative (variation, 200 mL and 6%). That patient presented with mild obstructive lung disease on the two spirometric tests performed. Table 2 shows a comparison between the two techniques employed in the present study regarding the bronchodilator test results.

For the technique with a spacer, the mean FEV<sub>1</sub> after bronchodilator use was significantly higher than the mean FEV<sub>1</sub> prior to bronchodilator use (mean  $\Delta$ FEV<sub>1</sub> = 0.25 L; 95% CI: 0.15-0.35; p < 0.001). For the usual technique, the mean FEV<sub>1</sub> after bronchodilator use was also significantly higher than the mean FEV<sub>1</sub> prior to bronchodilator use (mean  $\Delta$ FEV<sub>1</sub> = 0.24 L; 95% CI: 0.16-0.33; p < 0.001). However, as can be seen in Figure 1, there were no significant differences between the two techniques in terms of the variation in FEV<sub>1</sub> prior to and after bronchodilator use (mean  $\Delta$ FEV<sub>1</sub> = 0.01 L; 95% CI: -0.05 to 0.06; p = 0.824).

Table 3 shows the functional values prior to and after the administration of 400 µg of albuterol by the two techniques under study. There were no significant differences between the two spirometric tests in terms of the baseline values, and there were no significant differences

between the two techniques for bronchodilator administration in terms of the variation in FEV<sub>1</sub>.

## Discussion

The present study showed that there were no significant differences between the bronchodilator tests performed with the use of a spacer and those performed without the use of a spacer in terms of the variation in FEV<sub>1</sub> after the administration of 400 µg of albuterol via an MDI.

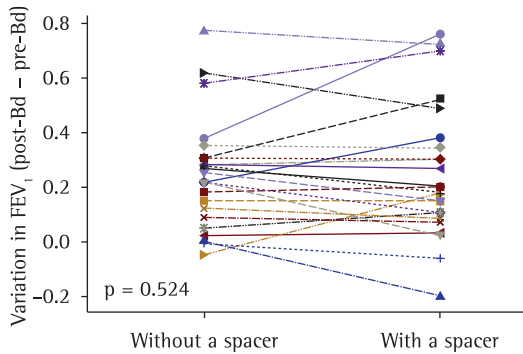
Inhalers and inhaled drugs can be evaluated by aerosol deposition techniques (in formulations with inert Teflon particles or with technetium-labeled medication), by measuring pulmonary deposition of aerosol (by determining the fine particle fraction or respirable fraction and the concentration of the drug in plasma or urine), and by the variation in pulmonary function measurements after drug administration.

Those studies are warranted primarily by the widespread use of inhaled drugs via an MDI in the treatment of numerous respiratory diseases. We searched the Medline, SciELO, and LILACS databases using the specific descriptors "asthma", "spirometry", and "inhalation spacers", as well as their counterparts in Portuguese, as search terms. We also used the Boolean operator "AND". As of January of 2011, we had found no studies comparing the bronchodilator test results obtained with the use of an MDI with a spacer and those obtained with the use of an MDI without a spacer. Therefore, it is impossible to compare the results of the present study with data in the literature. This is why we attempted to correlate the results of the present study with known data regarding the use of MDIs with and without spacers in the treatment of obstructive lung disease.

One group of authors incorporated Teflon particles into MDIs that were used by 8 patients with obstructive lung disease; the authors found that 8.8% of the dose was deposited in

**Table 2** - Comparison between the bronchodilator test results obtained with the use of a spacer and those obtained without the use of a spacer.

Results with a spacer	Results without a spacer		Total	p
	Positive	Negative		
Positive	8	0	8	1.000
Negative	1	15	16	
Total	9	15	24	



**Figure 1** – Variation in FEV<sub>1</sub> with and without the use of a spacer. Bd: bronchodilator.

the lungs, whereas 80% was deposited in the oropharynx.<sup>(17)</sup>

Various types of spacers have been developed with the objective of increasing pulmonary deposition and, consequently, the therapeutic effect of bronchoactive drugs, as well as of reducing the need for coordinating the triggering of the device with inhalation. By increasing the distance between the MDI and the mouth of the patient, spacers contribute to the evaporation of the propellant, which in turn reduces the speed and size of aerosol particles and leads to lower oropharyngeal deposition and greater pulmonary deposition.<sup>(18)</sup>

A study investigating 9 patients with airflow obstruction and comparing the delivery of radiolabeled aerosol via an MDI with a large-volume spacer with that of radiolabeled aerosol via an MDI without a large-volume spacer found that oropharyngeal deposition was reduced to 16% ( $p < 0.01$ ) and pulmonary deposition was increased to 21% ( $p < 0.01$ ) with the use of the large-volume spacer.<sup>(4)</sup> Increased pulmonary deposition was also demonstrated in another study, which involved 10 patients with airflow

obstruction and used radiolabeled aerosol delivered via an MDI with and without a large-volume spacer. The use of the correct technique for aerosol delivery in combination with the use of the spacer increased pulmonary deposition from 11.2% to 14.8% ( $p < 0.05$ ).<sup>(7)</sup>

We found no statistically significant differences between albuterol delivery via an MDI with a spacer with antistatic treatment and albuterol delivery via an MDI in isolation (the usual technique) in terms of the bronchodilator test results obtained. Although the design of our study differed from that of previous studies, we expected bronchodilator response to increase with the use of a spacer with antistatic treatment, given that previous studies have demonstrated greater pulmonary deposition when an MDI is used in combination a spacer. However, it is difficult to demonstrate differences between the use of an MDI without a spacer and that of an MDI with a spacer in terms of the clinical response to bronchodilators. This is due to the fact that the dose-response curve for  $\beta_2$  agonists rapidly reaches a plateau with the dose used in the two methods. Those doses elicit, in the tracheobronchial receptors, a maximum bronchodilator response in the central airways, which is the principal determinant of variations in FEV<sub>1</sub>.<sup>(19)</sup> Therefore, we can speculate that low doses of  $\beta_2$  agonists should be used in order to demonstrate clinical differences among the devices.

Other factors influence and explain the varying results of studies involving spacers: the volume and shape of spacers; the presence of an inhalation valve; the aerosol composition; the medication used; the inhalation technique; the antistatic treatment (or lack thereof); and the different methods of aerosol radiolabeling.<sup>(19)</sup>

**Table 3** – Functional values prior to and after the use of 400  $\mu$ g of albuterol administered with and without the use of a spacer in the 24 patients under study.<sup>a</sup>

Spirometric variables	Results	
	Without a spacer	With a spacer
Pre-Bd FEV <sub>1</sub> , L	3,01 $\pm$ 0.88	2.97 $\pm$ 0.93
Post-Bd FEV <sub>1</sub> , L	3.25 $\pm$ 0.85	3.22 $\pm$ 0.83
$\Delta$ FEV <sub>1</sub> , L	0.24 $\pm$ 0.20	0.25 $\pm$ 0.24*
Pre-Bd FEV <sub>1</sub> , % of predicted	88.75 $\pm$ 17.61	87.00 $\pm$ 18.23
Pre-Bd FEV <sub>1</sub> /FVC ratio, %	78.75 $\pm$ 12.15	77.73 $\pm$ 11.87
Pre-Bd FVC, L	3.80 $\pm$ 0.87	3.79 $\pm$ 0.92
Post-Bd FVC, L	3.88 $\pm$ 0.87	3.84 $\pm$ 0.89

Bd: bronchodilator. <sup>a</sup>Values expressed as mean  $\pm$  SD. \* $p = 0.824$ .



In a randomized, double-blind study involving 13 patients with asthma (mean age, 29.9 years), one group of authors compared the bronchodilator effect of 40 µg of clenbuterol delivered via an MDI used in isolation with that of 40 µg of clenbuterol delivered via an MDI used in combination with either of two types of spacers (large- and small-volume spacers).<sup>(20)</sup> The MDI was used with the open mouth technique, the device being placed 2 cm from the mouth of the patient. Clenbuterol significantly increased FEV<sub>1</sub> throughout the study period, regardless of which of the three methods under study was used. In comparison with the use of an MDI in isolation, the use of an MDI in combination with a large-volume spacer led to a significant increase in FEV<sub>1</sub> over the period of 15-90 min after bronchodilator use, whereas the use of an MDI in combination with a small-volume spacer caused significant bronchodilation only at 15 min. The authors concluded that the bronchodilator response is greater when MDIs are used in combination with spacers. However, that effect has little clinical relevance when patients use MDIs correctly.<sup>(20)</sup>

A crossover study involving 25 patients with asthma compared the bronchodilator effect of 200 µg of albuterol administered via a small-volume (7.5 cm) spacer with that of 200 µg of albuterol administered via a large-volume spacer (both spacers having received antistatic treatment) and found no differences between the two techniques.<sup>(16)</sup>

One study compared the bronchodilator effect of 100 µg of inhaled albuterol administered without the use of a spacer with that of 100 µg of inhaled albuterol administered with the use of small- and large-volume spacers. In 11 patients with stable asthma, there was a significant increase in PEF when small- and large-volume spacers with antistatic treatment were used.<sup>(10)</sup>

In a randomized study investigating 10 patients with stable, mild to moderate asthma, 90 µg of radiolabeled albuterol were used in order to compare the use of MDI in isolation with that of MDI in combination with four types of spacers in terms of the bronchodilator response. All of the spacers led to similar bronchodilator responses, with no significant differences among spacers or between each type of spacer and the MDI used in isolation.<sup>(21)</sup>

Our study involved patients who were clinically suspected of having asthma. Only 42% of the patients under study presented with obstructive lung disease (as revealed by spirometry). This possibly made it difficult to determine the bronchodilator response, given that in patients with normal spirometry results a variation of  $\geq 10\%$  in VEF<sub>1</sub> is required in order to characterize a positive response to bronchodilator use.<sup>(1)</sup> However, we chose to analyze patients clinically suspected of having asthma with the objective of including patients with normal spirometry results and evaluating the influence of large-volume spacers on the bronchodilator test results for those patients. This is due to the fact that patients with normal spirometry results and positive bronchodilator test results (variation of  $\geq 10\%$  in FEV<sub>1</sub>) are considered to have mild obstructive lung disease, which has clinical and therapeutic implications.

The age bracket of the patients under study possibly influenced the results obtained. We included young patients, the mean age being 27 years. Children and elderly individuals have greater difficulty in using MDIs because of the need to coordinate the triggering of the device with inhalation. However, we believe that that difficulty would have been minimized by the fact that, in the present study, the MDI was activated by the examiner. This would have reduced the frequency of incorrect use among children and elderly individuals, had we included such individuals.

The results of the present study showed that spirometry with bronchodilator test can be performed without the use of large-volume spacers as long as the MDI is used correctly and in a standardized manner.

Further studies involving a larger number of patients and including those with a diagnosis of airflow obstruction should be conducted.

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