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Heliox improves minute-ventilation variability during incremental maximal exercise in COPD patients

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ABSTRACT

Background: Expiratory airflow limitation during exercise is present in a certain fraction of patients with chronic obstructive pulmonary disease (COPD) and is associated with impaired exercise performance. **Objectives:** The aim of this study was to investigate whether normoxic Heliox (79% He-21%O_2) can improve minute-ventilation variability ($vV´E$) in patients with COPD. **Methods:** In a double-blind crossover study, 13 non-hypoxemic men (FEV_1 = 36.1 + 9.32 predicted) performed incremental cardiopulmonary tests to the tolerance limit (T*lim*) while receiving Heliox or room air (RA). Analysis of ventilation variability was performed using *Poincaré* analyses by SD_1 (standard deviation 1) and SD_2 (standard deviation 2), for minute ventilation, tidal volume, and respiratory rate. Ventilation responses during exercise, oxygen consumption, and exercise tolerance were analyzed. Cardiac output (QT) response was monitored by impedance cardiography. **Results:** Ventilation with Heliox resulted in a decrease in oxygen uptake [$V'O_2$, 1161.71 ± 351.11 vs. 1238.05 ± 330.93 mL/min, P <0.05] and carbon dioxide output [$V'CO_2$, 1217.41 ± 300.90 vs. 1288.02 ± 321.66 mL/min, P <0.05] compared to room air, due to an increase in ventilation (35.37 ± 9.55 vs, 31.05 ± 7.75 L, P <0.05) and ventilatory efficiency after Heliox inhalation (12.63 ± 2.91 vs 9.31 ± 4.15 %, P <0.05). The ventilation variability responses increased significantly with Heliox compared to room air. **Conclusions:** Normoxic Heliox increases minute-ventilation variability during high-intensity exercise in patients with moderate-to-severe COPD.

Keywords: Heliox; COPD; Dynamic hyperinflation; Ventilation; Fourier transformation

BACKGROUND

Expiratory airflow limitation during exercise is present in a certain fraction of patients with chronic obstructive pulmonary disease (COPD) and is associated with impaired exercise performance[1-4]. The literature cites the use of nitrogen replaced by inspired helium gas, known as normoxic Heliox[5] in this population. This replacement has been reported to reduce turbulence in medium to large airways, increase the rate of expiratory flow, and reduce the work of breathing, the degree of exercise-induced dynamic hyperinflation, and the intensity of dyspnea, thereby increasing exercise tolerance[6-10].

Studies carried out by our group[6,11] showed that the improvement in exercise tolerance is associated with an increase in the delivery of oxygen to the locomotor muscle (through improved cardiac output), as inferred by the longer delay in the deoxyhemoglobin kinetics time constant, showing a delay in peripheral extraction capacity, and increasing exercise time.

We believe that these effects can be partially explained by improvement in the minute ventilation variability ($vV´_E$), associated with improvement in the metabolic capacity of skeletal muscles[6]. The lower ventilation response makes it possible to limit dynamic lung hyperinflation and reduce respiratory rate[12,13], contributing to a decrease in respiratory burden and discomfort and improving cardiac output4[14].

Thus, the main objective of the present study was to investigate whether Heliox increases $vV´_E$ during incremental cardiopulmonary exercise in normoxemic COPD patients. Furthermore, as the role of this mechanism during maximal exercise has not previously been examined and as Heliox is expected to increase exercise tolerance[7,8,10], we also sought to investigate the contribution of this mechanism to the delivery of oxygen to the leg muscles during exercise.

METHODS

Subjects

Thirteen non-hypoxemic (resting PaO_2 > 60 mmHg) males with moderate-to-severe, stable COPD (FEV_1/FVC < 0.7 and post-bronchodilator FEV_1 < 60% pred)[6] volunteered to participate in the study. Subjects were free of any heart disease and musculoskeletal abnormalities. All participants signed a written informed consent form. The study protocol was approved by the Medical Ethics Committee of the Evangelical University of Goias (51596221.4.0000.5076), Brazil.

Study Protocol

The study was a double-blind randomized crossover investigation that involved two laboratory visits. During the first evaluation, the patients underwent a pulmonary function test and after 1h, the incremental cardiopulmonary test was performed randomly for the intervention (79% He-21% O_2) or room air (RA). After 72 hours, the second cardiopulmonary test was performed. Stress tests were performed with constant pace increases up to the tolerance limit (T*lim*, min).

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Measurements

Pulmonary function tests

Spirometry, lung diffusing capacity, and static lung volumes by body plethysmography were measured at baseline. Recorded values were compared with those predicted for the adult Brazilian population[15,16]. Arterial partial pressure for O_2 and CO_2 were determined in standard anaerobic conditions.

Exercise tests

Standard metabolic and ventilatory responses were measured breath-by-breath using a calibrated computer-based system (CardiO2 SystemTM, Medical Graphics, St. Paul, MN), as per previous studies[6,11].

The power increment rate during the incremental exercise test was 5-10 watts/min to provide a test duration of between 8-10 min. In each cardiopulmonary exercise test, a 12-lead electrocardiogram was used for continuous recording (Cardioperfect, Welch Allin, USA) and heart rate was automatically derived.

Carbon dioxide production (CO_2), oxygen uptake consumption ($V'O_2$), tidal volume (Vt), and respiratory rate (RR) were registered breath-by-breath. On the assumption that total lung capacity (TLC) remains constant during exercise, serial inspiratory capacity (IC) manoeuvers were performed to estimate DH (EELV= CPT - IC, L)[17]. Cardiac output (QT, L/min) and stroke volume (SV, L) were measured throughout the constant work rate test using impedance cardiography (PhysioFlow PF-05™, Manatec Biomedical, France)[18].

Ventilatory variability

The breath-by-breath results of minute ventilation (V_E), tidal volume (V_T), and respiratory rate (*f*r) were exported to an Excel spreadsheet (Microsoft Corporation, USA). *Poincaré* analysis was performed to calculate vV'_E using a custom R® program (http://www.R-project.org/), with breath-by-breath aliquots to obtain SD_1 (the length of the transverse line is defined as the SD_1 of the plot data in a perpendicular direction) and SD_2 (the length of the longitudinal line is defined as the SD_2 of the plot data) values, normalized by the number of points in V'_E [19-22].

Ventilatory efficiency

The new index ($\eta V'E$, %) was calculated from a $V'CO_2$ - $log10^{V'E}$ plot. The resultant plotted signal is described by the quadratic function $V'CO_2 = a*V'E^2 + b*V'E + c$, with the final component performing as a linear function ($\boldsymbol{b}*V'E + c$). We termed this slope coefficient (***b***) as the CO_2 output constant-rate (CO_2-CR). Thus, ventilatory efficiency could be calculated as $\eta V'E$ = (CO_2-CR/MVV predicted* 0.22*0.863)*100 [19,23].

Statistical Analysis

SPSS version 26.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). In order to contrast within-subject exercise responses, paired *t* or Wilcoxon tests were used as appropriate. A one-way repeated-measures analysis of variance (ANOVA) was used to compare the physiological variables. Pearson´s product moment correlation was used to assess the level of association between continuous variables. The strongest significant contributors were selected for a stepwise backward multiple regression analysis. The level of statistical significance was set at $p<0.05$ for all tests.

RESULTS

Subject characteristics

Patients presented age 65.21 ± 2.91 years and body mass index of 25.42 ± 4.41 kg/m^2 with severe forced expiratory volume in 1s (FEV_1) of 36.1 ± 9.32 % of predicted (1.08 ± 0.28 L) (n = 13), forced vital capacity (FVC) of 65.7 ± 12.45 % (2.35 ± 0.43 L), and inspiratory capacity (IC) of 70.1 ± 10.0 % (2.11 ± 0.26 L). As expected, considering the inclusion criteria, all patients were non-hypoxemic at rest.

Effects of Heliox during exercise

Heliox breathing was associated with significant increases in metabolic and ventilatory variables (Table 1; $p<0.01$), without differences in cardiac output and stroke volume. Interestingly, only minute-ventilation variability changed during the protocol (Table 2; $p<0.01$).

The change (Δ) found in ventilation variability during inhalation of Heliox compared to room air was shown to have a positive correlation with increasing load ($r = 0.603$; $p < 0.01$), and $\Delta \eta V'E$ (0.720; $p < 0.01$).

Table 1. Effects of Heliox and room air on physiological and subjective responses to incremental exercise

	Room air	Heliox
Subjects, n	13	13
Metabolic		
$V'O_2$ (mL/min)	1238.05 ± 330.93	1161.71 ± 351.11*
$V'CO_2$ (mL/min)	1288.02 ± 321.66	1217.41 ± 300.90*
RER	0.99 ± 0.08	1.10 ± 0.09*
Power (watts)	64.62 ± 17.74	78.92 ± 20.01*
T*lim* (s)	580.01 ± 234.62	551.54 ± 238.07
Ventilatory		
$V'E$ (L/min)	31.05 ± 7.75	35.37 ± 9.55*
$V'E$/power (L/watts)	0.51 ± 0.14	0.47 ± 0.22
*V*T (mL)	1057.81 ± 246.30	1148.23 ± 232.68*
*V*T/power (mL/watts)	17.77 ± 5.48	15.59 ± 6.07*
*f*R (breaths/min)	30.80 ± 4.61	28.90 ± 5.28*
*f*R /power (breaths/watts)	0.50 ± 0.14	0.41 ± 0.11*
η$V'E$ (%)	9.31 ± 4.15	12.63 ± 2.91*
CO_2ACR	2.33 ± 0.92	3.22 ± 0.94*
$V'E$-$V'CO_2$ slope	24.24 ± 6.15	31.41 ± 8.63*
Cardiovascular		
Cardiac output (L/min)	11.01 ± 1.95	11.31 ± 2.70
Stroke volume (mL)	90.74 ± 13.23	94.95 ± 14.98
Subjective		
Dyspnea scores	7 (5.0 - 8.0)	7 (5.0 – 9.0)
Leg effort scores	8 (5.0 – 8.0)	7 (5.0 – 9.5)

Note: Data are presented as mean ± SD or median (range). $V'O_2$, oxygen uptake; $V'CO_2$, carbon dioxide output; RER, respiratory exchange rate; T*lim*, tolerance limit; V_T: tidal volume; V_E: minute ventilation; MVV: maximal voluntary ventilation; *: p<0.05 for between-intervention differences at a given time point.

Table 2. Effects of Heliox and room air on ventilatory variability

Variables	Room air	Heliox
Ventilatory variability		
$SD_1V'E$	0.82 ± 0.21	1.01 ± 0.27*
SD_2 $V'E$	5.56 ± 3.24	6.34 ± 3.67*
SD_1 $V'E$ n	15.94 ± 4.57	22.69 ± 8.88*
SD_2 $V'E$ n	97.95 ± 27.52	99.61 ± 30.12
SD_1/SD_2 $V'E$	17.64 ± 7.11	22.88 ± 7.11*
Tidal volume variability		
SD_1VT	54.01 ± 21.99	54.98 ± 17.89
SD_2 VT	121.34 ± 64.15	126.91 ± 70.38
SD_1 VT n	500.68 ± 188.94	500.75 ± 180.55
SD_2 VT n	2194.27 ± 782.28	2014.65 ± 652.02
SD_1/SD_2 VT	50.07 ± 18.89	50.08 ± 18.05
Breathing rate variability		
SD_1 fR	1.65 ± 0.50	1.55 ± 0.55
SD_2 fR	4.16 ± 1.41	4.26 ± 1.48
SD_1 fR n	33.77 ± 16.97	26.31 ± 7.15
SD_2 fR n	82.27 ± 34.81	72.76 ± 27.44
SD_1/SD_2 fR	44.43 ± 19.84	40.71 ± 18.26

***Note:** Data expressed as mean ± SD; SD_1 and SD_2 = standard deviation of normalized ventilation ($V'E$), tidal volume (V_T), and respiratory breathing (fR). * p<0.05

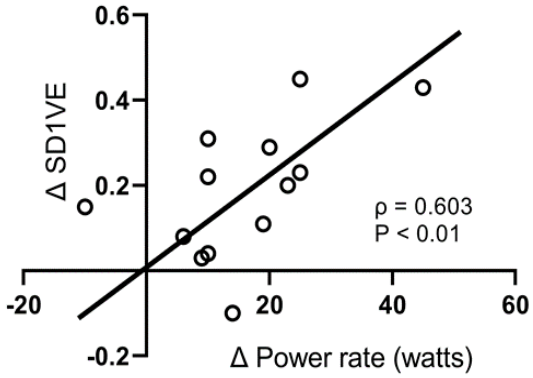

Figure 1. The relationship between changes (Δ = Heliox – room air) in SD_1VE and power rate (left panel). Collectively, these data suggest that the improvement in ventilation variability with Heliox increases the rate of load achieved during cardiopulmonary testing, which determines an improvement in ventilation efficiency. SD_1 and SD_2 = standard deviation of ventilation.

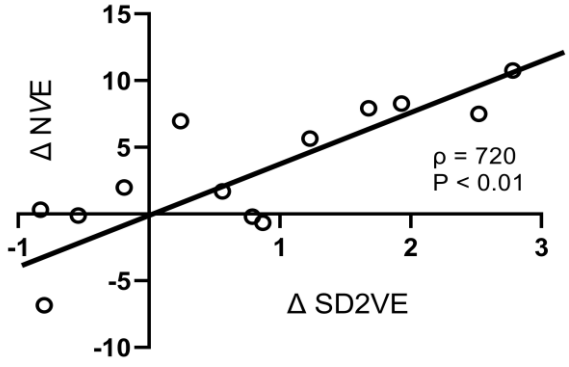

Figure 2. The relationship between changes (Δ = Heliox – room air) in SD_2VE with $\eta V'E$. Collectively, these data suggest that the improvement in ventilation variability with Heliox increases the rate of load achieved during cardiopulmonary testing, which determines an improvement in ventilation efficiency. SD_1 and SD_2 = standard deviation of ventilation; $\eta V'E$ = ventilatory efficiency.

DISCUSSION

The literature referring to Heliox is well documented, primarily on the effect that the Heliox 79%-21%O_2 mixture has on reducing the work of breathing and improving exercise tolerance in patients with COPD[1,6,9,10] and that in addition to its respiratory effects, reducing the intensity of dyspnea[7,9,10,24,25], Heliox improves oxygen supply and utilization[1,6].

This is the first study to investigate the effects of normoxic Heliox on the determinants of ventilatory variability during heavy-intensity exercise in patients with stable COPD. The main novel findings of the present study are that Heliox: *i)* increased minute ventilation variability during exercise tolerance, and ii) augmented ventilation efficiency, as evidenced by the increase in CO_2 removal with higher minute ventilation. These effects are in line with findings in animals[26], pediatric models of ARDS[26,27], and adult patients with respiratory failure due to exacerbation of COPD or asthma[28]. As expected, Heliox improved CO_2 elimination, due to the increase in tidal volume supply, with a significant reduction in respiratory rate[29], directly impacting the improvement in ventilation efficiency.

The gain in ventilatory efficiency is associated with better elimination of CO_2 per unit of ventilated air[23], which may depend on improved ventilation through improved biomechanics of respiration. Reports in the literature demonstrate that inhalation of Heliox may allow lower peak values of respiratory pressure in patients with ARDS[30]. On the other hand, studies have shown that increased ventilation with Heliox is associated with a reduction in the pressure difference between the alveoli and the mouth, which must be developed to generate a certain flow and, consequently, a lower respiratory metabolic cost. This effect is highly desirable in individuals with COPD, where ventilation may be a constraint on physical performance[31].

This finding is associated with characteristics specific to Heliox, as it establishes a more laminar ventilatory flow through small airways compared to oxygen[29,32,33]. These responses may be linked to the effect of Heliox on the reduction in resistance to airflow[34], thus increasing the maximum attainable expiratory airflow rate and maximum FVL expansion, and consequently increasing maximum ventilatory capacity[6,9,10,24,34,35]. In our study, we observed this increase in ventilatory response during exercise with Heliox, despite the lack of improvement in exercise tolerance time and dyspnea scores. Increased exercise time is directly associated with a greater reduction in expiratory flow limitation[6,35].

The effect of Heliox on $\dot{V}E$ was evident in our study. Studies have shown that high-intensity exercise with Heliox generates greater increments[36,37], because of the increase in V_T[38]. Several mechanisms may be associated with Heliox-induced hyperventilation[10,38]. Some authors have argued that the sustained low $PaCO_2$ observed in normal individuals is due, at least in part, to a drop in airway resistance under a high respiratory rate. In our study, we did not measure $PaCO_2$, but we found a greater increase in VT with Heliox, without changes in respiratory rate. This was evidenced by the increase in the $\dot{V}E$ and $\dot{V}CO_2$ ratio. On the other hand, in our study we also found lower $\dot{V}CO_2$ at the peak of the exercise. However, we cannot state that there was a reduction in metabolism due to increased demand on respiratory muscles and/or an increase in peripheral muscles.

Limitations

The present study was limited by the fact that we did not assess the dynamic hyperinflation response during exercise, and the effect of Heliox on arterial blood gas parameters and on the VD/VT ratio, although the literature has already demonstrated these effects. Another limitation of the study may be related to the non-applicability of the effect of Heliox in COPD patients with more advanced disease, who cannot tolerate higher exercise intensities, generating lower ventilatory responses.

CONCLUSION

In conclusion, Heliox breathing may benefit COPD patients by improving ventilation variability and facilitating a better ventilatory demand response during exercise, demonstrated through improved ventilation efficiency. We are aware of some potential limitations of our study, particularly in terms of the generalizability of the results to all COPD populations. Our results, however, suggest that Heliox may be useful, particularly in normoxemic patients. Further studies are needed to determine the potential for improving ventilation variability on clinical variables in patients with COPD.

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