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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, systolic blood pressure; DTPA – Tc^{99m}, diethylenetriaminepentaacetic acid technetium-99m; EPAP, expiratory positive airway pressure; FEV_1, 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; PEF, peak expiratory flow; RR, respiratory rate; ROIs, regions of interest; SBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation.

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(955 Mbq) of Technetium-99m and 0.9% saline to a total dose volume of 3 mL placed in a Venticis® II nebulizer attached to a closed, valved mask with PEP of 0 or 10 cm H2O. Both gas type and PEP level were blinded to the investigators. Images were acquired with a single-head scintillation camera with the longitudinal and transverse division of the right lung as regions of interest (ROIs). While all groups responded to bronchodilators, only group 1 showed increase in $FEV_1\%_{predicted}$ and IC compared to the other groups ($p < 0.04$). When evaluating the ROI in the vertical gradient we observed higher deposition in the middle and lower third in groups 1 ($p = 0.02$) and 2 ($p = 0.01$) compared to group 3. In the horizontal gradient, a higher deposition in the central region in groups 1 ($p = 0.03$) and 2 ($p = 0.02$) compared to group 3 and intermediate region of group 2 compared to group 3. We conclude that aerosol deposition was higher in groups with PEP independent of gas used, while bronchodilator response with Heliox + PEP improved FEV_1 % and IC compared to administration with Oxygen, Oxygen with PEP and Heliox alone. Trial registration NCT01268462.

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.[3–6]

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 studies[3–19] 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 dilation 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.[2–19]

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 $\alpha = 0.05$ and $1 - \beta = 0.80$. Sample size calculation was based on the percentage of predicted forced expiratory volume in the first second (FEV_1), 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 FEV_1 from 60 to 80% or severe asthma with predicted FEV_1 <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,[21] 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