

## Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients

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Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 97: 1637–1642, 2004. First published July 2, 2004; doi:10.1152/jappphysiol.01207.2003.—We tested the hypothesis that heliox breathing, by reducing lung dynamic hyperinflation (DH) and dyspnea (Dys) sensation, may significantly improve exercise endurance capacity in patients with chronic obstructive pulmonary disease [ $n = 12$ , forced expiratory volume in 1 s = 1.15 (SD 0.32) liters]. Each subject underwent two cycle ergometer high-intensity constant work rate exercises to exhaustion, one on room air and one on heliox (79% He-21% O<sub>2</sub>). Minute ventilation ( $\dot{V}_E$ ), carbon dioxide output, heart rate, inspiratory capacity (IC), Dys, and arterial partial pressure of CO<sub>2</sub> were measured. Exercise endurance time increased significantly with heliox [9.0 (SD 4.5) vs. 4.2 (SD 2.0) min;  $P < 0.001$ ]. This was associated with a significant reduction in lung DH at isotime (Iso), as reflected by the increase in IC [1.97 (SD 0.40) vs. 1.77 (SD 0.41) liters;  $P < 0.001$ ] and a decrease in Dys [6 (SD 1) vs. 8 (SD 1) score;  $P < 0.001$ ]. Heliox induced a state of relative hyperventilation, as reflected by the increase in  $\dot{V}_E$  [38.3 (SD 7.7) vs. 35.5 (SD 8.8) l/min;  $P < 0.01$ ] and  $\dot{V}_E$ /carbon dioxide output [36.3 (SD 6.0) vs. 33.9 (SD 5.6);  $P < 0.01$ ] at peak exercise and by the reduction in arterial partial pressure of CO<sub>2</sub> at Iso [44 (SD 6) vs. 48 (SD 6) Torr;  $P < 0.05$ ] and at peak exercise [46 (SD 6) vs. 48 (SD 6) Torr;  $P < 0.05$ ]. The reduction in Dys at Iso correlated significantly ( $R = -0.75$ ;  $P < 0.01$ ) with the increase in IC induced by heliox. The increment induced by heliox in exercise endurance time correlated significantly with resting increment in resting forced expiratory in 1 s ( $R = 0.88$ ;  $P < 0.01$ ), increase in IC at Iso ( $R = 0.70$ ;  $P < 0.02$ ), and reduction in Dys at Iso ( $R = -0.71$ ;  $P < 0.01$ ). In chronic obstructive pulmonary disease, heliox breathing improves high-intensity exercise endurance capacity by increasing maximal ventilatory capacity and by reducing lung DH and Dys.

chronic obstructive pulmonary disease; therapy

DYSPNEA (Dys) and exercise intolerance are the hallmarks of chronic obstructive pulmonary disease (COPD). In the most severe patients, and in particular in those with predominant emphysema, the reduction in exercise tolerance is mostly due to ventilatory limitation and early onset of intolerable Dys. Because of the increased expiratory flow limitation, the increase in ventilation during exercise produces lung dynamic hyperinflation (DH), testified by the progressive reduction in inspiratory capacity (IC) (22). Previous studies have demonstrated that the degree of DH correlates with exertional breathlessness in COPD (1, 2). O'Donnell and coworkers (22, 23) have shown that the lung DH, with its intrinsic mechanical

loading, contributes importantly to the perception of breathlessness for a given ventilation output, and it is likely to be the most important single factor limiting exercise tolerance in COPD patients.

Breathing low-density gas mixture, such as heliox (79% He-21% O<sub>2</sub>), should improve lung mechanics and exercise capacity in ventilatory-limited COPD patients. Very few and not conclusive data, however, exist on the effect of heliox on exercise tolerance in COPD and, because of different exercise protocols used, no definitive conclusion can be drawn (8, 16, 24, 25). In ventilatory-limited COPD, because of its effects on turbulent flow resistance (10), heliox should improve exercise tolerance at a high level of ventilation, e.g., close to the patient's maximal ventilatory capacity. Surprisingly, no studies have evaluated the effects of heliox on DH, pulmonary gas exchange, or ultimately on exercise endurance capacity in COPD.

We tested the hypothesis that, by reducing the degree of lung DH and the severity of Dys, heliox should improve the ability of COPD patients to sustain high-intensity bouts of exercise. We were also interested to verify whether heliox, because of its convective properties, is capable of improving lung gas-exchange efficiency during exercise; we are not aware of studies addressing this issue in COPD.

In a group of patients with moderate to severe COPD, we measured the changes in lung mechanics and gas-exchange parameters induced by heliox breathing during exhaustive high-intensity exercise. Clinical implications may be derived, indicating new therapeutic strategy aimed at ameliorating exercise capacity in ventilatory-limited COPD patients, allowing them to sustain a high-power output for a period of time long enough to induce a significant training effect.

### METHODS

Twelve male ambulatory patients with COPD volunteered for the study. Admission criteria included the clinical diagnosis of COPD (18), forced expiratory volume in 1 s (FEV<sub>1</sub>) < 50% predicted, functional residual capacity > 130% predicted, and moderate hypoxemia (room air arterial Po<sub>2</sub> > 60 Torr). Patients' pertinent characteristics are shown in Table 1. Exclusion criteria included clinically manifest cor pulmonale, cardiovascular illness, musculoskeletal abnormalities, or other diseases that may contribute to Dys and/or exercise intolerance. The experimental protocol was approved by the Committee for Protection of Human Subjects, University of Rome. Written, informed consent was obtained from each participant before initiation of the project.

**Study design.** On the enrollment day, all of the patients performed spirometry, N<sub>2</sub> wash-out (COSMED PFT, Rome, Italy), and arterial

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Table 1. Patient characteristics

Age, yr	68 (8)
Height, cm	173 (7)
Weight, kg	71 (7)
FEV <sub>1</sub>	
liters	1.15 (0.32)
% predicted	38 (10)
FVC	
liters	2.93 (0.57)
% predicted	76 (14)
FRC	
liters	5.58 (0.80)
% predicted	156 (19)
PaO <sub>2</sub> , Torr	76 (8)
PaCO <sub>2</sub> , Torr	43 (5)
W <sub>peak</sub> , W	81 (23)

Values are means with SD in parentheses. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; PaO<sub>2</sub>, arterial PO<sub>2</sub>; PaCO<sub>2</sub>, arterial PCO<sub>2</sub>; W<sub>peak</sub>, peak work rate.

blood-gas analysis (IL 1640, Instrumentation Laboratory, Lexington, MA). On the same day, all subject underwent an incremental (5 W/min) cycle ergometer (Bosch, ERG 551) exercise to volitional fatigue to measure peak work rate (i.e., the largest work rate completed for 1 min) (Table 1).

On the experimental day (a minimum of 48 h after the incremental test), based on the results of the incremental test, the subjects performed two constant work rate (CWR) tests separated by 90-min intervals, while breathing room air or heliox (79% He-21% O<sub>2</sub>). The test sequence was randomized. Subjects were blinded with respect to the mixture being breathed, as was the investigator evaluating subjective responses and performing data analysis. Patients were allowed to adapt to the mouthpieces for 10 min, during which time they breathed the gas mixture, and resting data were acquired. Thereafter, a CWR exercise at 80% of the maximal work rate achieved on the enrollment day, with a pedaling frequency of 50 rpm, was performed until exhaustion. The same encouragement was given in all tests. The tests were interrupted when the patient, because of intolerable Dys and/or leg fatigue, was not able to keep the pedaling frequency of 50 rpm. At peak exercise, patients were asked to estimate the intensity of Dys and leg fatigue by using a 12-point visual scale (12). To verify data repeatability, 7 of 12 patients were reevaluated with an identical randomized protocol. Mean values of two tests for the same experimental condition were utilized for statistical purposes, after good repeatability in measured variables was confirmed. Spirometry and blood gases were repeated before each bout of exercise to confirm clinical stability.

**Gas-exchange measurements.** Pulmonary gas exchange indexes were measured with the use of a breath-by-breath apparatus (COSMED Quark b<sup>2</sup>, Rome, Italy). Patients breathed through a mouthpiece attached to a photoelectric digital turbine (diameter 28 mm; resolution 4 ml) proximally linked to a two-way low-resistance valve (Hans Rudolph, 2700 large 2-way) that did not allow rebreathing. The inspiratory part of the valve was connected to a 30-liter Douglas bag in which the humidified mixtures (air/heliox), coming from gas tank mixtures, were collected. The same apparatus was utilized on air and on heliox. To attain an external apparatus resistance similar to that during air breathing, mesh screens were added to the tubing system during heliox breathing. Total resistance of the system was 0.6 cmH<sub>2</sub>O l/s at 3 l/s and 0.4 cmH<sub>2</sub>O l/s at 2 l/s during air breathing and 0.7 cmH<sub>2</sub>O l/s at 3 l/s and 0.4 cmH<sub>2</sub>O l/s at 2 l/s during heliox breathing. Expired gas was drawn from the distal part of the turbine by the use of a special sampler capillary of polymer Nafion (Permapure); CO<sub>2</sub> concentration was determined by a rapid-response analyzer (CO<sub>2</sub> infrared). Calibration of the system was performed, in air and heliox, immediately before each test, by using a 3-liter syringe

to calibrate the turbine, and a two-point calibration of the gas analyzer using gas mixture from tanks of standard gases. Corrections for the transport delay, from the mouthpiece to the sensor, and for the rise time of the analyzers during the calibrations procedure, on air and on heliox, were taken into account (6). CO<sub>2</sub> output ( $\dot{V}_{CO_2}$ ; STPD) and minute ventilation ( $\dot{V}_E$ ; BTPS) were measured for each breath by the use of a computerized system. Arterial oxygen saturation was measured continuously at rest and during exercise by means of a pulse oximetry (BIOX 3740, Ohmeda, Liberty Corner, NY). Heart rate was derived from R-wave-to-R-wave intervals measured from a 12-lead ECG.

**Blood samples.** Measurements of arterial partial pressure CO<sub>2</sub> (PaCO<sub>2</sub>) were obtained on arterialized venous blood samples (17). A catheter was placed on a backhand vein and connected to a line, which allow sampling during the exercise. The blood was arterialized by means of an infrared lamp positioned 35 cm over the hand. The catheter was flushed with heparinized saline. To avoid spurious dilution, 2 ml of blood were discarded before collection of the blood sample. Each blood sample was drawn into a heparinized syringe and immediately analyzed (IL 1650, Instrumentation Laboratory). The physiological dead space-to-tidal volume ratio ( $V_{DS}/V_T$ ), an index of lung gas exchange efficiency, was calculated by using the formula (28):

$$V_{DS}/V_T = 1 - (\dot{V}_{CO_2}/\dot{V}_E * 863/Pa_{CO_2}, \text{Torr})$$

**Lung mechanics parameters.** FEV<sub>1</sub> and IC were measured at rest, on air, and during heliox breathing, 10 min after the washin of the gas mixture. Resting maximal voluntary ventilation (MVV) was calculated by multiplying FEV<sub>1</sub> × 35 (11). V<sub>T</sub>, respiratory frequency, inspiratory time, and expiratory time were measured continuously. Mean expiratory flow (MEF = V<sub>T</sub>/expiratory time) and duty cycle (inspiratory time/respiratory cycle duration) were calculated. The development of DH during exercise was evaluated by measuring IC every 2 min during exercise and immediately before the end; verbal encouragement was given to make a maximal effort on top of a maximal inspiration before relaxing. IC/ $\dot{V}_E$  and the inspiratory reserve volume (IRV = IC - V<sub>T</sub>) were calculated.

**Statistical analysis.** Group data are presented as means with SD. Differences among measured parameters were determined by paired *t*-test. Pearson's product-moment correlation coefficient (*R*) was used to detect correlation among criterion variables. The level of statistical significance was set at *P* < 0.05. Data repeatability was assessed by calculating the intraclass correlation coefficients (*R*<sup>2</sup>) (7) with the use of dedicated SPSS software.

## RESULTS

At rest (Table 2), heliox breathing did not induce significant changes in lung mechanics and gas-exchange variables, except for a small but significant increase in FEV<sub>1</sub>.

Exercise  $\dot{V}_E$  and  $\dot{V}_{CO_2}$  responses, on air and on heliox, for the entire group of patients studied are shown in Fig. 1. Endurance

Table 2. Results at rest

	Air	Heliox	<i>P</i> Value
<i>n</i>	12	12	
FEV <sub>1</sub> , liters	1.15 (0.32)	1.31 (0.33)	<0.001
IC, liters	2.00 (0.50)	2.08 (0.49)	NS
$\dot{V}_E$ , l/min	14.2 (1.1)	13.5 (3.6)	NS
MEF, l/s	0.40 (0.09)	0.41 (0.13)	NS
$\dot{V}_{CO_2}$ , ml/min	310 (50)	290 (70)	NS
HR, beats/min	85 (10)	87 (11)	NS
$\dot{V}_E/\dot{V}_{CO_2}$	46.5 (9.2)	48.2 (11.7)	NS
PaCO <sub>2</sub> , Torr	42 (5)	42 (6)	NS

Values are means with SD in parentheses; *n*, no. of subjects. IC, inspiratory capacity;  $\dot{V}_E$ , minute ventilation; MEF, mean expiratory flow;  $\dot{V}_{CO_2}$ , CO<sub>2</sub> output; HR, heart rate; NS, not significant.

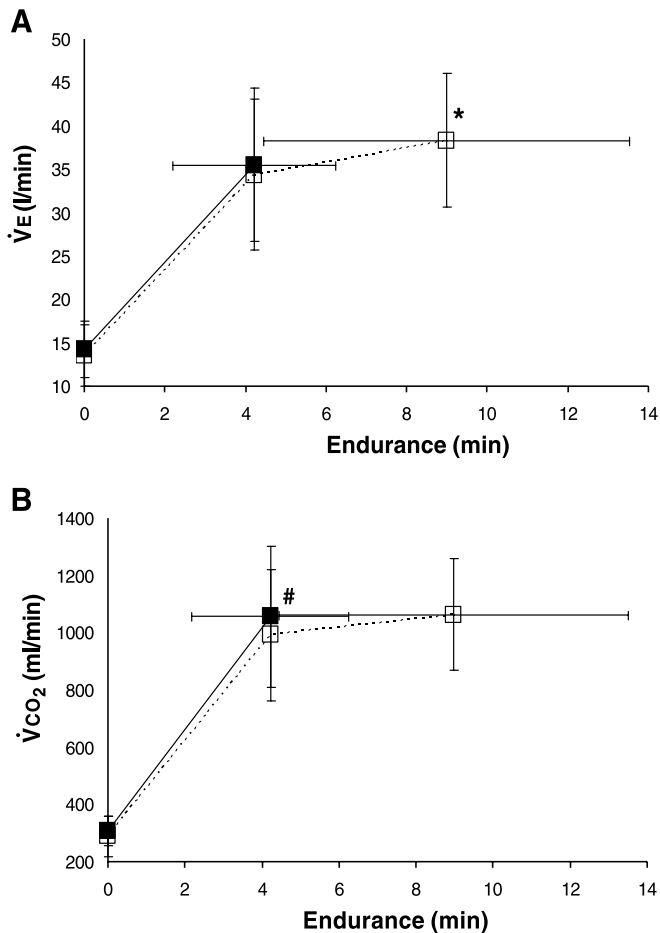


Fig. 1. Mean rates (with SD) of increase in minute ventilation ( $\dot{V}_E$ ; A) and  $\text{CO}_2$  output ( $\dot{V}_{\text{CO}_2}$ ; B) during constant work rate (CWR) exercise on air (■) and on heliox (□) in chronic obstructive pulmonary disease (COPD) patients ( $n = 12$ ). Mean endurance time increased significantly with heliox. Mean  $\dot{V}_E$  was higher at peak exercise, heliox vs. air,  $*P < 0.01$ . Mean  $\dot{V}_{\text{CO}_2}$  was reduced at isotime,  $\#P < 0.05$ . See RESULTS for further comments.

capacity increased significantly with heliox. At peak exercise,  $\dot{V}_E$  was higher in heliox compared with air breathing, whereas at isotime (Iso; when the patients stopped exercising during air breathing)  $\dot{V}_E$  was not different compared with air.  $\dot{V}_{\text{CO}_2}$  was significantly lower during heliox at Iso exercise.

Mean exercise data for the 12 patients studied are presented in Table 3. Mean exercise duration increased significantly during heliox breathing vs. air [9.0 (SD 4.5) vs. 4.2 (SD 2.0) min;  $P < 0.001$ ]. At Iso, this was associated with a significant increase in IC [1.97 (SD 0.40) vs. 1.77 (SD 0.41) liters;  $P < 0.001$ ], IRV, and IC/ $\dot{V}_E$ , and with a reduction in heart rate,  $\dot{V}_E/\text{MVV}$ , and DYS [6 (SD 1) vs. 8 (SD 1) score;  $P < 0.001$ ]. At peak exercise, in heliox compared with air breathing,  $V_T$ , IC, MEF,  $\dot{V}_E$ , and  $\dot{V}_E/\dot{V}_{\text{CO}_2}$  were significantly higher. By contrast, arterial oxygen saturation and lung gas-exchange efficiency (i.e.,  $V_{\text{DS}}/V_T$ ) were not affected by heliox breathing during exercise.

Flow-volume loops, at rest and at Iso, during air and heliox breathing, for two representative COPD patients are shown in Fig. 2. In both patients, heliox increased the size of the maximal resting flow-volume loop and reduced exercise DH; the latter was more pronounced in patient A, who was severely flow limited at rest. As shown in Fig. 3, analysis of operational volumes during exercise revealed a significant reduction in DH induced by heliox, as reflected by the increase in IC ( $\text{IC}_{\text{Iso}}$ ) and IRV at Iso.

The increase in exercise endurance time ( $\Delta\text{End}$ , where  $\Delta$  is change) induced by heliox correlated significantly with the increment in resting  $\text{FEV}_1$  ( $R = 0.88$ ;  $P < 0.01$ ), the increment of  $\text{IC}_{\text{Iso}}$  ( $\Delta\text{IC}_{\text{Iso}}$ ) ( $R = 0.70$ ,  $P < 0.02$ ), and the reduction in Dys at Iso ( $\Delta\text{Dys}_{\text{Iso}}$ ) (Fig. 4;  $R = -0.71$ ,  $P < 0.01$ ). Moreover, the increment of  $\text{IC}_{\text{Iso}}$  ( $\Delta\text{IC}_{\text{Iso}}$ ) correlated with the reduction in  $\text{Dys}_{\text{Iso}}$  (Fig. 4;  $R = -0.75$ ,  $P < 0.01$ ). No other correlations between pertinent variables were found. In particular, the severity of resting airflow obstruction and/or patients' maximal exercise capacity did not correlate with  $\Delta\text{IC}_{\text{Iso}}$  and/or  $\Delta\text{End}$ .

In Table 4 are shown the results of data reproducibility for the seven patients who repeated the air-heliox protocol twice;

Table 3. Results at peak and isotime

	Air	Heliox Isotime	<i>P</i> Value (vs. Air)	Heliox Peak	<i>P</i> Value (vs. Air)
Endurance, min	4.2 (2.0)			9.0 (4.5)	<0.001
Dys, score	8 (1)	6 (1)	<0.001	8 (1)	NS
$\dot{V}_E$ , l/min	35.5 (8.8)	34.4 (8.7)	NS	38.3 (7.7)	<0.01
$\dot{V}_E/\text{MVV}$ , %	89 (12)	75 (12)	<0.001	86 (17)	NS
$V_T$ , liters	1.30 (0.38)	1.30 (0.40)	NS	1.39 (0.36)	<0.001
<i>f</i> , breaths/min	28 (5)	27 (6)	NS	28 (6)	NS
IC, liters	1.77 (0.41)	1.97 (0.40)	<0.001	1.89 (0.41)	<0.01
IRV, liters	0.47 (0.19)	0.69 (0.22)	<0.001	0.49 (0.23)	NS
IC/ $\dot{V}_E$	0.05 (0.01)	0.06 (0.01)	<0.001	0.05 (0.01)	NS
Ti/Tt	0.43 (0.04)	0.42 (0.04)	NS	0.42 (0.03)	NS
MEF, l/s	1.03 (0.30)	1.02 (0.26)	NS	1.17 (0.28)	<0.001
$\dot{V}_{\text{CO}_2}$ , ml/min	1,070 (250)	990 (230)	<0.05	1,060 (190)	NS
$\dot{V}_E/\dot{V}_{\text{CO}_2}$	33.9 (5.6)	34.9 (5.5)	NS	36.3 (6.0)	<0.001
$\text{PaCO}_2$ , Torr	48 (6)	44 (6)	<0.05	46 (6)	<0.05
$V_{\text{DS}}/V_T$	0.45 (0.10)	0.43 (0.1)	NS	0.47 (0.10)	NS
$\text{SaO}_2$ , %	93 (3)	94 (2)	NS	93 (2)	NS
HR, beats/min	119 (12)	114 (11)	<0.01	121 (12)	NS
Leg fatigue	7 (2)	7 (1)	NS	8 (1)	NS

Values are means with SD in parentheses;  $n = 12$  subjects. Dys, dyspnea; MVV, maximal voluntary ventilation;  $V_T$ , tidal volume; *f*, respiratory frequency; IRV, inspiratory reserve volume; Ti, inspiratory time; Tt, duration of respiratory cycle;  $V_{\text{DS}}$ , dead space volume;  $\text{SaO}_2$ , arterial  $\text{O}_2$  saturation.

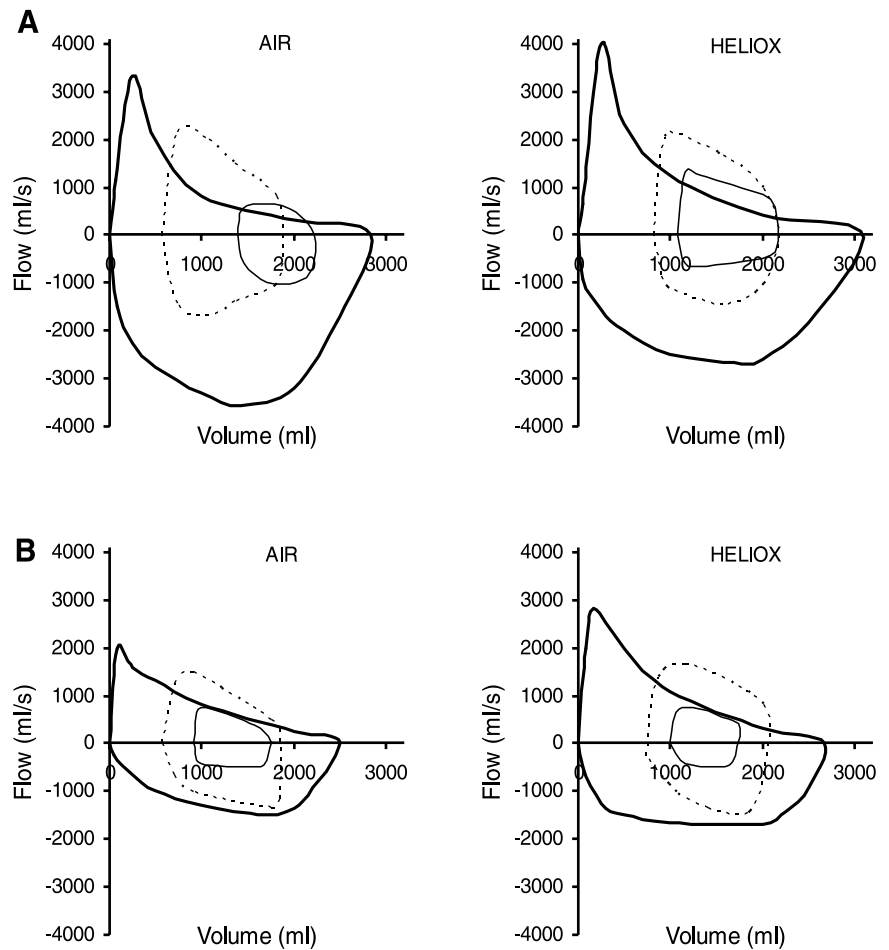


Fig. 2. Flow-volume curves for 2 representative COPD patients (A and B) on air (left) and on heliox (right). Shown are maximal flow-volume curve at rest (solid thick line) and tidal flow-volume curve at rest (solid thin line) and at isotime exercise (dashed line). In both A and B, subjects' heliox increased the size of maximal resting flow-volume curve and the degree of exercise dynamic hyperinflation (DH). In patient A, compared with B, the effect on DH was more evident.

good reproducibility is demonstrated by the high values of intraclass correlation coefficients ( $R^2$ ) calculated for all measured variables.

## DISCUSSION

The most important finding of our study is the observed twofold increase in endurance capacity induced by heliox

breathing in a group of COPD patients exercising at 80% of their maximal power output. The most likely explanation for our finding is that heliox improved maximal expiratory flow and maximal ventilatory capacity, as reflected by the increase in resting FEV<sub>1</sub> and by the increase in V<sub>T</sub>, MEF, and  $\dot{V}_E$  at peak exercise. Importantly, the improvement in maximal expiratory flow determined a significant reduction in DH and Dys, as reflected by the significant increase in IC, IRV, and IC/ $\dot{V}_E$  and decrease in Dys<sub>ISO</sub>. All of these positive changes in lung mechanics allowed the patients to markedly improve exercise endurance time; the observed correlations between  $\Delta IC_{ISO}$  vs.  $\Delta Dys_{ISO}$ ,  $\Delta IC_{ISO}$  vs.  $\Delta End$ , and  $\Delta Dys_{ISO}$  vs.  $\Delta End$  strongly support our hypothesis. Finally, it is likely that the exercise protocol used, capable of inducing high levels of ventilation relative to subject's maximal ventilation for a prolonged period of time, has amplified the effect of heliox breathing in reducing turbulent airway resistances. The beneficial effect of heliox on maximal  $\dot{V}_E$  has been demonstrated in normal subjects (27) and in subjects with mild airflow obstruction (5). Some authors have stated that increase in maximal  $\dot{V}_E$  induced by heliox occurs only in flow-limited subjects, and it is due to the reduction in respiratory impedance, which becomes greater as  $\dot{V}_E$  becomes higher (5).

In COPD patients, Dys on exertion is multifactorial in origin. Previous studies have demonstrated a close relationship between Dys sensation and the level of ventilation achieved during exercise (13, 14, 26). However, the variability in Dys

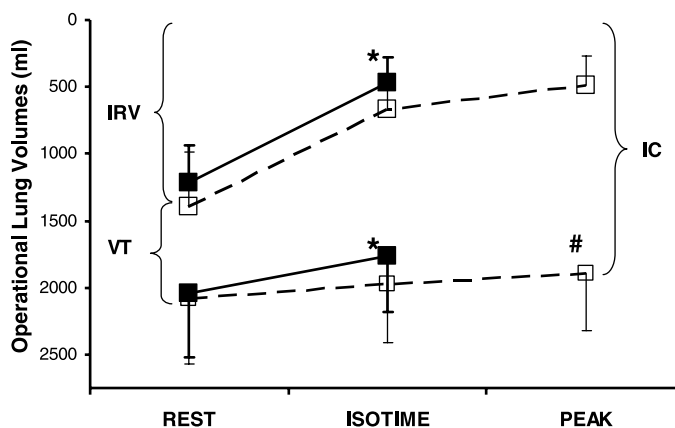


Fig. 3. Changes in operational lung volumes during exercise, on air (■) and on heliox (□). Values are means with SD. At isotime during heliox breathing, inspiratory capacity (IC) and inspiratory reserve volume (IRV) were significantly increased compared with air, \* $P < 0.01$ . At peak exercise on heliox, IC was higher compared with air breathing, # $P < 0.01$ . V<sub>T</sub>, tidal volume.

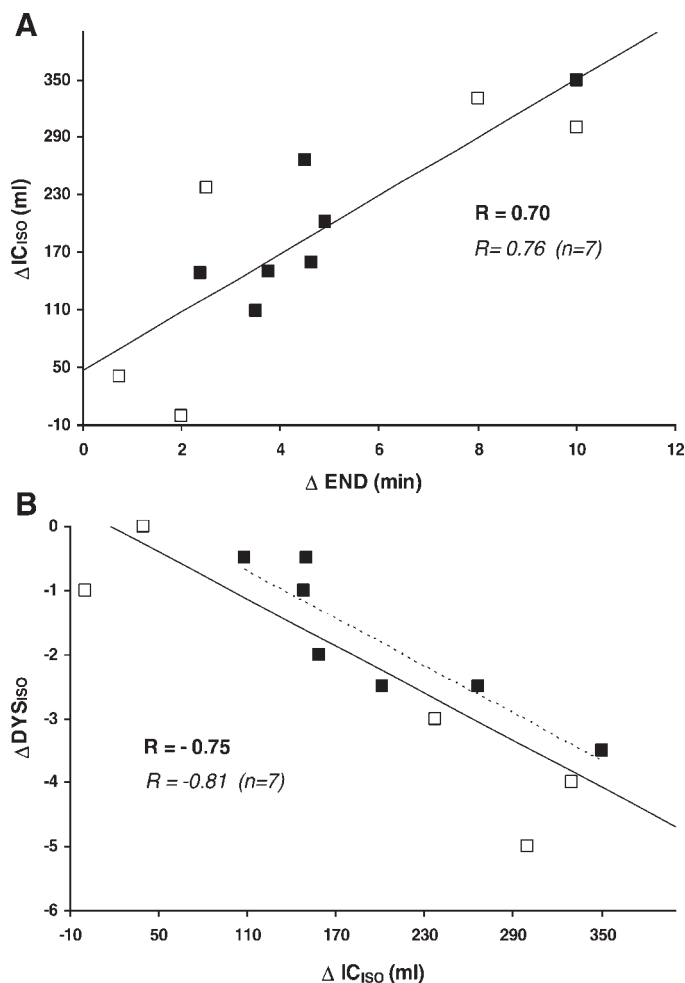


Fig. 4. A: correlation between the increase in IC at isotime ( $\Delta IC_{150}$ ) vs. increase in endurance time ( $\Delta End$ ) induced by heliox.  $\square$ , All patients ( $R = 0.70$ ,  $P < 0.02$ );  $\blacksquare$ , patients who repeated the protocol twice ( $n = 7$ ;  $R = 0.76$ ,  $P < 0.05$ ). B: correlation between the reduction of dyspnea at isotime ( $\Delta Dys_{150}$ ) vs.  $\Delta IC_{150}$  induced by heliox.  $\square$ , All patients ( $R = -0.75$ ,  $P < 0.01$ );  $\blacksquare$ , patients who repeated the protocol twice ( $n = 7$ ;  $R = -0.81$ ,  $P < 0.05$ ).

among COPD subjects for a given level of  $\dot{V}_E$  suggests that other factors play an important role. In patients with chronic airflow limitation, in contrast to normal subjects, end-expiratory lung volume (EELV) increases during exercise, and, to ensure an adequate increase in  $V_T$  and  $\dot{V}_E$ , COPD patients should use their IRV and develop DH. O'Donnell and Webb (23) were among the first to describe a close relationship between the degree of DH and the degree of Dys sensation in COPD patients during exercise. In their original study, they observed that the change in EELV was the strongest predictor of exertional breathlessness, accounting for 38% of variance in Borg scores (23). The results of the present study, according to which heliox breathing lowers the degree of Dys by reducing the degree of DH, are in agreement with the observation reported by O'Donnell and Webb (23).

In normal subjects during incremental exercise, Babb (3) observed that heliox reduces EELV (without a significant increment in end-inspiratory lung volume) and increases maximal  $\dot{V}_E$ . The same author, in a group of patients with mild airflow limitation, showed an increase in maximal expiratory

flow as for the effect of heliox (4, 5). Our results are in agreement with those of Babb: with heliox, we observed an increase in maximal  $\dot{V}_E$  and a reduction in DH. The reduction in DH was observed in all but one patient studied: the improvement in endurance time was more pronounced in those patients who showed a greater reduction in DH; in three patients heliox induced an increase in  $IC_{150}$  of  $>250$  ml that was associated with a remarkable improvement in endurance time.

In the present study, we observed a significant reduction in Dys associated with a small but significant increase in IC. Our results are in keeping with previous work in this field. O'Donnell and coworkers (21) observed a correlation between the reduction in Dys sensation and the increase in IC induced by 60% oxygen breathing. Very recently, Man and coworkers (15), who studied the effects of salmeterol on exercise DH, reported a significant reduction in Dys sensation associated with very small increments of IC. Again, we believe that the high-intensity CWR test utilized allowed us to clearly detect the beneficial effect of small changes in lung mechanics induced by heliox breathing on exercise capacity. In this respect, the observed small increment in  $FEV_1$  (+0.16 liter) induced by heliox at rest can be roughly translated in an increase in maximal  $\dot{V}_E$  of +5.6 l/min that, in a COPD patient with 1.3 liter of  $FEV_1$ , predicts a +12% increase in maximal ventilatory capacity. Such a difference may significantly influence submaximal exercise capacity in moderate to severe COPD patients, as suggested by Neder and coworkers (19) in their original study on the exercise power-duration relationship in COPD.

Our results are in apparent contrast with those of Raimondi and coworkers (24) that utilized an experimental setting similar to ours but reached different conclusions. Possible explanations for the differences observed are as follows: 1) the more severe patients studied by Raimondi et al. (mean  $FEV_1$  0.74 liter) compared with ours (mean  $FEV_1$  1.14 liter); and 2) more importantly, the different exercise protocol used to select the work rate for the CWR exercise. Raimondi et al. used a maximal test with 18 W/min increments that lasted only 4–6 min, whereas we used a 5 W/min protocol that allowed us to better select the workload for the constant work test. In the

Table 4. Intra-class correlation coefficients

	Air		Heliox	
	$R^2$	$P$	$R^2$	$P$
Endurance	0.86	<0.01	0.94	<0.001
$FEV_1$	0.92	<0.01	0.91	<0.01
$Dys_{peak}$	0.83	<0.01	0.81	<0.05
$Dys_{150}$			0.79	<0.05
$IC_{peak}$	0.87	<0.01	0.76	<0.05
$IC_{150}$			0.88	<0.01
$\dot{V}_{E_{peak}}$	0.87	<0.01	0.93	<0.01
$\dot{V}_{E_{150}}$			0.92	<0.001
$\dot{V}_{CO_2_{peak}}$	0.75	<0.05	0.86	<0.01
$\dot{V}_{CO_2_{150}}$			0.80	<0.05
$PaCO_2_{peak}$	0.96	<0.001	0.91	<0.001
$PaCO_2_{150}$			0.93	<0.001
$HR_{peak}$	0.86	<0.01	0.85	<0.01
$HR_{150}$			0.94	<0.01

$n = 7$  Subjects.  $Dys_{peak}$ , peak Dys;  $Dys_{150}$ , isotime Dys;  $IC_{peak}$ , peak IC;  $IC_{150}$ , isotime IC;  $\dot{V}_{E_{peak}}$ , peak  $\dot{V}_E$ ;  $\dot{V}_{E_{150}}$ , isotime  $\dot{V}_E$ ;  $\dot{V}_{CO_2_{peak}}$ , peak  $\dot{V}_{CO_2}$ ;  $\dot{V}_{CO_2_{150}}$ , isotime  $\dot{V}_{CO_2}$ ;  $PaCO_2_{peak}$ , peak  $PaCO_2$ ;  $PaCO_2_{150}$ , isotime  $PaCO_2$ ;  $HR_{peak}$ , peak HR;  $HR_{150}$ , isotime HR.

study of Raimondi, in fact, the CWR test elicited a supramaximal response in  $\dot{V}_E$  that was 127% of the predicted MVV; by contrast, in our study,  $\dot{V}_E$  during CWR exercise on air was 89% of predicted MVV.

In normal individuals, heliox breathing during exercise induces sustained hyperventilation and hypocapnia (3, 9, 27). The effect on  $\dot{V}_E$  is more evident during high-intensity efforts (3, 4), because the increment in  $\dot{V}_E$  is mostly due to an increase in  $V_T$  (27). Various mechanisms have been suggested to explain the state of hyperventilation induced by heliox. Ward and coworkers (27) proposed that the sustained low- $\text{PaCO}_2$  values observed in normal subjects are due, at least in part, to a fall in airway resistances at a high ventilatory rate. In agreement with the previous above-mentioned published data, we observed higher  $V_T$ , MEF,  $\dot{V}_E/\dot{V}_{\text{CO}_2}$ , and lower  $\text{PaCO}_2$  values at peak exercise, suggesting that, even in severely ventilatory-limited COPD patients, heliox breathing induces a state of "relative hyperventilation" (e.g., relative to the level of  $\text{CO}_2$  produced). Regarding the hypothesis that heliox, because of its convective properties, may also improve exercise lung gas-exchange efficiency in COPD, we did not find any significant change in  $V_{\text{Ds}}/V_T$  at rest or during exercise. Nemery and coworkers (20) reported that heliox breathing does not affect  $V_{\text{Ds}}/V_T$  at rest and during moderate CWR exercise in normal individuals. To our knowledge, no data are available in the literature on the effect of heliox on arterial blood gases and on  $V_{\text{Ds}}/V_T$  in COPD with which to compare our data. The results of the present study do not support a beneficial effect of heliox on lung gas mixing and exchange in COPD during exercise.

Interestingly, the changes in lung mechanics induced by heliox were associated with a reduction in  $\dot{V}_{\text{CO}_2}$  values at Iso. Whether these changes may reflect a reduction in metabolic demand from respiratory and/or peripheral exercise muscles, we cannot answer.

In conclusion, heliox breathing, by reducing airflow limitation, DH, and Dys sensation, is capable of improving high-intensity exercise endurance capacity in moderate to severe COPD patients. 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 helpful, particularly in patients with severe airflow limitation and high levels of exercise DH. Further studies are needed to verify the potential role of heliox supplementation during exercise rehabilitation programs in COPD patients.

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