Evaluation of lung function and deposition of aerosolized bronchodilators carried by heliox associated with positive expiratory pressure in stable asthmatics: A randomized clinical trial

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KEYWORDS
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Summary
While administration of medical aerosols with heliox and positive airway pressure are both used clinically to improve aerosol delivery, few studies have differentiated their separate roles in treatment of asthmatics. The aim of this randomized, double blinded study is to differentiate the effect of heliox and oxygen with and without positive expiratory pressure (PEP), on delivery of radiotagged inhaled bronchodilators on pulmonary function and deposition in asthmatics. 32 patients between 18 and 65 years of age diagnosed with stable moderate to severe asthma were randomly assigned into four groups: (1) Heliox + PEP (n = 6), (2) Oxygen + PEP (n = 6), (3) Heliox (n = 11) and (4) Oxygen without PEP (n = 9). Each group received 1 mg of fenoterol and 2 mg of ipratropium bromide combined with 25 mCi

Abbreviation List: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; DTPA – Tc 99m, diethyleneetriaminepentaacetic acid technetium-99m; EPAP, expiratory positive airway pressure; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; IPPB, intermittent positive pressure breathing; HR, heart rate; PEP, positive expiratory pressure; PEEP, positive end expiratory pressure; PEEPi, intrinsic positive end expiratory pressure; FEV , peak expiratory flow; RR, respiratory rate; ROI, regions of interest; SBP, systolic blood pressure; SpO2, peripheral oxygen saturation.

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Introduction

In moderate to severe asthmatic subjects, airway obstruction has been associated with heterogeneous distribution of inhaled drugs with preferential deposition in central airways and less compromised areas, resulting in lower drug effectiveness.1,2

Heliox-driven aerosol drug administration has been increasingly used in recent years to transport aerosols deeper into the central and peripheral airways during severe airway obstruction with greater efficiency than air or oxygen, resulting in more homogenous deposition of aerosolized medications with potentially greater clinical response to bronchodilators.3–5

Although heliox-driven aerosol delivery of short acting bronchodilators has been reported to elicit better bronchodilator response compared to administration with air or oxygen, the results remain mixed across investigators. The application of positive pressure to the airway during aerosol administration has been associated with better response to short acting bronchodilators than administration with ambient pressures. Application of positive expiratory pressure (PEP) with fixed orifice resistors, expiratory positive airway pressure (EPAP) with spring loaded threshold resistors, high frequency oscillators with weighted ball or spring loaded resistors and continuous positive airway pressure (CPAP) have been reported to improve clinical response with bronchodilator administration.7–10

Several studies9–19 have focused on ways to optimize aerosol therapy for moderate to severe asthmatics through the combination of positive airway pressure and reduced density gas mixtures with nebulization. Positive expiratory pressure (PEP), has been shown to promote dilution of airways and decrease pulmonary resistance, while improving response to inhaled bronchodilators. Mixtures of helium with oxygen (heliox) have been shown to increase peripheral delivery of aerosol during nebulization.12–19

Despite the demonstrated benefits of applying external positive airway pressure and the use of heliox gas mixture during nebulization, few randomized controlled studies have evaluated the association between these two variables in treatment of asthmatics. The aim of this study is to evaluate the influence of heliox and PEP as independent variables during administration of radiotagged bronchodilator aerosols on both pulmonary function and pulmonary deposition in stable moderate to severe asthmatics.

Methods

Sample

The sample size was calculated based on a pilot study with five patients in each group, totaling 20 patients. G. Power Software 3.1 was used, considering α = 0.05 and 1 – β = 0.80. Sample size calculation was based on the percentage of predicted forced expiratory volume in the first second (FEV1), as it best characterizes the degree of airway obstruction. The protocol was approved by the Human Research Ethics Committee (protocol no.437/2008), according to resolution 196/96, and all study patients gave their informed written consent.

Inclusion criteria were patients with clinical diagnosis of persistent moderate to severe asthma, with percent of predicted FEV1 from 60 to 80% or severe asthma with predicted FEV1 < 60% for more than one year.20 All patients received combination therapy with bronchodilators and corticosteroids long term (Formoterol – 12 mcg and Budesonide – 400 mcg) and they are instructed to discontinue medication 24 h prior to the study.

Excluded from the study were patients: unable to understand or perform the spirometric maneuver or who failed to maintain proper positioning to obtain scintigraphic images; those with a history of smoking in the last three years, combined with a consumption of more than 100 cigarettes per year or who had smoked for at least 10 years; other pulmonary comorbidities such as chronic obstructive pulmonary disease (COPD), bronchiectasis and tuberculosis' sequelae, pregnancy and any contraindication to the use of PEP,4,5 such as active hemoptysis, acute sinusitis, facial surgery, oral, cranial or facial trauma, nosebleed, esophageal surgery and nausea.

Study design

In this double-blind study, patients were randomly allocated into four groups according to the type of propellant
gas (Oxygen or Heliox) and the use of PEP (0 or 10 cm H2O): Heliox + PEP (Group 1), Oxygen + PEP (Group 2), Heliox (Group 3) and Oxygen (Group 4). Simple randomization was used in a draw where each patient had the same chance to participate in any of the four groups (Figure 1). The gas used was blinded by covering the cylinders and asking the subjects not to talk during administration. The level of PEP was blinded by using an identical valve without resistance for patients in Groups 3 and 4.

Clinical evaluation
Initially, all patients underwent clinical evaluation consisting of an anamnesis and measurement of cardiopulmonary parameters such as respiratory rate (RR), peripheral oxygen saturation (SpO2) measured by pulse oximetry (MD 300 D Beijing, China); heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) obtained using Welch Allyn™ DS 44-11 CB, USA; inspiratory capacity (IC); spirometric parameters (portable MicroLoop spirometer, Cardinal Health, digital volume transducer, England). All parameters reassessed following scintigraphy.

Spirometry
To obtain spirometric values, patients were asked to perform FEV1, peak expiratory flow (PEF) and forced vital capacity (FVC) were analyzed, calculating the predicted percentage FEV1 in accordance with the American Thoracic Society.22 For IC, the patient was instructed to inspire to total lung capacity and then to return to normal breathing, and the mean of two largest ICs of at least three acceptable tests were used, and had to agree within 5% or 60 mL.23

Lung inhalation scintigraphy
Diethylenetriaminopentaacetic acid was labeled with 925 MBq (25 mCi) Technetium-99m (DTPA – Tc99m) and combined with 1 mg of fenoterol bromide and 2 mg of ipratropium using 0.9% saline solution to a total dose volume of 3 mL.

A non-invasive delivery system was used that consists of a closed, nontoxic orofacial mask (Vital signs – West Sussex, UK) with two unidirectional valves – inspiratory and expiratory branch – connected to the nebulizer for radioisotopes Ventics® II Medical device, class II, CE 0459 (Ventibox/CIS Bio International, France). PEEP of 0 or 10 cm H2O administered with a valve (Vital Signs, Toyota, NY), attached to the expiratory port. The nebulizer was fed by a flow of 8 L/min oxygen for the oxygen group and 11 L/min of heliox as established by Hess et al.24 The mask was sealed to the patient’s face to prevent leaks and maintain proper PEP (Figure 2). When driven by heliox, flow was adjusted to the suitable flow for the gas mixture (White Martins).25

Inhalation was administered with subjects in an upright sitting position over 9 min. Patients were previously advised to breathe slowly and deeply through the mouth, making one inspiratory pause for 3 s. After inhalation, patients were instructed to rinse their mouth and drink water to clear their throat and esophagus of radioaerosol deposited in these regions. Subjects were advised to remain silent during and for 2 min after administration of aerosol, since heliox modifies voice timbre temporarily.19

At the end of inhalation, images were obtained with a single-head scintillation camera (STARCAM 3200 AC/T GE Medical Systems – UK), and stored in a 256 × 256 pixel matrix. Patients were placed in the supine position and instructed not to move during the imaging process. The images were obtained over 5 min. For analysis of pulmonary deposition, the division was held in the right lung regions of interest (ROIs).26,27

Statistical analysis
Sample distribution was analyzed using the Kolmogorov–Smirnov and Levene tests. Non-categorical variables were examined with Fisher’s exact test. For between-group comparisons, the ANOVA test was used for variables with normal distribution, with subsequent Tukey’s. Data were

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**Figure 1** Flow chart.
observed when evaluating peripheral region between the groups (Figures 4 and 5).

Discussion

PFT response

Nebulization of bronchodilators administered with heliox and PEP resulted in a greater increase in FEV₁ % and IC than aerosol administration with oxygen and PEP or either heliox or oxygen alone.

The increase in IC could be explained by the physical characteristics of heliox, which allows the formation of a less turbulent airflow, thereby generating more flow and time during expiration, leading to a reduction in dynamic hyperinflation and increase in IC. On the other hand, the use of PEP prevents airway collapse during expiration, decreases expiratory resistance, prolongs expiratory time and reduces the intrinsic positive end expiratory pressure (PEEP),51 promoting an increase in IC.

A significant increase in FEV₁ was observed in the heliox + PEP group, which did not occur in other groups. Our findings can be correlated with those of Tsai et al.28 who assessed 54 stable asthmatic patients before and after nebulization with bronchodilators associated with PEPP and observed improvement with respect to FEV₁, PEF, FVC, as well as improvement in mucociliary clearance. Our findings corroborate the results of a previous by Brandão et al.,27 where 59 asthmatic patients were evaluated in the emergency room and significant improvement in pulmonary function were found when heliox was associated with another factor, in this study, the posture.

The use of nebulization with β₂-agonists and PEP has been studied by a number of authors,7,8,11 showing improvement in pulmonary function in asthmatic patients. Christensen et al.7,8 assessed the influence of nebulized β₂-agonists with or without PEP in asthmatic patients in terms of improved PEF and observed a significant increase when they were combined, corroborating our findings.

Our results are similar to those of Christensen et al.7,8 and Tsai et al.28 when they observed an improvement in pulmonary function associating PEP to another factor, in this case heliox, not observing the same behavior when compared to groups without PEP. Heliox alone has no bronchodilating properties, despite its physical properties such as low density and high viscosity in relation to oxygen, which promotes the formation of less turbulent transitional flow. As for PEP, it tends to split the airways open during expiration, shifting the points of equal pressure centrally, possibly allowing greater retention of the drug in more distal airways, optimizing bronchodilation in patients with expiratory flow limitation.

Deposition and distribution

The ROI in horizontal and vertical gradient, was greater deposition of particles in the middle and lower third and in central and intermediate regions respectively in the groups associated with PEP. No differences were noted between the groups using heliox and oxygen with PEP. Probably, the presence of PEP resulted in greater total deposition of particles. Studies that evaluate the deposition of radiation...
activity using positive pressure are limited. Experiments conducted in our laboratory, comparing radioaerosol deposition with oxygen associated with non-invasive ventilation using two pressure levels in healthy subjects, showed no increase in radioaerosol deposition when compared to nebulization without pressure support.\(^\text{11}\) Dolovich et al.\(^\text{14}\) assessed the deposition of radiation activity form aerosol in patients with stable chronic bronchitis compared use of the same nebulizer with Intermittent Positive Pressure Breathing (IPPB) and breathing spontaneously reporting no increase in peripheral deposition of aerosol with IPPB, but a greater particle impaction in the upper airway and lower deposition to the lung compared to nebulizer alone.

Contrary to the findings of França et al.\(^\text{11}\) and Dolovich et al.,\(^\text{14}\) our findings show a greater deposition in the lung bases in transverse direction associated with PEP, independent of the gas used. This difference may be attributed to different ways to deliver positive pressure and the population studied, the studies by França et al.\(^\text{11}\) and Dolovich et al.\(^\text{14}\) use bi-level ventilation and IPPB and evaluated healthy subjects and patients with stable chronic bronchitis respectively. As with Farago et al.,\(^\text{30}\) the increased deposition found in our study possibly occurred because PEP promotes airway dilation, providing access for greater deposition of the inhaled drug and preventing the collapse of unstable airways during expiration as occurs in asthma and COPD. This improvement may occur by increasing collateral ventilation providing better airflow to lung periphery.

We observed a higher index of lung deposition in the middle and lower third of the lung compared to the upper third, and greater deposition was found in the central and intermediate regions when compared to peripheral regions, showing little to no impact on proximal airways in the longitudinal section in groups with PEP. Moreover, an irregular deposition pattern was observed in scintigraphic images in some patients, since bronchopulmonary obstruction may affect variable pulmonary segments. In lungs regions with mild to severe obstruction, of the presence of transitional and turbulent flow seems to favor deposition by impaction, concentrating the radiation activity in hot spots close to areas of obstruction which could explain the greater central deposition.

**Table 1** Characteristics of the sample and spirometric values baseline.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Heliox + PEEP</th>
<th>O(_2) + PEEP</th>
<th>Heliox</th>
<th>O(_2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>40.17 ± 11.37</td>
<td>51.67 ± 10.42</td>
<td>49.18 ± 5.56</td>
<td>46.78 ± 11.37</td>
<td>0.190*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>4M/2F</td>
<td>2M/4F</td>
<td>2M/4F</td>
<td>2M/9F</td>
<td>0M/9F</td>
</tr>
<tr>
<td>BMI (Kg/m(^2))</td>
<td></td>
<td>26.11 ± 6.81</td>
<td>26.17 ± 3.27</td>
<td>27.90 ± 4.42</td>
<td>25.95 ± 5.34</td>
<td>0.807*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td>72.17 ± 7.73</td>
<td>79 ± 8.46</td>
<td>83.82 ± 13.03</td>
<td>80 ± 10.82</td>
<td>0.235*</td>
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<tr>
<td>RR (rpm)</td>
<td></td>
<td>13.33 ± 3.5</td>
<td>17 ± 3.46</td>
<td>18.09 ± 3.75</td>
<td>16.22 ± 3.38</td>
<td>0.091*</td>
</tr>
<tr>
<td>SPO(_2) (%)</td>
<td></td>
<td>97 ± 0.89</td>
<td>97 ± 1.26</td>
<td>97 ± 1.18</td>
<td>97.67 ± 0.70</td>
<td>0.456*</td>
</tr>
<tr>
<td>IC (L)</td>
<td></td>
<td>2.35 ± 0.68</td>
<td>2.17 ± 0.22</td>
<td>1.86 ± 0.27</td>
<td>1.82 ± 0.28</td>
<td>0.054*</td>
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<tr>
<td>FEV(_1) (%) pred</td>
<td></td>
<td>56.50 ± 14.77</td>
<td>51.63 ± 4.58</td>
<td>51.05 ± 11.66</td>
<td>56.55 ± 10.87</td>
<td>0.624*</td>
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<tr>
<td>FVC (%) pred</td>
<td></td>
<td>73.16 ± 19.40</td>
<td>66.73 ± 15.03</td>
<td>68.97 ± 16.02</td>
<td>72.66 ± 10.40</td>
<td>0.838*</td>
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<tr>
<td>PEF (%) pred</td>
<td></td>
<td>43.60 ± 10.06</td>
<td>36.26 ± 14.29</td>
<td>34.08 ± 12.84</td>
<td>40.55 ± 14.74</td>
<td>0.531*</td>
</tr>
<tr>
<td>FEV(_1)FVC (%) pred</td>
<td></td>
<td>33.66 ± 12.42</td>
<td>38.05 ± 4.74</td>
<td>32.45 ± 9.58</td>
<td>35.22 ± 14.73</td>
<td>0.794*</td>
</tr>
<tr>
<td>FEV(_1)/FVC (%)</td>
<td></td>
<td>73.50 ± 9.11</td>
<td>80.01 ± 12.91</td>
<td>75.69 ± 10.59</td>
<td>78.11 ± 11.14</td>
<td>0.731*</td>
</tr>
</tbody>
</table>

Values in Mean ± SD. BMI = body mass index, HR = heart rate, RR = respiratory rate; SpO\(_2\) = oxygen saturation. Heliox = heliox 80/oxygen 20, O\(_2\) = Oxygen, PEEP = positive end expiratory pressure; IC = inspiratory capacity, FEV\(_1\) % pred = percentage of predicted for forced expiratory volume in 1 s, FVC % pred = percentage of predicted forced vital capacity, PEF % pred = percentage of predicted for peak expiratory flow, FEV\(_1\) FVC % pred = percentage of predicted for forced expiratory flow between 25 and 75%, FEV\(_1\) /FVC % pred = percent predicted for the ratio of forced expiratory volume in 1 s and forced vital capacity.

\(\text{a ANOVA.}\)

\(\text{b Fisher Exact Test.}\)

**Figure 3** Predict (%) FEV\(_1\) and inspiratory capacity.
Methodological differences may explain apparent contradictions our findings and those of Anderson et al.,
Darquenne and Prinsk, and Bandi et al. In the study performed by Anderson et al., patients were evaluated at
different times for the retention of radionuclides within 48 h after inhalation, patients being their own control.
In our study, patients were assessed immediately after inhalation and until 1 h and 20 min after. In our study, the use of a
nebulizer designed for use in nuclear medicine studies may be producing smaller particles than standard clinical jet nebulizers and these smaller particles are less affected by reduced turbulence with use of heliox. Another methodological difference lies in the fact that all patients included in our study were instructed to discontinue their medication, such as short or long duration corticosteroids and bronchodilators, 12 h before the experiment. In the study carried out by Anderson et al., no mention is made regarding drug discontinuation. In the study by Bandi et al., the subjects were evaluated twice and used as their own control and analysis for deposition differed from that used in this study.

On the other hand, Darquenne and Prinsk conducted a study in healthy subjects and observed that ventilation distribution depends primarily on gravity. However, in asthmatics, it depends on the difference of inspiratory flow as well as the level of obstruction.

Published studies have evaluated deposition of aerosol carried by heliox. Piva et al., in two randomized controlled studies in children with severe distal airway obstruction, assessed radioaerosol distribution using heliox or oxygen as nebulization vehicles in pulmonary scintigraphy. Better deposition and distribution was reported in both studies with heliox when compared to oxygen, and these benefits became more evident in the presence of peripheral airway obstruction.

This is the first study that links PEP with heliox in stable asthmatics. In this group, bronchodilator nebulization and heliox associated with PEP provided significant improvement in pulmonary function. Drug deposition was greater in the middle third and lower portions of the lungs, regardless of type of carrier gas used with PEP. In evaluating IC, groups with PEP showed higher values irrespective of aerosol spray used, demonstrating that the use of PEEP in nebulization was preponderant in improving pulmonary function and IC in the subjects studied.

Few randomized controlled studies have evaluated the benefits of aerosol therapy associated with PEP and heliox in asthmatics between episodes.

In asthmatics, different degrees of airway obstruction promote heterogeneous drug deposition during nebulization. Deposition is greatest in less affected areas and in central airways, thereby compromising the benefits of aerosol therapy in these patients. The administration of aerosol with PEP appears to improve the distribution of aerosol in these patients.

Limitations

The present investigation was performed in stable moderate to severe asthmatics. It was not possible to provide this same level of analysis with patients during exacerbation of their asthma in the emergency department. Consequently, it remains unclear whether the studied interventions would have similar benefits in treatment of patients presenting to the emergency department during exacerbation.

In this study it was not possible for the test in order to identify allergens in atopic individuals as well as performing the measurement of exhaled nitric oxide important data for characterization of asthma.

Clinical implications

Our findings demonstrate that administration of aerosol with PEP (with either heliox or oxygen) improves distribution of aerosol, while the combination of PEP and Heliox improves clinical response in moderate to severe stable asthmatics. While administration of bronchodilator aerosols with heliox have been reported in treatment of severe asthmatics in the emergency room and acute care setting, reports evaluating use of positive airway pressure in these patients is less common prior to institution of ventilatory support. Application of aerosol with EPAP PEP or CPAP with Heliox in spontaneously breathing patients may have a beneficial role in treatment, in both the acute and ambulatory environments. Thus, the use of heliox with PEP was easily tolerated and may be useful as an early intervention for asthmatics at early signs of exacerbation. Further studies will be required to determine the role of combined Heliox with PEP in the emergency department.

Figure 4 Number of counts in upper, middle and lower regions.

Figure 5 Number of counts in central, intermediary and periphery.
Conclusion

In moderate to severe asthmatics, administration of inhaled bronchodilators with 10 cm H2O of PEP with Heliox showed greater improvement in pulmonary function than use of heliox alone. Further studies in the comparing administration of inhaled bronchodilators with various forms of positive airway pressure (PEP, EPAP, CPAP and PEEP) with Heliox to determine their impact on clinical outcomes should be encouraged.

Disclosure

The authors have disclosed a relationship with White Martins Gases Industriais/Praxair.

Conflict of interests

All authors declare no conflict of interest.

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James Fink — responsible for methodological adjustments, statistical analysis, reporting and final draft of the article.

Luciana Alcoforado — responsible for implementing the research protocol, assessment, randomization and treatment of patients, treatment of scintigraphic and spirographic data, statistical analysis and writing the article.

Daniela Cunha Brandão — responsible for recording the work in clinicaltrial.gov; methodological adjustments, data collection, statistical analysis and adjustment of the final draft of the article.

Simone Brandão — Medical radiologist responsible for the acquisition protocol of scintigraphic images, methodological adjustments related to the scintigraphic images, presentation of results and adjustments to the final draft of the article.

Vitoria Lima — responsible for screening patients and data collection.

Catarina Rattes — researcher responsible for data collection, screening and treatment of patients scintigraphic images.

References