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Exercise Tolerance with Helium-Hyperoxia versus Hyperoxia in Hypoxaemic Patients with COPD

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ABSTRACT

The purpose of this study was to investigate whether helium-hyperoxia (HeHOx) would allow greater tolerance to maximal and sub-maximal exercise compared to HOx on isolation in hypoxemic COPD patients under long-term O_2 therapy (LTOT).

On a double-blind study, 24 GOLD IV males (FEV_1= 35.2 ± 10.1 % pred, PaO_2= 56.2 ± 7.5 mmHg) were submitted to incremental and constant-load cycling at 70-80% peak work rate while breathing HOx (60% N_2, 40% O_2) or HeHOx (60% He, 40% O_2).

HeHOx improved resting airflow obstruction and lung hyperinflation in all but 2 patients ($p<0.05$). Peak work rate and time to exercise intolerance were higher with HeHOx than HOx in 17/24 (70.8 %) and 14/21 (66.6 %) patients, respectively ($p<0.05$). End-expiratory lung volumes were lower with He-HOx despite a higher ventilatory response ($p<0.05$). He-HOx speeded on-exercise O_2 uptake kinetics by ~ 30%, especially in more disabled and hyperinflated patients. Fat-free mass was the only independent predictor of higher peak work rate with He-HOx (r^2= 0.66; $p<0.001$); in contrast, none of the resting characteristics or exercise responses were related to improvements in time to exercise intolerance ($p>0.05$).

Helium is a valuable ergogenic aid when added to HOx for most LTOT-dependent patients with advanced COPD.

Keywords: Chronic Obstructive Pulmonary Disease, Chronic Respiratory Failure, Exercise Testing, Helium, Hyperoxia, Long-Term Oxygen Therapy.

INTRODUCTION

Exercise tolerance is severely reduced in patients with end-stage chronic obstructive pulmonary disease (COPD) under long-term O_2 therapy (LTOT) [1]. Exercise impairment further contributes to diminish their mobility on daily-life and might even be related to lower survival [2]. Moreover, these patients are frequently unable to exercise at intensities which are sufficiently high to derive full physiological benefit from training [3]. There is, therefore, renewed interest in evaluating non-pharmacological adjuncts to improve tolerance to dynamic exercise of O_2-dependent patients [as reviewed in ref. [4]].

In this context, increases in inspired O_2 fraction (hyperoxia, HOx) have understandably been the standard of care to enhance exercise tolerance in patients under LTOT [5]. This is justified by the overwhelming evidence that HOx decreases the ventilatory demands, the rate of dynamic hyperinflation and breathlessness [6,7] whilst enhancing the cardiocirculatory adjustments to exertion [8]. More recently, adding helium (He) to HOx (HeHOx) [9-13] has opened a new perspective to further improve their exercise tolerance. Of note, HeHOx also delayed dynamic hyperinflation and lowered the ventilatory drive - at least in non-hypoxemic patients [9-13]. Moreover, helium in normoxia significantly accelerated O_2 uptake ($\dot{V}O_2$) kinetics [14,15] and reduced muscle fatigue [16], an effect that might be related to its deflating effects leading to improved central hemodynamics and convective O_2 delivery [14,17].

Unfortunately, HeHOx is still an expensive gas mixture and its administration is rather cumbersome compared to HOx on isolation. In addition, substantial heterogeneity in the exercise responses to helium has been reported [18,19] and some studies in non-hypoxemic patients were unequivocally negative [20-22]. It should also be acknowledged that as HOx alone has marked beneficial consequences on exercise capacity in hypoxemic patients [5] the effect size of any complementary intervention should be of great magnitude to make a measurable difference. Although encouraging data on this regard have been provided by Hussain et al. [13] in patients with severe airflow obstruction, none of their patients were hypoxemic under LTOT. To the best of the authors´ knowledge, therefore, no previous study has contrasted the beneficial effects of HeHOx and HOx on exercise tolerance in this sizeable patient sub-population.

The present study is the first head-to-head comparison between HeHOx and HOx to enhance exercise capacity in patients with COPD who are hypoxemic at rest and during exercise and are under LTOT. We hypothesized that, compared to HOx alone, adding helium to HOx would accelerate $\dot{V}O_2$ kinetics, decrease dynamic hyperinflation, and improve tolerance to incremental and constant load exercise. Confirmation of these hypotheses would lend novel support for the combination of helium and HOx as an ergogenic aid for end-stage COPD.

METHODS

Subjects

Fifty-one sedentary males with severe-to-very severe COPD [23] from the long-term oxygen therapy (LTOT) outpatient clinic of the Division of Respiratory Division of the Sao Paulo Hospital, Federal University of Sao Paulo, Brazil were invited for study participation. Twenty-seven patients were excluded due to severe cardiovascular co-morbidity, tracheostomy, osteomuscular limitation to cycling, recent exacerbation or change in the medication status (within 1 month) or lack of interest in exercise studies. The remaining 24 patients had no evidences of ischaemic heart disease, left ventricular dysfunction (ejection fraction <60% assessed by Doppler echocardiography), or severe pulmonary hypertension (estimated systolic pulmonary arterial pressure <40 mm Hg). All subjects had signed a written informed consent and the study protocol was approved by the medical ethics committee of Federal University of Sao Paulo. Additional methodological information on this topic is provided in the *On-Line Data Supplement*.

Study Protocol

This was a randomized, crossover, and double-blinded study. On the first visit, patients underwent pulmonary function tests and anthropometric measurements. They were then randomly assigned to receive HeHOx or HOx during incremental and constant work rate tests (IWR and CWR tests on visits 2 and 3, respectively). On a given

day, the tests with each mixture were separated by a 60-min resting interval. Detailed justification of the study protocol is provided in the *On-Line Data Supplement*.

Measurements

Body composition assessment

Fat-free mass (kg) was determined by a tetrapolar electrical bioimpedance device (BIA 450 Bioimpedance analyser, Biodynamics, Seattle, WA, USA).

Pulmonary function tests

The pneumotachometer (PreVent Pneumotach, Medical Graphics Corporation (MGC), St. Paul, MN, USA) was calibrated with the experimental gas mixture (HeHOx or HOx) before each spirometry. Spirometry, maximal voluntary ventilation (MVV, L/min) and inspiratory capacity (IC, L) maneuvers (to estimate end-expiratory lung volume (EELV, L) were performed with the flow-module of a metabolic cart (CardiO_2 System, MGC, MN, USA). Static lung volumes (total lung capacity (TLC, L) and residual volume (RV, L)) by constant-volume body plethysmography (CPF System, MGC) and arterial blood gases (ABL 330™, Radiometer, Copenhagen, Denmark) were measured with the patients breathing room air.

Cardiopulmonary exercise tests

The gas mixtures (HeHOx or HOx) were directed via a closed circuit to a 120-L latex-neoprene balloon (Douglas bag) and thereafter to the inspiratory port of a low-resistance two-way valve (2700 series, Hans-Rudolph Inc. MO, USA). The

pneumotachometer (PreVent Pneumotach, Medical Graphics Corporation (MGC), St. Paul, MN, USA) was attached in series to the valve and a face mask. In order to blind the mixture under study for the accompanying physician and the patient, a screen was placed in front of the gas cylinders and the patient was instructed to avoid talking during the whole experiment (i.e., to avoid the characteristic changes in voice tone when helium is breathed). The subjects breathed the experimental mixtures for at least 15 minutes before each test to maximize intra-pulmonary distribution. The tests were performed on an electronically-braked cycle ergometer (Corival, Lode, Groningen, Germany) at 50 ± 5 rpm which was controlled by the CardiO_2 System. In the IWR tests, the rate of power increment was 5 W/min for all participants. The CWR tests were performed to the limit of tolerance (T*lim*, s) at 70–80% peak work rate (WR) under HOx. In patients with very low exercise capacity (i.e., peak WR < 40 W), the test was performed at 30 W to secure $\dot{V}O_2$ amplitude which was sufficiently high for the kinetics analysis [24]. Assuming that resting TLC remains constant during exercise, changes in IC were taken to reflect variations in EELV (TLC – IC) [25]. Development of exercise-induced dynamic hyperinflation was defined as progressive reduction in IC during exercise. The patients rated shortness of breath and leg effort using the 0–10 Borg scale each 2 min before the IC maneuvers. Additional methodological information on this topic is provided in the *On-Line Data Supplement*.

Central hemodynamics.

Cardiac output (CO, L/min) and stroke volume (SV, mL) were measured non-invasively during the CWR tests using an impedance cardiography device (*PhysioFlow PF-05, Manatec Biomedical, France*). The PhysioFlow™ device and its methodology have been thoroughly described elsewhere [26] and are summarised in the *On-Line Data Supplement*. Previous studies in our laboratory with this system indicated that despite a consistent trend for CO overestimation (ranging from 12 % to 26%), changes from rest were both reproducible and responsive to interventions [27].

Data analysis

Due to the extreme intolerance to IWR exercise of some patients, physiological data were analyzed both at the lowest sub-maximal WR that elicited response amplitudes amenable to inter-subject comparisons for most patients (iso-WR) and at peak WR. In the CWR test, responses were analyzed both at isotime (the shortest length of time that a patient tolerated the test) and at Tlim. For the kinetics analyses, breath-by-breath $\dot{V}O_2$ data were interpolated each second (*SigmaPlot 10.0; Systat Software Inc., San Jose, CA, USA*) and fitted by the following monoexponential equation [28]:

$$[Y]_{(t)} = [Y]_{(b)} + Ap\,(1 - e^{-(t-TDp)/\tau p})$$

where *b* and *p* refer to baseline unloaded cycling and primary component, respectively, and A, TD, and τ are the amplitude, time delay, and time constant of the exponential response, respectively. The overall kinetics were determined by the mean response time (MRT = **τ** + TD). Since values for haemodynamic data did not follow a mono-exponential pattern of response in all patients, the half time ($t_{1/2}$, s) was calculated.

Statistical analysis

The SPSS version 15.0 statistical software was used for data analysis (*SPSS, Chicago, IL, USA*). Results are presented as mean ± SD or median (range). Mean ± SE, however, was used in some Figures to improve readability. In order to contrast exercise responses with HOx and HeHOx, paired *t* (or Wilcoxon for non-parametric data) tests were used. Mixed-design ANOVA model (Split-plot ANOVA (SPANOVA)) contrasted the responses over time and between-interventions. Population variances of the repeated measurements and the population correlations among all pairs of measures equality (sphericity) were tested by Mauchly's test and the homogeneity of inter-correlations were tested by Box´s M. Pearson's product moment correlation was used to assess the level of association between continuous variables. Stepwise backward regression analysis was used to establish the independent predictors of improvement in exercise tolerance with HeHOx. The level of statistical significance was set at $p<0.05$ for all tests.

RESULTS

Subject characteristics

Patients had severe (FEV_1 between 49% and 30% predicted; N= 13) to very severe (FEV_1 < 30% predicted; N= 11) airflow limitation (23), increased static lung volumes and chronic breathlessness (Medical Research Council dyspnea score ≥ 3). As expected from the inclusion criteria, all patients were hypoxemic at rest and 10/24 (41.7 %) of them were hypercapnic ($PaCO_2$ > 45 mmHg) (Table 1).

Effects of HeHOx on spirometric variables

Compared to HOx, all but 2 patients had larger FEV_1 and FVC with HeHOx (increases typically within the range of 100-200 mL and 200-400 mL, respectively (10-25 % baseline for both) ($p<0.05$). Therefore, HeHOx significantly increased maximal expiratory flows in proportion to volume recruitment, i.e., helium enlarged the maximum flow-volume loop. In addition, EELV was reduced allowing larger tidal volume (V_T) expansion (data shown in Table E1, *On-Line Data Supplement*).

Responses to progressive exercise in HOx

Maximal exercise capacity in HOx was moderately-to-severely diminished in all patients (peak WR < 70% predicted)(29) being associated with decreased ventilatory reserve (high $\dot{V}_E$ /MVV) and further increases in the EELV (Table 2 and Figure 1A). There were significant increases in $P_{ET}CO_2$ from rest to peak exercise in all patients

(Table 2). Dyspnea, leg effort and a combination of both were the limiting symptoms in 8 patients each.

Effects on He-HOx on responses to incremental exercise

Compared to HOx, HeHOx improved peak WR in 17/24 (70.8%) patients with most of them showing 5-to-10 W increases (median (interquartile range)= 6 (3-9) W or 9(6-23) %baseline; $p<0.05$; Table 2; and Figure 2, *left*). This was associated with lower carbon dioxide output ($\dot{V}CO_2$), decreased EELV (Figure 1A), larger V_T, lower duty cycle, greater mean ins and expiratory flows, and higher $\dot{V}_E/\dot{V}CO_2$ with lower $P_{ET}CO_2$ (Table 2 and Figure E1, *On-Line Data Supplement*). At an iso-WR of 30 W (N= 19), CO was also larger with HeHOx, an effect related to greater SV (Table 2). The main limiting symptom(s) (breathlessness or and/ot leg effort) remained essentially unaltered with HeHOX (data not shown).

Effects on He-HOx on responses to constant load exercise

For technical or cooperation issues, 3 patients did not perform the CWR tests. HeHOx increased Tlim in 14/21 (66.6 %) of them with a large variability in the observed benefit (ranging from 109.5 (20.5 – 204.8) s or 32.5 (7.3 – 77.3) % baseline ($p<0.05$; Table 3; and Figure 2, *right*). The physiological effects of HeHOx either at isotime or at Tlim were consistent with those found in the IWR test, including a lower EELV (Table 3 and Figure 1B). Of note, HeHOx led to faster $\dot{V}O_2$ kinetics which was associated with similar trends ($p= 0.07$) in the CO (Table 4). The speeding effect of HeHOX on $\dot{V}O_2$ kinetics was

moderately related to lower peak $\dot{V}O_2$ under HOx and higher TLC and FRC (r values ranging from 0.48 to 0.61, $p<0.05$).

Predictors of improvement in exercise tolerance with HeHOx

Higher static lung volumes and more preserved FFM correlated with improvement in peak WR with HeHOx (r values ranging from 0.46 to 0.72, $p<0.05$). In a multiple regression analysis which considered TLC and FFM, however, only the last variable remained an independent predictor of peak WR ($r^2= 0.61$, $p<0.01$). In contrast, none of the sensorial (i.e., Borg scores) or physiological responses were significantly related to higher Tlim with HeHOx; in fact, improvement in TLim varied more than 5 fold for a typical 100-200 mL reduction in resting EELV ($p>0.05$).

DISCUSSION

This is the first study to compare the efficacy of the standard therapy for correcting exercise-related hypoxemia (HOx) against helium *plus* HOx (HeHOx) in improving exercise tolerance in hypoxemic COPD patients under LTOT. Consistent with our hypotheses, maximal and sub-maximal exercise tolerance were greater with HeHOx than HOx. As previously described in non-hypoxaemic patients [10,12,18], HeHOx improved maximal expiratory flow rates and reduced EELV by ~ 100 mL, an effect that was maintained throughout the exercise bouts despite a higher ventilatory response to a lower metabolic demand. HeHOx also accelerated the primary component of on-exercise VO_2 kinetics. These data provide novel evidence that adding helium to HOx allows hypoxemic COPD patients under LTOT to reach higher work rates and sustain them for longer. From a clinical perspective, this might prove useful to increase patients´ mobility (using a portable delivery system) and tolerance to exercise training.

There is renewed interest in using adjunct tools to improve exercise tolerance in severely-disabled patients with COPD [30]. These strategies range from novel approaches such as non-invasive positive pressure ventilation [27] and neuromuscular electrical stimulation [31] to "older" adjuncts such as O_2 supplementation (HOx) (6,7) and low-density gas breathing (helium) (9-13). In this context, the present results are encouraging in relation to the adding benefits of helium to HOx in hypoxemic patients as maximal and sub-maximal exercise capacity further increased in 2/3 of them. However, despite HeHOX has consistently improved resting airflow limitation and lung hyperinflation, there was a large variability on the magnitude of increase in endurance time with HeHOx. Part of this

variability might be related to the hyperbolic nature of the power-duration relationship [32] which determines that the potential for improvement in Tlim increases as the individual WR becomes closer to the asymptote ("critical power")[33]. It is noteworthy that the resting physiological variables were poorly predictive of changes in Tlim with HeHOx. Previous studies have suggested that any benefit from HeHOx would be particularly observed in patients with more central airflow limitation [13,34,35] which would allow them to maintain the same ventilation (or even higher as in the present study) with a lower EELV. In practical terms, however, our data, suggest that if HeHOX is to be used as an ergogenic aid in advanced COPD under LTOT its positive effects should be unequivocally demonstrated in individual patients.

In relation to the physiological effects of HeHOx on the respiratory system, our findings confirm those of Eves et al [10] in less severe patients and those of Hussain et al. in non-hypoxemic patients of similar spirometric severity [13]. It is legitimate to assume that the deflating effects of helium coupled with the lower pressure to overcome frictional resistance [13] may have summed up with the lower ventilatoy drive induced by HOx [3,4] to diminish the elastic and the resistive work of breathing [6]. The resistive inspiratory work may also have been reduced [34,35]. In fact, the potential for helium to improve expiratory flow limitation increases with disease severity and with higher flow rates [34], i.e., the precise conditions found in the present study. Despite the heightened ventilatory response with HeHOX), breathlessness scores remained unaltered thereby emphasizing the important consequences of breathing on a more compliant portion of the individual pressure-volume relationship [25].

Consistent with previously reported data in non-hypoxemic patients [14,15], helium accelerated $\dot{V}O_2$ kinetics at the transition to exercise. In contrast to those studies, however, this has been achieved under similar CaO_2 which indicates improved convective O_2 delivery and/or enhanced potential for muscle O_2 utilization. We cannot rule out a role for a faster CO response on this regard as there was a clear trend of HeHOx in concomitantly accelerating CO kinetics. In fact, SV and CO were higher with HeHOX than HOx at iso-WR during the incremental test. Part of the CO might have also been redirected to the unloaded respiratory muscles to the working peripheral muscles [27]. Louvaris and colleagues, for instance, recently described that compared to room air normoxic heliox increased quadriceps blood flow at similar CO in patients with COPD showing dynamic hyperinflation [35]. Moreover, it remains to be investigated whether any CO-mediated increases in cerebral blood flow [36] with helium [37] would contribute to increase cerebral O_2 delivery during exercise in these patients.

Another interesting finding of the present study was the independent role of fat-free mass (a likely surrogate of leg muscle mass) to predict the extent at which the patients beneficiated from HeHOx in improving peak WR. This suggests that once the ventilatory constraints were ameliorated with HeHOx peripheral muscle mass became more of a limiting factor to reach higher WRs. This interpretation is in line with the findings of Butcher et al. who reported that more hyperinflated patients in whom HeHOx was particularly effective had neuromuscular findings indicative of muscle fatigue at exercise cessation [38]. Whether this would also be the case during walking is still uncertain.

The present study has some relevant limitations. For ethical reasons, patients were not submitted to exercise in normoxia as all of them, by inclusion, were under LTOT. Nevertheless, we recognize that this precluded the analysis of the physiological effects of HOx *per se*. As a cross-sectional study, we were unable to address whether HeHOx does constitute a cost-effective strategy to improve patients performance during rehabilitation and/or activities of daily living, an issue that remains controversial [8,17,19]. Nevertheless, the increase in Tlim at the CWR test suggests that HeHOx would enable patients to continue higher levels of training. Finally, despite the minimal clinically-important differences (MCID) for peak WR and Tlim have not yet been established in hypoxemic patients, the observed median improvement were close to the MCID established in less severe patients, i.e., 10 W [39] and 33% baseline [40], respectively.

In summary, helium added benefit to HOx in accelerating $\dot{V}O_2$ kinetics, decreasing the operational lung volumes, and enhancing maximal and sub-maximal exercise tolerance in most of our LTOT-dependent patients with advanced COPD. These findings indicate that helium is a valuable complementary ergogenic aid for these patients. Our study sets the scene for larger randomized trials to determine the adjunct role of HeHOx to improve daily life mobility and exercise tolerability during pulmonary rehabilitation in this severely-disabled population.

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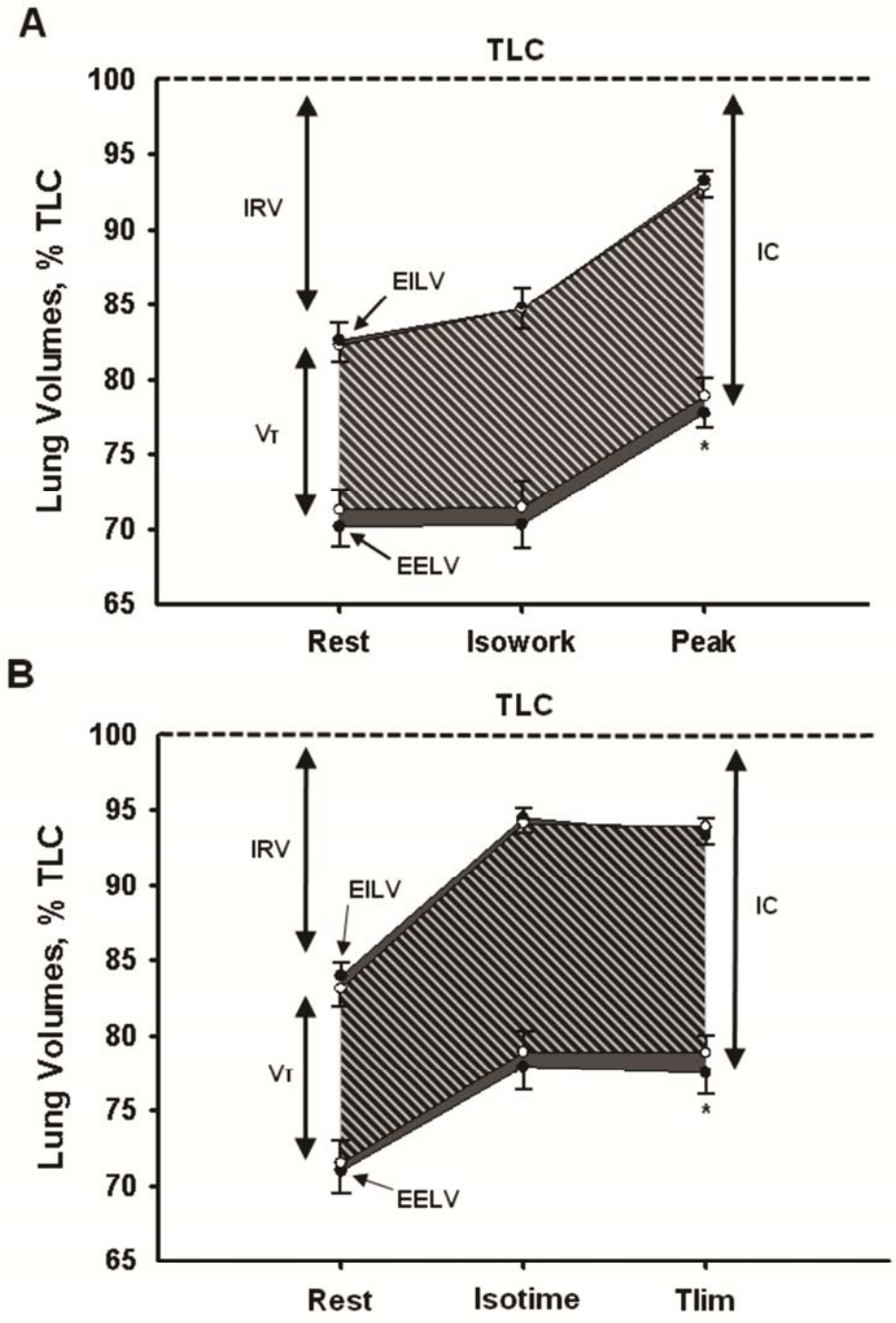
FIGURE LEGENDS

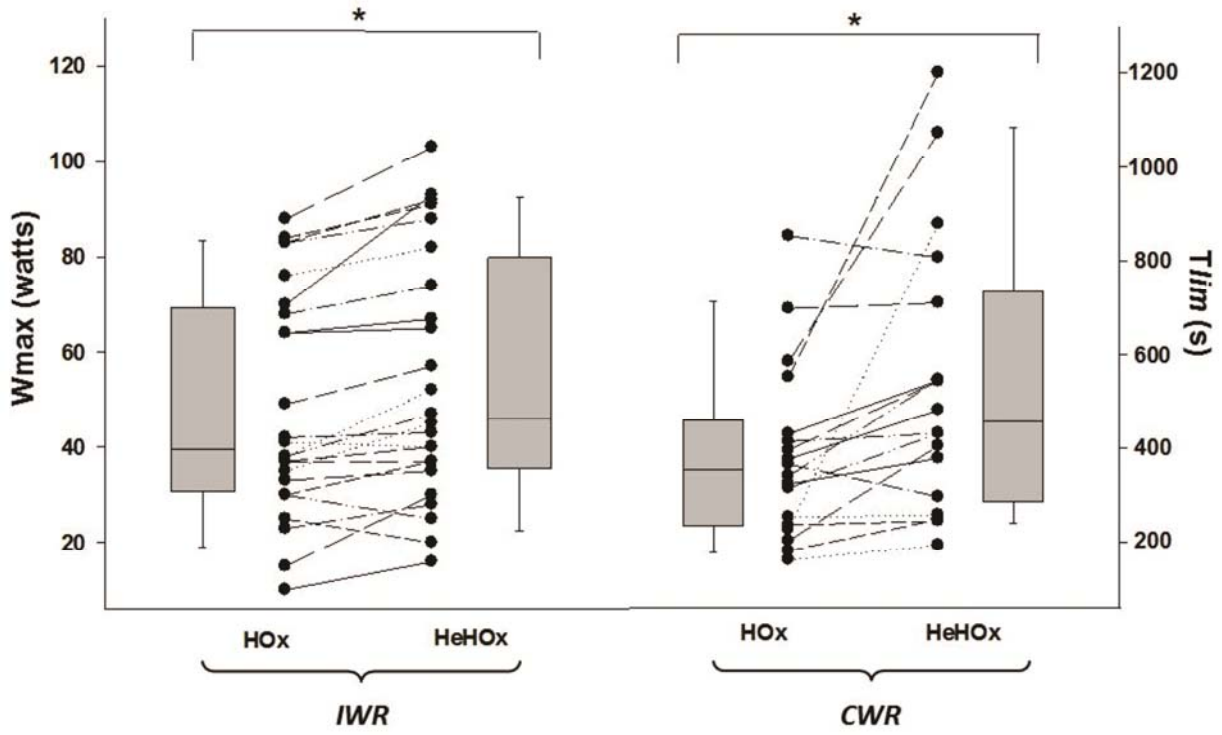
FIGURE 1. Effects of hyperoxia (*open circles*) and helium-hyperoxia (*closed circles*) on the operational lung volumes in response to incremental (*panel A*, N= 24) and constant (*panel B*, N= 21) work rate tests.



Footnotes: variables are mean ± SE. *Definition of abbreviations*: TLC= total lung capacity, IC= inspiratory capacity, V_T = tidal volume, IRV= inspiratory reserve volume, EILV= end-

inspiratory lung volume, EELV= end-expiratory lung volume. * p < 0.05 for between-intervention differences at a given time point.

FIGURE 2. Effects of hyperoxia (HOx) and helium-hyperoxia (HeHOx) on peak work rate (WR) in response to an incremental WR test (IWR, *left*; N= 24) and on time to exercise intolerance in a constant WR test (CWR, *right*; N= 21).



Footnotes: * p<0.05

Table 1. Subject characteristics (N= 24).

Variables	Mean ± SD
Demographic/anthropometric	
Age, years	64 ± 8
Body mass index, kg/m^2	25.7 ± 3.9
Fat free mass index, kg/m^2	18.7 ± 2.7
Pulmonary function	
FEV_1, L [% predicted]	1.07 ± 0.36 [35.2 ± 10.1]
FVC, L [% predicted]	2.41 ± 0.58 [64.7 ± 15.4]
IC, L [% predicted]	2.09 ± 0.38 [69.2 ± 12.0]
TLC, L [% predicted]	7.14 ± 1.14 [110.8 ± 13.7]
RV, % predicted	198.7 ± 56.5
IC/TLC	0.30 ± 0.06
Arterial blood gases	
P_aO_2, mmHg	56.2 ± 7.5
P_aCO_2, mmHg	43.4 ± 7.6
SaO_2, %	88.1 ± 4.9

Variables are mean ± SD. *Definition of abbreviations*: FEV_1= forced expiratory volume in one second, FVC= forced vital capacity, IC= inspiratory capacity, TLC= total lung capacity, RV= residual volume, P_aO_2= arterial partial pressure for oxygen, P_aCO_2= arterial partial pressure for carbon dioxide, SaO_2= arterial oxygen saturation.

Table 2. Effects of hyperoxia (HOx) and helium-hyperoxia (HeHOx) on physiological and subjective responses to incremental exercise.

Variables are mean ± SD. *Definition of abbreviations*: IC= inspiratory capacity, EELV= end-expiratory lung volume, IRV= inspiratory reserve volume, VT = tidal volume, f= breathing

Variables	Iso WR (30 W) (N= 19)		Peak WR (N- 24)	
	HOx	**HeHOx**	**HOx**	**HeHOx**
Work rate, W	----------	----------	48 ± 23	54 ± 26*
Operating lung volumes				
IC, L	2.05 ± 0.39	2.14 ± 0.44	1.46 ± 0.34	1.53 ± 0.28*
EELV, L	5.29 ± 1.20	5.20 ± 1.16	5.65 ± 1.13	5.57 ± 1.12*
IRV, L	1.10 ± 0.39	1.11 ± 0.45	0.47 ± 0.20	0.49 ± 0.30
VT /IC	0.50 ± 0.10	0.52 ± 0.11	0.69 ± 0.10	0.68 ± 0.16
Metabolic				
$\dot{V}CO_2$, mL/min	697 ± 121	619 ± 94*	915 ± 304	870 ± 304*
Cardiovascular				
CO, L/min	8.7 ± 1.9	9.6 ± 1.3*	11.4 ± 1.9	12.2 ± 2.5
HR, beats/min	101 ± 14	104 ± 11	120 ± 17	123 ± 18
SV, mL	84 ± 12	92 ± 9*	95 ± 11	99 ± 15
Ventilatory				
$\dot{V}_E$, L/min	25. 66 ± 3.20	27.77 ± 3.09*	29.58 ± 8.68	33.15 ± 10.21*
VT , mL	993 ± 137	1085 ± 123*	994 ± 231	1040 ± 290*
f , breaths/min	26 ± 4	26 ± 3	30 ± 6	31 ± 6
$\dot{V}_E$/MVV	0.70 ± 0.18	0.68 ± 0.14*	0.89 ± 0.18	0.88 ± 0.15
$\dot{V}_E$/ $\dot{V}CO_2$	27.2 ± 4.6	45.6 ± 7.1*	33.0 ± 7.2	39.0 ± 8.5*
T_I / T_{TOT}	0.34 ± 0.06	0.32 ± 0.07*	0.34 ± 0.07	0.33 ± 0.07*
VT /T_I, L/s	1.30 ± 0.28	1.53 ± 0.42*	1.49 ± 0.50	1.76 ± 0.67*
VT /T_E, L/s	0.65 ± 0.10	0.66 ± 0.09	0.75 ± 0.23	0.83 ± 0.26*
Gas exchange				
$P_{ET}CO_2$, mmHg	41 ± 8	35 ± 7*	49 ± 10	45 ± 11*
SpO_2, %	98 ± 1	98 ± 1	100 ± 16	97 ± 2
Subjective				
Dyspnea scores	3.7 (1.0 – 5.0)	3.0 (1.0 – 6.0)	7.0 (5.0 - 8.5)	7.0 (5.0 - 9.0)
Leg effort scores	4.0 (3.0 – 7.0)	4.0 (2.0 – 7.0)	7.0 (5 - 8.5)	7.0 (5.5 - 10)

frequency, $\dot{V}_E$= minute ventilation, MVV= maximal voluntary ventilation, $\dot{V}CO_2$= carbon dioxide output, T_I= inspiratory time, T_E= expiratory time, T_{TOT}= total respiratory time, P_{ET}= end-tidal partial pressure, SpO_2= oxyhemoglobin saturation by pulse oximetry. * $p < 0.05$ for between-intervention differences at a given time point.

Table 3. Effects of hyperoxia (HOx) and helium-hyperoxia (HeHOx) on physiological and subjective responses to constant load exercise (N= 21).

Variables	Isotime		T*lim*	
	HOx	**HeHOx**	**HOx**	**HeHOx**
Exercise time, sec	330 (234-462)	330 (234-462)	354 (234-462)	456 (288-738)*
Operating lung volumes				
IC, L	1.50 ± 0.27	1.56 ± 0.30	1.45 ± 0.27	1.55 ± 0.30*
EELV, L	5.76 ± 1.17	5.70 ± 1.22	5.70 ± 1.14	5.60 ± 1.15*
IRV, L	0.44 ± 0.23	0.42 ± 0.23	0.43 ± 0.15	0.48 ± 0.15
VT /IC	0.71 ± 0.12	0.74 ± 0.11	0.72 ± 0.09	0.71 ± 0.06
Metabolic				
$\dot{V}CO_2$, mL/min	995 ± 246	855 ± 193*	997 ± 248	878 ± 187*
Cardiovascular				
CO, L/min	11.8 ± 2.4	11.5 ± 2.6	12.0 ± 2.4	12.3 ± 2.9
HR, beats/min	122 ± 17	117 ± 18*	123 ± 17	122 ± 18
SV, mL	97 ± 18	98 ± 12	98 ± 18	100 ± 15
Ventilatory				
$\dot{V}_E$, L/min	30.6 ± 8.1	31.6 ± 8.3	30.7 ± 8.3	33.1 ± 8.5*
VT , mL	1043 ± 213	1140 ± 209*	1040 ± 211	1090 ± 191
f , breaths/min	30 ± 6	28 ± 5	30 ± 6	31 ± 6
$\dot{V}_E$/MVV	0.92 ± 0.20	0.82 ± 0.18*	0.92 ± 0.20	0.86 ± 0.18
$\dot{V}_E$/ $\dot{V}CO_2$	31.4 ± 6.3	37.6 ± 7.8*	31.3 ± 6.3	38.3 ± 8.1*
T_I / T_{TOT}	0.30 ± 0.03	0.28 ± 0.04*	0.30 ± 0.03	0.27 ± 0.04*
VT /T_I, L/s	1.71 ± 0.42	1.94 ± 0.46*	1.73 ± 0.43	2.08 ± 0.48*
VT /T_E, L/s	0.73 ± 0.21	0.73 ± 0.21	0.73 ± 0.22	0.76 ± 0.21
Gas exchange				
$P_{ET}CO_2$, mmHg	47 ± 10	42 ± 9*	47 ± 10	41 ± 10*
SpO_2, %	98 ± 1	98 ± 1	100 ± 16	97 ± 2
Subjective				
Dyspnea scores	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)	6.0 (5.0 - 7.5)	5.0 (3.3 - 7.0)
Leg effort scores	5.0 (3.0 – 7.0)	6.0 (4.0 – 7.8)	6.0 (3.0 - 8.0)	6.5 (4.3 – 8.0)

Variables are mean ± SD or median (range). *Definition of abbreviations*: see Table 3.
* $p < 0.05$ for between-intervention differences at a given time point.

Table 4. Kinetics of metabolic and hemodynamic responses on the transition to constant load exercise under hyperoxia (HOx) and helium-hyperoxia (HeHOx) (n=18).

	HOx	HeHOx
$\dot{V}O_2$		
τ, *s*	60.8 (48.9 – 90.2)	47.0 (42.5 – 56.1) *
Time delay, s	31.0 (22.4 – 37.6)	30.5 (22.3 – 36.9)
Mean response time , s	89.8 (79.3 – 115.5)	81.5 (64.9 – 36.9) *
Amplitude, mL/min	697 (518 – 835)	570 (466 – 672) *
Hemodynamic		
CO		
Half-time, s	87.7 (57.4 – 101.2)	75.6 (51.8 – 103.1)
Amplitude, L/min	5.00 (3.51 – 6.14)	4.37 (3.15 – 5.40)
HR	72.5 (52.3 – 101.0)	66.3 (50.5 – 95.4)
Half-time, s		
Amplitude, beats/min	34 (23 – 46)	32 (26 – 41)

Variables are median (range). *Definition of abbreviations*: $\dot{V}O_2$ =oxygen uptake, **τ** = time constant CO= cardiac output. HR= heart rate. *p<0.05.