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AIRWAYS DISEASE

Effect of Heliox- and Air-Driven Nebulized Bronchodilator Therapy on Lung Function in Patients with Asthma

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Abstract

Background This study compares the effect of heliox-driven to that of air-driven bronchodilator therapy on the pulmonary function test (PFT) in patients with different levels of asthma severity.

Methods One-hundred thirty-two participants were included in the study. Participants underwent spirometry twice with bronchodilator testing on two consecutive days. Air-driven nebulization was used one day and heliox-driven nebulization the other day in random order crossover design. After a baseline PFT, each participant received 2.5 mg of albuterol sulfate nebulized with the randomized driving gas. Post bronchodilator PFT was repeated after 30 min. The next day, the exact same protocol was repeated, except that the other driving gas was used to nebulize the drug. Participants were subgrouped and analyzed according to their baseline FEV_1 on day 1: Group I, $FEV_1 \geq 80$ %; Group II, 80 % > FEV_1 > 50 %; Group III, $FEV_1 \leq 50$ %. The proportion of participants with greater than 12 % and 200-mL increases from their baseline FEV_1 and the changes from baseline in PFT variables were compared between heliox-driven versus air-driven bronchodilation therapy.

Results The proportion of participants with >12 % and 200-mL increases from their baseline FEV_1 with air- or heliox-driven bronchodilation was not different with respect to the proportion of participants with baseline $FEV_1 \geq 80$ % (20 vs. 18 %, respectively) and 80 % > FEV_1 > 50 % (36 vs. 43 %, respectively), but it was significantly greater with heliox-driven bronchodilation in participants with $FEV_1 \leq 50$ % (43 vs. 73 %, respectively; $p = 0.01$). Changes from baseline FVC, FEV_1, FEV_1/FVC, $FEF_{25-75\ \%}$, FEF_{max}, $FEF_{25\ \%}$, $FEF_{50\ \%}$, and $FEF_{75\ \%}$ were significantly larger with heliox-driven versus air-driven bronchodilation in participants with baseline $FEV_1 \leq 50$ %.

Conclusion Improvements in PFT variables are more frequent and profound with heliox-driven compared to air-driven bronchodilator therapy only in asthmatic patients with baseline $FEV_1 \leq 50$ %.

Keywords Heliox · Air · Nebulization · Bronchodilator · Pulmonary function test · Asthma

Introduction

The effectiveness of nebulized bronchodilator therapy in patients with acute or chronic obstructive airway disease depends on the site of aerosol deposition in the trachea-bronchial tree [1–4]. When nebulizing bronchodilators with either 100 % oxygen or air (21 % oxygen and 79 % nitrogen), much of the mass of inhaled aerosols is deposited in the nasopharynx, the trachea, and the large airways and little of the drug is delivered to the distal airways [1, 2]. The unfavorable distribution may compromise the anticipated positive bronchodilator effect. This phenomenon can be more pronounced during exacerbations of obstructive airway disease because of increased airway resistance resulting in turbulent airflow [3, 4].

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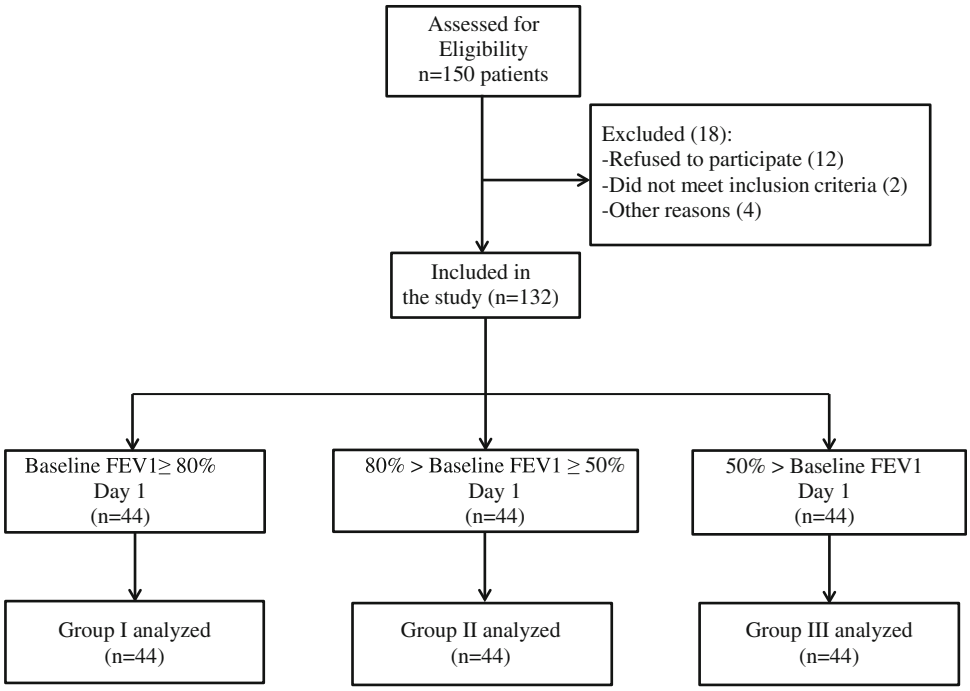

Fig. 1 The CONSORT flow diagram of the study

Heliox (80:20) (a mixture of 80 % helium and 20 % oxygen) is less dense than both air and oxygen. Helium is a chemically inert, odorless, tasteless, poorly soluble, non-combustible gas that has no bronchodilator or anti-inflammatory properties [3, 5, 6]. Because of its lower density and greater safety, heliox may be a better vehicle for the delivery of aerosolized bronchodilator drugs resulting in a superior distribution and deposition of the bronchodilator agents into the distal airways and thus a better response to bronchodilator therapy [7, 8]. Several previous studies have shown that heliox-driven β2-agonist aerosol therapy can improve measures of lung function and dyspnea scores when compared to air- or oxygen-driven β2-agonist aerosol therapy [7–11]. However, most of these studies were done with no stratification with respect to the severity of airway obstruction [8, 10, 11].

The aim of this study was to compare the effect of heliox-driven to air-driven β2-agonist aerosol therapy on pulmonary functions tests (PFT) among asthmatic patients with different levels of severity of airway obstruction.

Methods

Study Sample

This study was approved by the Institutional Review Board at the American University of Beirut, and written informed consent for participation was obtained from each participant. Subjects of both genders, 18 years or older, not known to have obstructive lung diseases and who were referred to the Pulmonary Laboratory at the American University of Beirut Medical Center for their first pre- and post-bronchodilator PFT were considered for the study. Pregnant women, morbidly obese patients (body mass index >35 kg/m^2), and patients who had an acute exacerbated shortness of breath in the week prior to enrollment were excluded from the study. One hundred fifty participants were assessed with eligibility criteria and 132 participants completed the study procedure (Fig. 1).

Bronchodilator Testing

Participants underwent spirometry twice with bronchodilator testing on two consecutive days, at the same time of the day, and were randomly assigned to receive air-driven or heliox-driven nebulization of 2.5 mg of albuterol sulfate (0.5 mL of the 0.5 % solution, diluted to a final volume of 3 mL with 0.9 % sodium chloride solution) one day and heliox-driven nebulization of the same drug the other day.

After performing baseline spirometry, the nebulized bronchodilator treatment was administered for 10 min at a flow rate of 8 L/min with the randomized driving gas. A dedicated flowmeter, calibrated for heliox (80:20) yet similar to the oxygen flowmeter, was used whenever heliox was the driving gas for nebulization. Nebulization of the bronchodilator was performed using a small-volume nebulizer interfaced with a non-rebreathing oronasal mask and a large reservoir bag (Intersurgical, Berkshire, UK) to avoid dilution with air during heliox-driven nebulization. The same setup was used for air-driven nebulization. Post-bronchodilator PFT was repeated 15–30 min after termination of nebulization. The next day, the exact protocol

was used except that the other driving gas was used to nebulize the drug.

Randomization and Blinding

Simple randomization was done by selecting one of two identical sealed envelopes containing the two possible sequences of nebulizing gas sources for days 1 and 2. The patients and the personnel conducting the PFTs were blinded to the driving gas used to nebulize the bronchodilator. The heliox and compressed air cylinders were totally covered and the patients were instructed not to talk during and after nebulization of the bronchodilator to prevent heliox-related voice changes from affecting the blinding.

Pulmonary Function Test

Pulmonary function tests were performed using a Collins CPF PF system (Ferraris Respiratory, Plano, TX, USA) that was calibrated prior to each use as per the manufacturer's recommendations. Pre- and post-heliox-driven or compressed air-driven PFTs, which included forced exhaled volume in 1 s (FEV_1), forced vital capacity (FVC), maximal midexpiratory flow rate ($FEF_{25–75\ \%}$), maximal expiratory flow rate (FEF_{max}), and forced expiratory flow at 25 % ($FEF_{25\ \%}$), 50 % ($FEF_{50\ \%}$) and 75 % ($FEF_{75\ \%}$) of the vital capacity were determined and analyzed according to the American Thoracic Society guidelines [12]. The prediction equations used to obtain the percentage predicted values of the spirometry variables were automatically provided by the Collins CPF PF system and based on the equations of Morris et al. [13, 14] and Cherniack and Raber [15]. All patients were well trained and instructed on performing PFTs before the tests and were coached on all the appropriate breathing maneuvers throughout the PFT procedure. Continuous noninvasive oxyhemoglobin saturation was monitored in all participants throughout all the study procedures.

Data Analysis

In this crossover design, each participant served as his/her own control. Participants were subgrouped according to their baseline FEV_1 on day 1: Group I, patients with $FEV_1 \geq 80$ %; Group II, patients with $80\ \% > FEV_1 > 50\ \%$; Group III, patients with $FEV_1 \leq 50$ % (Fig. 1) [16]. Patients who showed >12 % and 200-mL increases from their baseline FEV_1 were considered responders to bronchodilator treatment. The proportion of responders to bronchodilator therapy was determined in each airway obstruction severity subgroup and compared with respect to air-driven versus heliox-driven nebulization using the χ^2 test. Also, the changes from baseline of the different PFT measures were compared between air-driven and heliox-driven bronchodilator therapy using the ANOVA test with the Scheffe's test for post hoc analysis and Student's t test. The level of statistical significance was $p < 0.05$.

Based on a power analysis with a type I error of 5 %, type II error of 20 %, a statistical significance level of 5 %, and a clinical significance of 10 % change in FEV_1 between the two driving gases, it was found that a total of at least 132 patients would be needed in the study.

Results

The participants' demographics and physiological parameters are presented in Table 1. Except for baseline FEV_1 on day 1, the percentage of predicted FEV_1, and the pack-year smoking history, there were no statistically significant differences among the three groups. No supplemental oxygen was needed for any participant in any of the three groups. The baseline spirometric values on days 1 and 2 were not different for each of the three groups (Table 2).

The percentages of participants who showed a >12 % and a more than 200-mL increase in FEV_1 with both air-driven and heliox-driven bronchodilation were not different than participants with baseline $FEV_1 \geq 80$ % (20 vs. 18 %, respectively, $p = 1.00$) and $80\ \% >$ baseline $FEV_1 > 50\ \%$ (36 vs. 43 %, respectively, $p = 0.66$). However, for participants with baseline $FEV_1 \leq 50$ %, the percentage of participants who showed a >12 % and a more than 200-mL increase in FEV_1 was significantly higher with heliox-driven compared to air-driven bronchodilation (73 vs. 43 %, respectively, $p = 0.01$).

The changes in spirometric values with air-driven and heliox-driven bronchodilation for participants in Groups I, II, and III are presented in Tables 3, 4, and 5, respectively. In Group I, only the changes in FEF_{max} and $FEF_{25\ \%}$ were significantly greater with heliox-driven bronchodilation (Table 3). In Group II, only the changes in FEV_1 and FVC were significantly greater with heliox-driven bronchodilation (Table 4). However, in Group III, the changes in all spirometric measures were significantly greater with heliox-driven bronchodilation (Table 5).

Discussion

The current study shows that nebulization of bronchodilators administered with heliox (80:20) resulted in significantly greater improvements in spirometry measurements than aerosol administration with room air in asthmatic patients with severe airway obstruction (baseline $FEV_1 \leq 50$ %). Furthermore, our data show that there are no

Table 1 Patients characteristics

	Group I ($n = 44$)	Group II ($n = 44$)	Group III ($n = 44$)	p value
Age (years)	51 ± 14	52 ± 13	53 ± 8	0.61
Gender (M/F)	21/23	22/22	23/21	0.91
Height (cm)	163 ± 10	162 ± 8	164 ± 7	0.45
Weight (kg)	74 ± 18	71 ± 12	74 ± 11	0.58
BSA (kg/cm^2)	27 ± 5	27 ± 4	27 ± 3	0.86
Smoker (Y/N)	19/25	18/26	20/24	0.91
Pack-years	8.6 ± 13.3	11.5 ± 16.8	22.2 ± 28.8*	0.006
Inhaled corticosteroids (Y/N)	19/25	23/21	26/18	0.33
FEV_1 (L)	2.73 ± 0.77	1.70 ± 0.52	1.11 ± 0.28	<0.001
FEV_1 (% of predicted)	99 ± 13	63 ± 10	40 ± 8	<0.001

Values are presented as mean ± SD

* $p < 0.05$ vs. Group I

Table 2 Baseline spirometric values on days 1 and 2

Variables	Group I ($n = 44$)		Group II ($n = 44$)		Group III ($n = 44$)	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
FEV_1 (L)	2.73 ± 0.77	2.74 ± 0.78	1.70 ± 0.52	1.68 ± 0.52	1.11 ± 0.28	1.13 ± 0.29
FVC (L)	3.66 ± 1.08	3.64 ± 1.07	2.82 ± 0.91	2.78 ± 0.86	2.59 ± 0.64	2.60 ± 0.62
FEV_1/FVC (%)	75 ± 8	76 ± 7	62 ± 11	60 ± 11	44 ± 10	44 ± 11
$FEF_{25–75\ \%}$ (L/s)	2.38 ± 1.03	2.40 ± 1.04	0.98 ± 0.51	0.99 ± 0.52	0.43 ± 0.16	0.45 ± 0.16
FEF_{max} (L/s)	6.50 ± 1.83	6.52 ± 1.80	4.28 ± 1.37	4.26 ± 1.37	3.29 ± 1.02	3.32 ± 1.02
$FEF_{25\ \%}$ (L/s)	5.91 ± 1.68	5.94 ± 1.66	3.09 ± 1.56	3.11 ± 1.54	1.40 ± 1.0	1.42 ± 0.99
$FEF_{50\ \%}$ (L/s)	3.54 ± 1.46	3.57 ± 1.44	1.39 ± 0.75	1.42 ± 0.75	0.59 ± 0.34	0.59 ± 0.32
$FEF_{75\ \%}$ (L/s)	0.94 ± 0.49	0.96 ± 0.50	0.42 ± 0.25	0.44 ± 0.25	0.21 ± 0.10	0.21 ± 0.08

Values are presented as mean ± SD

Table 3 Changes in spirometric measures with air- and heliox-driven bronchodilation in patients with baseline $FEV_1 \geq 80$ %

	Group I ($n = 44$)		
	Air-driven	Heliox-driven	p value
ΔFEV_1 (L)	0.21 ± 0.29	0.22 ± 0.04	0.71
ΔFVC (L)	0.08 ± 0.21	0.11 ± 0.23	0.16
ΔFEV_1/FVC (%)	3.06 ± 6.64	2.61 ± 6.06	0.36
$\Delta FEF_{25–75\ \%}$ (L/s)	0.54 ± 0.63	0.50 ± 0.48	0.53
ΔFEF_{max} (L/s)	0.14 ± 1.18	0.66 ± 1.22	0.001
$\Delta FEF_{25\ \%}$ (L/s)	0.31 ± 1.43	0.65 ± 1.39	0.03
$\Delta FEF_{50\ \%}$ (L/s)	0.67 ± 0.91	0.62 ± 0.90	0.71
$\Delta FEF_{75\ \%}$ (L/s)	0.34 ± 0.44	0.32 ± 0.33	0.57

Values are presented as mean ± SD

Table 4 Changes in spirometric measures with air- and heliox-driven bronchodilation in patients with $80\ \% > FEV_1 > 50\ \%$

	Group II ($n = 44$)		
	Air-driven	Heliox-driven	p value
ΔFEV_1 (L)	0.22 ± 0.32	0.28 ± 0.41	0.04
ΔFVC (L)	0.19 ± 0.31	0.25 ± 0.35	0.04
ΔFEV_1/FVC (%)	3.10 ± 6.00	3.84 ± 6.96	0.27
$\Delta FEF_{25–75\ \%}$ (L/s)	0.20 ± 0.43	0.32 ± 0.56	0.07
ΔFEF_{max} (L/s)	0.68 ± 1.10	0.82 ± 1.10	0.29
$\Delta FEF_{25\ \%}$ (L/s)	0.71 ± 1.14	0.93 ± 1.00	0.14
$\Delta FEF_{50\ \%}$ (L/s)	0.33 ± 0.68	0.46 ± 0.78	0.15
$\Delta FEF_{75\ \%}$ (L/s)	0.07 ± 0.22	0.14 ± 0.31	0.15

Values are presented as mean ± SD

significant benefits in using heliox instead of room air for nebulizing β2-agonist drugs in patients with baseline $FEV_1 \geq 80$ % or baseline $50\ \% < FEV_1 < 80\ \%$.

Heliox (80:20) is less dense than room air or oxygen and can be expected to be a better vehicle for the delivery of aerosolized bronchodilator drugs than room air or oxygen. In patients with obstructive lung diseases, heliox improves gas flow through high-resistance airways by providing higher flow rates with given pressures in turbulent or near-turbulent flows [17] and by preventing the transition from laminar to turbulent flow. Moreover, the resulting decreased momentum loss with heliox in the high-resistance upper airways and through obstructed regions can allow better ventilation of and aerosol delivery to the smaller airways and alveoli [18], thus resulting in a more efficient distribution and deposition of the bronchodilator agents [19, 20]. Piva et al. [19] showed that when heliox rather than oxygen was used as a vehicle for radiolabeled aerosol, there was better lung deposition of the radiolabeled particles, with the effect being more pronounced in patients

Table 5 Changes in spirometric measures with air- and heliox-driven bronchodilation in patients with baseline $FEV_1 \leq 50$ %

	Group III ($n = 44$)		
	Air-driven	Heliox-driven	p value
$DFEV_1$ (L)	0.20 ± 0.20	0.46 ± 0.30	0.001
DFVC (L)	0.34 ± 0.40	0.66 ± 0.47	0.001
$DFEV_1$/FVC (%)	1.79 ± 4.80	6.17 ± 9.71	0.001
$DFEF_{25–75\ \%}$ (L/s)	0.10 ± 0.13	0.43 ± 0.44	0.001
$DFEF_{max}$ (L/s)	0.42 ± 0.70	1.10 ± 0.84	0.001
$DFEF_{25\ \%}$ (L/s)	0.24 ± 0.36	0.84 ± 0.80	0.001
$DFEF_{50\ \%}$ (L/s)	0.09 ± 0.19	0.53 ± 0.64	0.001
$DFEF_{75\ \%}$ (L/s)	0.03 ± 0.12	0.24 ± 0.29	0.001

Values are presented as mean ± SD

with severe lower airway obstruction. Using a radionuclide approach, Darquenne and Prisk [2] compared upper respiratory tract deposition with heliox (80:20) versus that with room air and showed that heliox increased the deposition of aerosols in the distal airways and alveoli.

The clinical effects of heliox-driven aerosol drug administration have been studied and compared to those of air-driven or oxygen-driven aerosol drug administration, with different findings. Kress et al. [11] showed that during acute asthma exacerbations in 23 patients who presented to the emergency room, albuterol nebulized with heliox led to a more significant improvement (32–65 %) in spirometry measures when compared with albuterol nebulized with oxygen (14–27 %). Also, Bag et al. [9] reported that heliox-driven bronchodilation improved FEV_1, FVC, and FEF_{max} significantly more than air-driven bronchodilation in 31 patients with clinically stable asthma. Lee et al. [20] showed that heliox-driven bronchodilation resulted in a more rapid and greater improvement in peak expiratory flows and dyspnea scores in patients with severe asthma exacerbations who presented to the emergency room. In a systematic review, Colebourn et al. [21] concluded that the use of heliox to drive nebulizers in patients with acute asthma improves airflow measures. Our findings are similar to the previous studies that showed positive beneficial effects of heliox-driven bronchodilation on spirometry measurements [9, 11, 20, 21]. However, the current study is different in several ways. First, our study, in which each participant served as his/her own control, stratified asthmatic subjects according to their baseline FEV_1 and divided the participants into three different groups ($FEV_1 \geq 80$ %; 80 % > FEV_1 > 50 %; and $FEV_1 \leq 50$ %) [16]. Our data show that heliox-driven bronchodilation presents clinically significant benefits in spirometry measurements and may be more advantageous than air-driven bronchodilation only in patients with baseline $FEV_1 \leq 50$ %. Second, all our patients were studied using both driving gases on two consecutive days, decreasing the likelihood of changes in their clinical conditions, in contrast to the study of Bag et al. [9], where patients were studied on two separate days, 1–7 days apart. Third, the participants in our study were stable asthmatics; this is in contrast to previous studies that have shown beneficial effects of heliox in nebulizing bronchodilators in unstable asthmatic patients during their acute exacerbations [3, 11]. Finally, our study included the highest number of stable asthmatics that were stratified according to severity of their airway obstruction and were studied randomly on two consecutive days with heliox-driven and air-driven nebulization of bronchodilators.

In contrast, several previous clinical studies reported no benefits or advantages for heliox-driven bronchodilation compared to air-driven or oxygen-driven bronchodilation [22–25]. Most of these studies were conducted in asthmatic patients with severe exacerbations and presenting to the emergency room, where the main evaluated parameters were respiratory rate, oxygen saturation, peak expiratory flows, and dyspnea scores. The current study differs from others in that our patients are clinically stable asthmatic patients who underwent spirometry testing in the pulmonary function lab.

The difference in pack-year smoking history was different only between participants with baseline $FEV_1 \leq 50$ % and participants with baseline $FEV_1 \geq 80$ %. However, in this double-blinded crossover study, each patient served as his/her own control and received nebulized β2-agonist drugs with both heliox and room air on two separate and consecutive days. Subsequently, all observed clinical effects can be attributed and due to the use of two different nebulizing gases (i.e., heliox versus room air).

Two improved PFT measures (FEF_{max} and $FEF_{25\ \%}$) seen in Group I were not maintained in Group II. This inconsistency could be due to a minimal mathematical effect that arose because we established two baselines on two different days. Although we confirmed that these two baselines were statistically comparable, there will always be the possibility that minimal differences in baselines on two different days could lead to these isolated inconsistencies in the changes seen in the PFT measures.

The main limitation of our study was that we did not use radiolabeled bronchodilators to assess and compare the distribution and deposition of these drugs with heliox-driven and air-driven bronchodilation. However, we believe that the significant improvements seen in the spirometry measurements with heliox-driven bronchodilation over air-driven bronchodilation must have been due to superior delivery and deposition of the bronchodilator with heliox-driven bronchodilation therapy [2, 8, 11]. Also, our study did not assess the role of the patient's posture during bronchodilator therapy. Brandão et al. [26] showed that

when the torso leans forward at a 50–60° angle and the elbows rest on the thighs, there are greater improvements in FEV_1 during heliox-driven bronchodilation. However, our patients maintained the same posture, with the torso upright, during the two consecutive days of the study, and, as such, there was no difference in posture that could have influenced our results. Finally, in our study it was difficult to exclude mild COPD in asthmatic patients who smoke; however, the clinical pictures and medical histories of the patients who were enrolled are more consistent with asthma. Nevertheless, that each patient was his/her own control and that the two reversibility studies with the two nebulizing gases were performed only one day apart suggest that the observed clinical differences can be due to mainly the use of heliox versus room air rather than the medical conditions of the participants. Furthermore, several studies [27–29] have shown that the beneficial effects of heliox in stable COPD patients at rest are only sporadic, which suggests that heliox is not a therapeutic option in spontaneously breathing and resting COPD patients.

In conclusion, for asthmatic patients with baseline FEV_1 $\leq$50 %, albuterol nebulized with heliox (80:20) leads to more significant improvements in spirometry measurements when compared to albuterol nebulized with air. This is likely due to the low-density gas improving albuterol deposition in the distal airways. However, heliox-driven nebulization of albuterol might not provide significant improvements in spirometry measurements and any other clinical benefits over air-driven bronchodilation in stable asthmatic patients with baseline FEV_1 >l50 %. Heliox-driven nebulized bronchodilator use may be considered for reversibility testing in asthmatics with baseline FEV_1 <50 %.

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Conflict of interest None.

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