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 submaximal exercise compared to hyperoxia (HOx) on isolation in hypoxaemic chronic obstructive pulmonary disease (COPD) patients under long-term oxygen therapy.

In a double-blind study, 24 males in the Global Initiative for Chronic Obstructive Lung Disease functional class IV (forced expiratory volume in 1 s 35.2±10.1% predicted and arterial oxygen tension 56.2±7.5 mmHg) were submitted to incremental and constant load cycling at 70–80% peak work rate while breathing HOx (60% nitrogen and 40% oxygen) or HeHOx (60% helium and 40% oxygen).

HeHOx improved resting airflow obstruction and lung hyperinflation in all but two patients ($p<0.05$). Peak work rate and time to exercise intolerance were higher with HeHOx than HOx in 17 (70.8%) out of 24 patients and 14 (66.6%) out of 21 patients, respectively ($p<0.05$). End-expiratory lung volumes were lower with HeHOx, despite a higher ventilatory response ($p<0.05$). HeHOx speeded on-exercise oxygen 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 HeHOx ($r^2=0.66$, $p<0.001$); 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 long-term oxygen therapy-dependent patients with advanced COPD.

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Introduction

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

In this context, increasing the inspired oxygen fraction (hyperoxia (HOx)) has understandably been the standard of care to enhance exercise tolerance in patients undergoing LTOT [5]. This is justified by the overwhelming evidence that HOx decreases ventilatory demands, the rate of dynamic hyperinflation and breathlessness [6, 7] while enhancing cardiocirculatory adjustments to exertion [8]. More recently, adding helium to HOx (HeHOx) [9–13] has opened a new perspective to further improving exercise tolerance in these patients. Of note, HeHOx also delayed dynamic hyperinflation and lowered ventilatory drive, at least in nonhypoxemic patients [9–13]. Moreover, helium in normoxia significantly accelerated oxygen uptake (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 haemodynamics and convective oxygen delivery [14, 17].

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

The present study is the first head-to-head comparison between HeHOx and HOx to enhance exercise capacity in patients with COPD who are hypoxaemic at rest and during exercise and are under LTOT. We hypothesised that, compared to HOx alone, adding helium to HOx would accelerate 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

51 sedentary males with severe-to-very-severe COPD [23] from the LTOT outpatient clinic of the Division of Respiratory Diseases of the São Paulo Hospital (São Paulo, Brazil) were invited to participate in the study. 27 patients were excluded due to severe cardiovascular comorbidity, tracheostomy, osteomuscular limitation to cycling, recent exacerbation, change in 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 mmHg). All subjects signed written informed consent forms and the study protocol was approved by the medical ethics committee of the Federal University of São Paulo. Additional methodological information on this topic is provided in the online supplementary material.

Study protocol

This was a randomised, crossover, 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 (IWR and CWR, respectively) tests at 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 online supplementary material.

Measurements

Body composition assessment

Fat-free mass was determined by a tetrapolar electrical bioimpedance device (BIA 450 Bioimpedance Analyzer; 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. The spirometry maximal voluntary ventilation (MVV) and inspiratory capacity (IC) manoeuvres (to estimate end-expiratory lung volume (EELV)) were performed with the flow-module of a metabolic cart (CardiO$_2$ System; MGC). Static lung volumes (total lung capacity (TLC) and residual volume) 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., Shawnee, KS, USA). The pneumotachometer (PreVent Pneumotach) 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 $\geqslant$15 min before each test to maximise intrapulmonary distribution. The tests were performed on an electronically braked cycle ergometer (Corival; Lode, Groningen, Germany) at 50$\pm$5 rpm, controlled by the CardiO$_2$ System (MGC). In the IWR tests, the rate of power increment was 5 W·min^{-1} for all participants. The CWR tests were performed to the limit of tolerance (Tlim) at 70–80% peak work rate under HOx. In patients with very low exercise capacity (*i.e.* peak work rate $<$40 W), the test was performed at 30 W to secure a V'_{O_2} amplitude that 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 2 min before the IC manoeuvres. Additional methodological information on this topic is provided in the online supplementary material.

Central haemodynamics

Cardiac output and stroke volume were measured noninvasively during the CWR tests using an impedance cardiography device (PhysioFlow PF-05; Manatec Biomedical, Petit Ebersviller, France). The PhysioFlow device and its methodology have been described thoroughly elsewhere [26] and are summarised in the online supplementary material. Previous studies in our laboratory with this system indicated that despite a consistent trend for overestimation of cardiac output (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 analysed both at the lowest submaximal work rate that elicited response amplitudes amenable to intersubject comparisons for most patients (iso-work rate) and at peak work rates. In the CWR test, responses were analysed both at isotime (the shortest length of time that a patient tolerated the test) and at Tlim. For the kinetics analyses, breath-by-breath 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 was calculated.

Statistical analysis

SPSS version 15.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). Results are presented as mean$\pm$SD or median (range). However, mean$\pm$SE was used in some figures to improve readability. In order to contrast exercise responses with HOx and HeHOx, paired t-tests (or Wilcoxon tests for nonparametric data) were used. A 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 intercorrelations was tested by Box's *M* statistic. Pearson's product moment correlation was used to assess the level of association between continuous variables.

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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 (forced expiratory volume in 1 s (FEV_1) 49–30% predicted; n=13) to very severe (FEV_1 <30% pred; n=11) airflow limitation [23], increased static lung volumes and chronic breathlessness (Medical Research Council dyspnoea score ⩾3). As expected from the inclusion criteria, all patients were hypoxaemic at rest and 10 (41.7%) out of 24 of them were hypercapnic (arterial carbon dioxide tension >45 mmHg) (table 1).

Effects of HeHOx on spirometric variables

Compared to HOx, all but two patients had greater FEV_1 and forced vital capacity with HeHOx (increases typically within the range of 100–200 mL and 200–400 mL, respectively (10–25% of 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 greater tidal volume (V_T) expansion (data shown in online supplementary table E1).

Responses to progressive exercise in HOx

Maximal exercise capacity in HOx was moderately-to-severely diminished in all patients (peak work rate <70% pred) [29], being associated with decreased ventilatory reserve (high minute ventilation (V'_E)/MVV) and further increases in the EELV (table 2 and fig. 1a). There were significant increases in end-tidal carbon dioxide tension (P_{ETCO_2}) from rest to peak exercise in all patients (table 2). Dyspnoea, leg effort and a combination of both were the limiting symptoms in eight patients each.

Effects on HeHOx on responses to incremental exercise

Compared to HOx, HeHOx improved peak work rate in 17 (70.8%) out of 24 patients, with most of them showing 5- to 10-W increases (median (interquartile range) 6 W (3–9 W) or 9% (6–23%) of baseline; $p<0.05$) (table 2 and fig. 2, left panel). This was associated with lower carbon dioxide output (V'_{CO_2}), decreased EELV (fig. 1a), greater V_T, reduced duty cycle, greater mean inspiratory and expiratory flows and higher V'_E/V'_{CO_2} with lower P_{ETCO_2} (table 2 and online supplementary figure E1). At an iso-work rate of 30 W (n=19), cardiac output was also greater with HeHOx, an effect related to greater stroke volume (table 2). The main limiting symptom(s) (breathlessness or and/or leg effort) remained essentially unaltered with HeHOx (data not shown).

Effects on HeHOx on responses to constant load exercise

For technical or cooperative reasons, three patients did not perform the CWR tests. HeHOx increased T_{lim} in 14 (66.6%) out of 21 patients with a large variability in the observed benefit (109.5 s (20.5–204.8 s) or 32.5% (7.3–77.3%) of baseline; $p<0.05$) (table 3 and fig. 2, right panel). The physiological effects of

TABLE 1 Subject characteristics

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 (% pred)	1.07±0.36 (35.2±10.1)
FVC L (% pred)	2.41±0.58 (64.7±15.4)
IC L (% pred)	2.09±0.38 (69.2±12.0)
TLC L (% pred)	7.14±1.14 (110.8±13.7)
RV % pred	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
S_{aO_2} %	88.1±4.9

Data are presented as mean±SD. n=24. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; IC: inspiratory capacity; TLC: total lung capacity; RV: residual volume; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation.

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

	Iso-work rate (30 W)		Peak work rate	
	HOx	HeHOx	HOx	HeHOx
Subjects n	19	19	24	24
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
V_T/IC	0.50±0.10	0.52±0.11	0.69±0.10	0.68±0.16
Metabolic				
V'_{CO_2} mL·min^{-1}	697±121	619±94*	915±304	870±304*
Cardiovascular				
Cardiac output L·min^{-1}	8.7±1.9	9.6±1.3*	11.4±1.9	12.2±2.5
Heart rate beats·min^{-1}	101±14	104±11	120±17	123±18
Stroke volume mL	84±12	92±9*	95±11	99±15
Ventilatory				
V'_E L·min^{-1}	25.7±3.2	27.8±3.1*	29.6±8.7	33.2±10.2*
V_T mL	993±137	1085±123*	994±231	1040±290*
Breathing frequency breaths·min^{-1}	26±4	26±3	30±6	31±6
V'_E/MVV	0.70±0.18	0.68±0.14*	0.89±0.18	0.88±0.15
V'_E/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*
V_T/t_I L·s^{-1}	1.30±0.28	1.53±0.42*	1.49±0.50	1.76±0.67*
V_T/t_E L·s^{-1}	0.65±0.10	0.66±0.09	0.75±0.23	0.83±0.26*
Gas exchange				
P_{ETCO_2} mmHg	41±8	35±7*	49±10	45±11*
S_{pO_2} %	98±1	98±1	100±16	97±2
Subjective				
Dyspnoea 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 (5.0–8.5)	7.0 (5.5–10.0)

Data are presented as mean±SD or median (range), unless otherwise stated. IC: inspiratory capacity; EELV: end-expiratory lung volume; IRV: inspiratory reserve volume; V_T: tidal volume; V'_{CO_2}: carbon dioxide output; V'_E: minute ventilation; MVV: maximal voluntary ventilation; t_I: inspiratory time; t_{TOT}: total respiratory time; t_E: expiratory time; P_{ETCO_2}: end-tidal carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. *: $p<0.05$ for between-intervention differences at a given time point.

HeHOx either at isotime or at Tlim were consistent with those found in the IWR test, including a lower EELV (table 3 and fig. 1b). Of note, HeHOx led to faster V'_{O_2} kinetics which were associated with similar trends ($p=0.07$) in cardiac output (table 4). The speeding effect of HeHOX on V'_{O_2} kinetics was moderately related to lower peak V'_{O_2} under HOx and higher TLC and functional residual capacity ($r=0.48$–0.61, $p<0.05$).

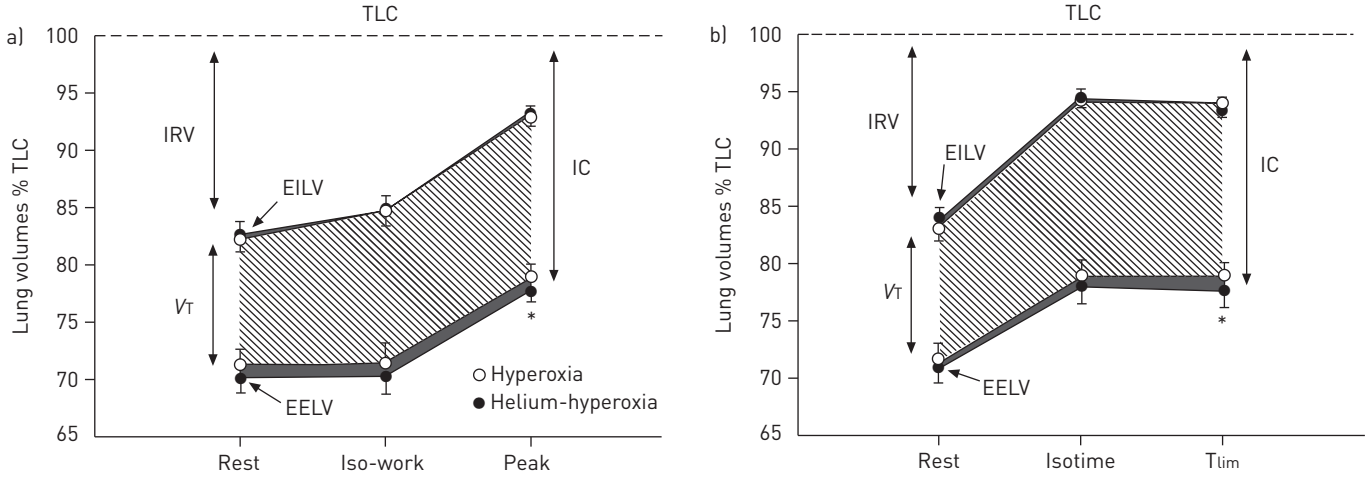

FIGURE 1 Effects of hyperoxia and helium-hyperoxia on operational lung volumes in response to a) incremental (n=24) and b) constant (n=21) work rate tests. Data are presented as mean±SE. TLC: total lung capacity; IC: inspiratory capacity; V_T: tidal volume; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume; iso-work: the lowest submaximal work rate achieved by most subjects; isotime: the shortest length of time that patients tolerated the test; Tlim: limit of tolerance. *: $p<0.05$ for between-intervention differences at a given time point.

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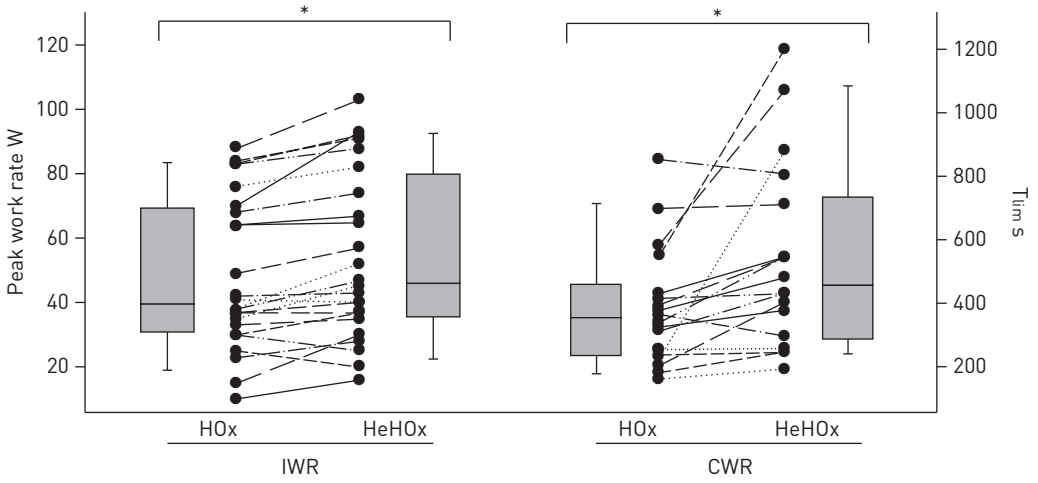

FIGURE 2 Effects of hyperoxia (HOx) and helium-hyperoxia (HeHOx) on peak work rate in response to an incremental work rate test (IWR, left; n=24) and on time to exercise intolerance (Tlim) in a constant work rate test (CWR, right; n=21). *: $p<0.05$.

Predictors of improvement in exercise tolerance with HeHOx

Higher static lung volumes and more preserved fat-free mass correlated with improvement in peak work rate with HeHOx (r=46–0.72, $p<0.05$). In a multiple regression analysis which considered TLC and fat-free mass; however, only the last variable remained an independent predictor of peak work rate ($r^2=0.61$, $p<0.01$). In contrast, none of the sensorial (*i.e.* Borg scores) or physiological responses were significantly

TABLE 3 Effects of hyperoxia (HOx) and helium-hyperoxia (HeHOx) on physiological and subjective responses to constant load exercise

	Isotime		Tlim	
	HOx	HeHOx	HOx	HeHOx
Exercise time s	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
V_T/IC	0.71±0.12	0.74±0.11	0.72±0.09	0.71±0.06
Metabolic				
V'_{CO_2} mL·min^{-1}	995±246	855±193*	997±248	878±187*
Cardiovascular				
Cardiac output L·min^{-1}	11.8±2.4	11.5±2.6	12.0±2.4	12.3±2.9
Heart rate beats·min^{-1}	122±17	117±18*	123±17	122±18
Stroke volume mL	97±18	98±12	98±18	100±15
Ventilatory				
V'_E L·min^{-1}	30.6±8.1	31.6±8.3	30.7±8.3	33.1±8.5*
V_T mL	1043±213	1140±209*	1040±211	1090±191
Breathing frequency breaths·min^{-1}	30±6	28±5	30±6	31±6
V'_E/MVV	0.92±0.20	0.82±0.18*	0.92±0.20	0.86±0.18
V'_E/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*
V_T/t_I L·s^{-1}	1.71±0.42	1.94±0.46*	1.73±0.43	2.08±0.48*
V_T/t_E L·s^{-1}	0.73±0.21	0.73±0.21	0.73±0.22	0.76±0.21
Gas exchange				
P_{ETCO_2} mmHg	47±10	42±9*	47±10	41±10*
S_{pO_2} %	98±1	98±1	100±16	97±2
Subjective				
Dyspnoea 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)

Data are presented as mean±SD or median (range). n=21. Tlim: time to exercise intolerance; IC: inspiratory capacity; EELV: end-expiratory lung volume; IRV: inspiratory reserve volume; V_T: tidal volume; V'_{CO_2}: carbon dioxide output; V'_E: minute ventilation; MVV: maximal voluntary ventilation; t_I: inspiratory time; t_{TOT}: total respiratory time; t_E: expiratory time; P_{ETCO_2}: end-tidal carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. *: $p<0.05$ for between-intervention differences at a given time point.

TABLE 4 Kinetics of metabolic and haemodynamic responses on the transition to constant load exercise under hyperoxia (HOx) and helium-hyperoxia (HeHOx)

	HOx	HeHOx
$V'O_2$		
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^{-1}	697 (518–835)	570 (466–672)*
Haemodynamics		
Cardiac output		
Half-time s	87.7 (57.4–101.2)	75.6 (51.8–103.1)
Amplitude L·min^{-1}	5.00 (3.51–6.14)	4.37 (3.15–5.40)
Heart rate		
Half-time s	72.5 (52.3–101.0)	66.3 (50.5–95.4)
Amplitude beats·min^{-1}	34 (23–46)	32 (26–41)

Data are presented as median (range). n=18. $V'O_2$: oxygen uptake; τ: time constant. *: $p<0.05$.

related to higher Tlim with HeHOx; in fact, improvement in Tlim varied more than fivefold 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 hypoxaemia (HOx) against HeHOx in improving exercise tolerance in hypoxaemic COPD patients undergoing LTOT. Consistent with our hypotheses, maximal and submaximal exercise tolerance were greater with HeHOx than HOx. As previously described in nonhypoxaemic 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 $V'O_2$ kinetics. These data provide novel evidence that adding helium to HOx allows hypoxaemic COPD patients undergoing LTOT to reach higher work rates and to 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 adjunctive tools to improve exercise tolerance in severely disabled patients with COPD [30]. These strategies range from novel approaches such as noninvasive positive pressure ventilation [27] and neuromuscular electrical stimulation [31] to "older" adjuncts such as oxygen supplementation (HOx) [6, 7] and low-density gas breathing (helium) [9–13]. In this context, the present results are encouraging in relation to the benefits of adding helium to HOx in hypoxaemic patients, as maximal and submaximal exercise capacity further increased in two-thirds of them. However, although 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 work rate becomes closer to the asymptote ("critical power") [33]. It is noteworthy that 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 patients with less severe symptoms and those of Hussain *et al.* [13] in nonhypoxaemic patients having similar spirometric severity. 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 ventilatory 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,

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breathlessness scores remained unaltered, thereby emphasising the important consequences of breathing on a more compliant portion of the individual pressure–volume relationship [25].

Consistent with previously reported data in non-hypoxaemic patients [14, 15], helium accelerated $V'O_2$ kinetics at the transition to exercise. In contrast to those studies, however, this was achieved under similar arterial oxygen content, which indicates improved convective oxygen delivery and/or enhanced potential for muscle utilisation of oxygen. We cannot rule out a role for a faster cardiovascular response on this regard as there was a clear trend of HeHOx in concomitantly accelerating cardiac output kinetics. In fact, stroke volume and cardiac output were higher with HeHOx than HOx at iso-work rate during the incremental test. Part of the cardiac output might have also been redirected from the unloaded respiratory muscles to the working peripheral muscles [27]. LOUVARIS *et al.* [35], for instance, recently described that compared to room air normoxic heliox increased quadriceps blood flow at similar cardiac output in patients with COPD showing dynamic hyperinflation. Moreover, it remains to be investigated whether any cardiac output-mediated increases in cerebral blood flow [36] with helium [37] would contribute to increase cerebral oxygen 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 benefitted from HeHOx in improving peak work rate. This suggests that once the ventilatory constraints were ameliorated using HeHOx, peripheral muscle mass became more of a limiting factor to reach higher work rates. This interpretation is in line with the findings of BUTCHER *et al.* [38] who reported that more hyperinflated patients in whom HeHOx was particularly effective had neuromuscular findings indicative of muscle fatigue at exercise cessation. 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 undergoing LTOT. Nevertheless, we recognise 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 constitutes a cost-effective strategy to improve patient performance during rehabilitation and/or activities of daily living, an issue that remains controversial [8, 17, 19]. Nevertheless, the increase in T_{lim} at the CWR test suggests that HeHOx would enable patients to continue higher levels of training. Finally, although the minimal clinically important differences (MCID) for peak work rate and T_{lim} have not yet been established in hypoxaemic patients, the observed median improvements were close to the MCID established in less severe patients, *i.e.* 10 W [39] and 33% of baseline [40], respectively.

In summary, helium added benefit to HOx in accelerating $V'O_2$ kinetics, decreasing operational lung volumes, and enhancing maximal and submaximal 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 randomised trials to determine the adjunctive role of HeHOx to improve mobility in daily life and exercise tolerance during pulmonary rehabilitation in this severely disabled population.

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