

# Hyperventilation with He–O<sub>2</sub> breathing is not decreased by superimposed external resistance

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Accepted 7 August 2002

## Abstract

The purpose of this study was to determine the effect of imposed external resistance on the ventilatory response to He–O<sub>2</sub> breathing during peak exercise. To accomplish this purpose, separate inspiratory and expiratory external resistances were applied to offset for the decrease in intrapulmonary airway resistance with He–O<sub>2</sub> breathing. Seven men and three women ( $69 \pm 3$  years, mean  $\pm$  S.D.) with normal pulmonary function performed graded cycle ergometry to exhaustion breathing room air, He–O<sub>2</sub> (79% He, 21% O<sub>2</sub>), He–O<sub>2</sub> with imposed expiratory resistance, and He–O<sub>2</sub> with imposed inspiratory resistance. Ventilation ( $\dot{V}_E$ ), lung mechanics, and  $P_{ETCO_2}$  were measured during each 1 min increment in work rate and were analyzed by one-way ANOVA for repeated measures at rest, ventilatory threshold (VTh), and peak exercise. In response,  $\dot{V}_E$  was increased and  $P_{ETCO_2}$  was decreased at VTh ( $P < 0.01$ ) and peak exercise ( $P < 0.01$ ) whenever breathing He–O<sub>2</sub>. Thus,  $\dot{V}_E$  was increased during exercise above VTh with He–O<sub>2</sub> breathing regardless of increases in inspiratory or expiratory external resistance. In conclusion, these data suggest that inspiratory resistive unloading is no more important than expiratory resistive unloading to the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing during heavy and peak exercise. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Exercise, external resistance, He–O<sub>2</sub>; Gases, inspired, He–O<sub>2</sub>; Mammals, humans; Resistance, external; Ventilation, He–O<sub>2</sub> breathing

## 1. Introduction

The proposed mechanisms for hyperventilation with He–O<sub>2</sub> breathing in humans include decreased airflow turbulence at high ventilatory rates

(Spitler et al., 1980; Brice et al., 1991), reflex mechanisms (Hussain et al., 1985), stimulation of irritant receptors (Ward et al., 1982), and decreased mechanical ventilatory constraints (i.e. decreased expiratory flow limitation and dynamic hyperinflation; Babb, 1997a; McClaran et al., 1998, 1999). Recently, we observed that the decrease in pulmonary resistance with He–O<sub>2</sub> breathing at rest was highly predictive of the

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ventilatory response to He–O<sub>2</sub> breathing during peak exercise (Babb, 2001). It appeared that the increase in ventilation ( $\dot{V}_E$ ) during peak exercise was associated with the resistive unloading of the airways alone (Babb, 2001), however, if this was primarily due to an unloading of the inspiratory and expiratory muscles or an alteration of expiratory airway mechanics was not discernible.

Others have reported that decreasing the load on the inspiratory respiratory muscles has little effect on  $\dot{V}_E$  in humans (Krishnan et al., 1996; Gallagher and Younes, 1989; Harms et al., 1997) and animals (Forster et al., 1994; Pan et al., 1987). In contrast, the expiratory muscles have a substantial workload during exercise and contribute importantly to ventilatory output during exercise (Kayser et al., 1997; Krishnan et al., 2000). Also, expiratory airway mechanics are very important determinants of maximal expiratory flow and  $\dot{V}_E$  during peak exercise. Because the determinants of maximal expiratory flow are so different from that of inspiratory flow, we thought that expiratory airway mechanics could be more sensitive to the effects of He–O<sub>2</sub> breathing.

We reasoned that an increase in external resistance to offset for the decrease in intrapulmonary airway resistance could attenuate the increase in  $\dot{V}_E$  during He–O<sub>2</sub> breathing. We also reasoned that examination of inspiratory and expiratory effects separately would provide further insight into the mechanisms by which  $\dot{V}_E$  is regulated during He–O<sub>2</sub> breathing. Thus, the purpose of the present study was to determine the effect of imposed external resistance on the ventilatory response to He–O<sub>2</sub> breathing during peak exercise. To accomplish this purpose, separate inspiratory and expiratory external resistances were applied to offset for the decrease in intrapulmonary airway resistance with He–O<sub>2</sub> breathing and the effect on  $\dot{V}_E$  was examined. We hypothesized that increased expiratory external resistance would attenuate the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing while increased inspiratory resistive loading would have little effect. This would indicate that expiratory airway mechanics are more important to the response of He–O<sub>2</sub> breathing than unloading of inspiratory resistance (Gallagher and Younes, 1989; Krishnan et al., 1996; Harms et al., 1997).

## 2. Methods

### 2.1. Subjects

Older adults (65–75 year) were studied because our previous findings were based on data obtained in older men and women. Volunteers were recruited through local advertisements. None of the subjects had a history of asthma, cardiovascular disease, or musculoskeletal abnormalities that would preclude maximal exercise, or had participated in regular vigorous exercise for the last 6 months. In accordance with the Institutional Review Board, all details of the study were discussed with the volunteers and informed consent was obtained. All qualified participants were familiarized to exercise on the cycle ergometer and instructed to avoid food, caffeine, and smoking for at least 2 h prior to exercise testing. One subject was a current smoker (M, one pack per day; 57 pack year) and five subjects had a history of cigarette smoking (mean  $\pm$  S.D.; 25  $\pm$  9 year; 35  $\pm$  16 pack year). Additionally, two former smokers had a history of cigar smoking (three per day for 17 year) and pipe smoking (ten per day for 14 year). As a group, it had been 25  $\pm$  12 year since the former smokers had quit smoking. Volunteers were accepted for study if their pulmonary function was considered normal.

### 2.2. Pulmonary function

All subjects had standard spirometry, lung volume, and diffusing capacity determinations (SensorMedics model 6200 body plethysmograph, Yorba Linda, CA). Pulmonary function was performed according to guidelines of the American Thoracic Society (1987). Predicted values were based on norms by Knudson et al. (1976), Enright et al. (1993), Goldman and Becklake (1959), Burrows et al. (1961).

### 2.3. Resting respiratory mechanics

Maximal flow–volume loops and pressure–volume loops were measured in a pressure-corrected volume-displacement body plethysmograph to eliminate the gas compression artifact (Sensor-

Medics 6200). Transpulmonary pressure ( $P_{TP}$ ) was estimated using an esophageal balloon placed approximately 45 cm from the nostril (Milic-Emili et al., 1964). Isovolumetric–pressure flow curves (IVPF curves) were constructed (Olafsson et al., 1969) and subsequently used to determine the minimum pressure necessary to obtain maximal flow ( $P_{crit}$ ) as previously described (Babb, 1997a). These  $P_{crit}$  data were used solely to confirm expiratory flow limitation during exercise (see below).

#### 2.4. Gas exchange measurements

Measurements of oxygen uptake ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) were made with the use of a custom gas exchange system that was computerized. It was not possible to use the gas exchange system when breathing He–O<sub>2</sub> due to the deleterious effects of helium on mass spectrometer operation. Ventilatory threshold (VTh) was determined from the comparison of gas exchange indices (Caiozzo et al., 1982) and the V-slope method (Wasserman et al., 1987; Sue et al., 1988). VTh was designated as the work rate that was most congruent among the different threshold determination methods. End tidal CO<sub>2</sub> (PETCO<sub>2</sub>) was measured when breathing room air, as well as when breathing He–O<sub>2</sub>, with the use of the Poet TE CO<sub>2</sub> monitor (model 602/11, Criticare systems Inc., Waukesha, WI).

#### 2.5. Breathing mechanics

Expiratory and inspiratory flows were measured continuously during the exercise tests as described previously (Babb, 1997a). An esophageal balloon was placed as described above for continuous measurements of  $P_{TP}$  during the second through fifth maximal exercise tests (Babb, 1997a). Maximal flow–volume and pressure–volume loops were determined at rest, while the subjects were seated on the cycle ergometer just before the baseline measurements, and within 2 min after terminating exercise, to determine if exercise had induced bronchodilation or bronchoconstriction, which none of the subjects experienced.

Inspiratory capacity (IC) was measured at rest and during exercise to determine placement of tidal flow–volume loops within the maximal flow–volume loop as described previously (Babb, 1997a). End-expiratory lung volume (EELV) was estimated from measurement of IC (EELV = TLC – IC) and reported as a percentage of TLC. End-inspiratory lung volume was calculated (EILV = EELV + V<sub>T</sub>) and expressed as a percentage of TLC. IC was measured during the last 20 sec of each exercise increment and tidal flow–volume and pressure–volume loops were measured continuously.

#### 2.6. Inspired gas mixtures

During rest and exercise, inspired gas was provided from a large inspiratory reservoir as described previously (Babb, 1997a). The bag was filled with either room air or 21% O<sub>2</sub>, and balance He, which were humidified similarly to that of room air as in prior studies (Babb, 1997a,b).

#### 2.7. Imposed resistances

External resistance (i.e. valve, tubing, and pneumotachographs) was matched between the room air and He–O<sub>2</sub> conditions. By matching external apparatus resistance, the He–O<sub>2</sub> effect was restricted to the respiratory airways. In the subsequent tests, external resistance was increased either during inspiration or expiration. This increased external resistance was used to offset the usual decline in intrapulmonary resistance observed with He–O<sub>2</sub> breathing (Fig. 1). Resistance was increased by partially closing valves, which were part of the external inspiratory and expiratory circuitry. The subjects were blinded to the inclusion or exclusion of external resistance.

#### 2.8. Study protocol

After screening, all subjects performed five maximal exercise tests (Fig. 2). The first test was a preliminary exercise test to clear subjects for further participation in the study. The second and third tests were performed either breathing room air or a gas mixture of 21% O<sub>2</sub> and 79% He. The

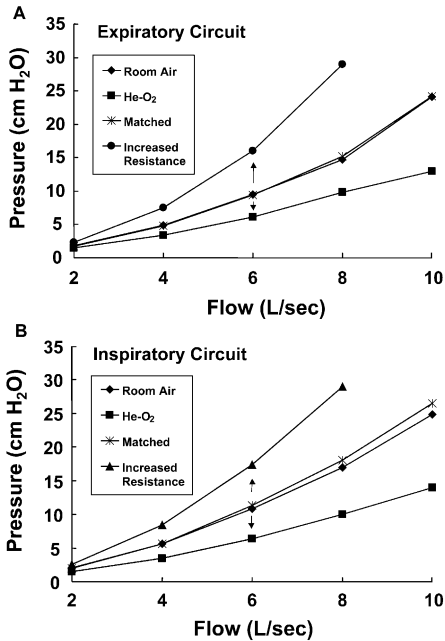


Fig. 1. Panel A: pressure (cmH<sub>2</sub>O)–flow (L/sec) curves for expiratory breathing circuit (i.e. tubing, valve, and pneumotachograph) with room air, He–O<sub>2</sub> with resistance matched to that of room air, and He–O<sub>2</sub> with increased expiratory resistance to offset for decreased intrapulmonary resistance with He–O<sub>2</sub> breathing. Panel B: pressure (cmH<sub>2</sub>O)–flow (L/sec) curves for inspiratory breathing circuit (i.e. tubing, valve, and pneumotachograph) with room air, He–O<sub>2</sub> with resistance matched to that of room air, and He–O<sub>2</sub> with increased inspiratory resistance to offset for decreased intrapulmonary resistance with He–O<sub>2</sub> breathing.

order was randomized. The fourth and fifth tests were performed breathing a gas mixture of 21% O<sub>2</sub> and 79% He. One test had increased external

inspiratory resistance imposed (He–O<sub>2</sub>+R<sub>I</sub>) and the other test had increased external expiratory resistance imposed (He–O<sub>2</sub>+R<sub>E</sub>). The order of tests four and five were also randomized. Subsequent randomized repeat testing demonstrated no effect of test order (data not shown).

### 2.9. Exercise protocol

All the exercise tests followed the same sequence of procedures. Testing began with the subjects seated on the cycle ergometer while baseline measurements were made. After 3 min of baseline measurements, the subjects performed graded cycle ergometry on an electronically braked cycle ergometer (model CPE 2000, MedGraphics, St. Paul, MN). Exercise began at 10 W for the women or 20 W for the men and was incremented by 10 or 20 W, respectively, every minute. The test continued until the subjects stopped because of exhaustion or the test was stopped because they could not keep the pedal rate at a frequency above 50 rpm. Heart rate was monitored continuously through the use of a 12 lead electrocardiogram (model CS-100, Schiller, Baar, Switzerland) and blood pressure was monitored with the use of an automated system (model 4240, Suntech, Raleigh, NC). Arterial saturation was monitored at rest and continuously throughout the first exercise test by pulse oximetry (Ohmeda model 3700, Louisville, CO). Ratings of perceived exertion (Borg 20 point scale) and perceived breathlessness (Borg 10 point

## PROTOCOL

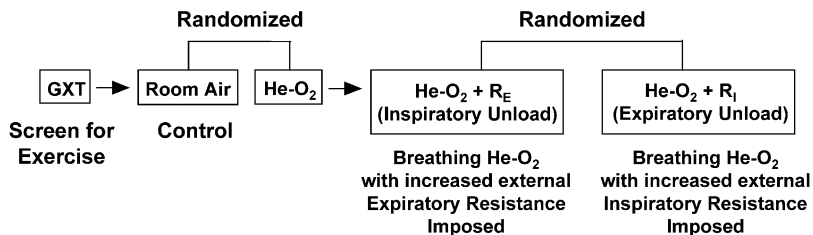


Fig. 2. Protocol design diagram. GXT, graded exercise test; R<sub>I</sub>, inspiratory resistance; R<sub>E</sub>, expiratory resistance.

scale) were taken with the use of the procedures outlined by [American College of Sports Medicine \(1991\)](#) and were recorded at each work rate during the exercise test.

### 2.10. Data analysis

An interactive computer program developed in this laboratory as previously described ([Babb, 1997a,b](#)) was used to determine  $V_T$ ,  $f_b$ ,  $\dot{V}_E$ , and exercise tidal flow–volume and pressure–volume loops. Pulmonary resistance was computed on a breath-by-breath basis with multiple linear regression by the method of least-squares for a whole breath and two half breaths (i.e. expiration and inspiration) as described in method one and two by [Officer and colleagues \(Officer et al., 1998\)](#). Pulmonary resistance was estimated with the use of  $P_{TP}$  and flow; external resistance was estimated with the use of  $P_o$  and flow; and total resistance was determined with the use of  $P_{PL}$  and flow (i.e. both intrapulmonary and external resistance). Each resistance was determined using five to ten breaths preceding the measurement of IC, and then averaged. The mechanical work of breathing against the lung was estimated per breath from the area enclosed by the dynamic tidal pressure–volume loop ( $P_{TP}$ ) with the addition of that portion of a triangle describing work that fell outside the tidal pressure–volume loop (i.e. part of inspiratory elastic work) ([McGregor and Becklake, 1961](#)), and then averaged. Expiratory flow limitation was defined as the percentage of  $V_T$  ( $\%V_T$ ) where tidal expiratory flow impinged on maximal expiratory flow and where  $P_{TP}$  simultaneously exceeded  $P_{crit}$  as described previously ([Babb, 1997a,b](#)). Data were analyzed at rest, at  $V_{Th}$ , and during peak exercise.

The difference between means across all conditions was tested with the use of a one-way ANOVA for repeated measures at rest,  $V_{Th}$ , and peak exercise. In some cases, the difference between means was tested with the use of paired  $t$ -tests. Relationships among physiologic variables were analyzed by Pearson's correlation coefficients.

## 3. Results

### 3.1. Subjects

Seven men and three women with a mean age of  $69 \pm 3$  year ( $\pm$ S.D.) participated in the study (ht. =  $174 \pm 9$  cm, wt. =  $76 \pm 16$  kg). Pulmonary function data, as presented in [Table 1](#), were consistent with normal lung function. Compared with room air,  $FEV_1$  ( $8 \pm 7\%$ ), peak expiratory flow ( $29 \pm 10\%$ ), and expiratory flow at 50% of force vital capacity (FVC) ( $98 \pm 35\%$ ) were increased significantly ( $P < 0.01$ ) when breathing He–O<sub>2</sub> (data not shown). Breathing He–O<sub>2</sub> did not significantly change FVC.

Peak exercise values are presented in [Table 2](#) for the preliminary screening, room air, and He–O<sub>2</sub> exercise tests. Peak exercise capacity was normal in these subjects based on  $\dot{V}O_2$  and HR as a percentage of age and gender corrected norms. However, the  $\dot{V}_E/MVV$  ratio was slightly higher than the normal range for older adults ([DeLorey and Babb, 1999](#); [Blackie et al., 1991](#)). Peak exercise time (data not shown) and peak work rate were not different with breathing He–O<sub>2</sub>. Likewise, RPE and RPB at peak exercise were not different when breathing He–O<sub>2</sub>.

### 3.2. Resistances

The various measures of resistance for expiration and inspiration during maximal exercise are shown in [Fig. 3](#). External resistance, as calculated from  $P_o$ , was not different during inspiration, and only slightly lower, despite being significant ( $P = 0.049$ ), during expiration with the He–O<sub>2</sub> test, which further demonstrates that matching of the external resistance between room air and He–O<sub>2</sub> was fairly well accomplished as planned. During expiration with He–O<sub>2</sub>+R<sub>E</sub> (i.e. inspiratory unloading plus imposed expiratory resistance) and during inspiration with He–O<sub>2</sub>+R<sub>I</sub> (i.e. expiratory unloading plus imposed inspiratory resistance), external resistance was increased as planned, which demonstrates that the external resistance load was markedly greater during these conditions ([Fig. 3](#)). Total resistance, as determined from  $P_{PL}$  and flow, showed the same pattern as

Table 1  
Pulmonary function

FVC (%Pred)	FEV <sub>1</sub> (%Pred)	FEV <sub>1</sub> /FVC (%)	MVV (%Pred)	RV/TLC (%)	TLC (%Pred)	D <sub>L</sub> CO (%Pred)
108 ± 10	102 ± 12	72 ± 4	104 ± 10	33 ± 5	102 ± 9	102 ± 13

Subjects: seven men and three women. Values mean ± S.D. FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 sec; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity; D<sub>L</sub>CO, diffusing capacity; and %Pred, percent of predicted.

external resistance and confirmed that the resistive load was increased during expiration, and during inspiration, respectively, over that of He–O<sub>2</sub> breathing alone, as designed. Only during expiration with He–O<sub>2</sub> breathing + R<sub>E</sub> was total resistance slightly less than room air breathing, but it was still greater than in the other He–O<sub>2</sub> tests. Pulmonary resistance, as calculated with P<sub>TP</sub> and flow, was reduced ( $P < 0.01$  or  $< 0.001$ ) in all conditions with He–O<sub>2</sub> breathing as planned. Therefore, the strategy for imposing increased external resistance during expiration or inspiration in order to offset for the decrease in intrapulmonary resistance functioned closely as planned.

### 3.3. Ventilation

$\dot{V}_E$  was significantly ( $P < 0.01$ ) higher ( $14 \pm 8$ ,  $14 \pm 12$ , and  $11 \pm 5\%$ , respectively, mean ± S.D.) during peak exercise when breathing He–O<sub>2</sub> regardless of the imposition of external expiratory resistance or external inspiratory resistance (Fig. 4).  $\dot{V}_E$  was also higher at VTh ( $P < 0.001$ ) when breathing He–O<sub>2</sub> ( $14 \pm 9$ ,  $14 \pm 9$ , and  $16 \pm 8\%$ , respectively). There were no changes in  $\dot{V}_E$  at rest. Related variables at rest, VTh, and peak exercise when breathing room air and He–O<sub>2</sub> are shown in Tables 3 and 4. The increase in  $\dot{V}_E$  at peak exercise was due to an increase in tidal

Table 2  
Peak exercise tests results

Variables	GXT	Room air	He–O <sub>2</sub>	He–O <sub>2</sub> +R <sub>E</sub>	He–O <sub>2</sub> +R <sub>I</sub> <sup>a</sup>
Workload (W)	128 ± 54	128 ± 50	131 ± 50	131 ± 48	127 ± 54
Time (min)	7.0 ± 1.7	7.1 ± 1.5	7.3 ± 1.5	7.2 ± 1.4	7.1 ± 1.7
$\dot{V}O_2$ (%Pred)	115 ± 28	113 ± 25 <sup>a</sup>	–	–	–
HR (%Pred)	98 ± 10	99 ± 9	99 ± 10	101 ± 8	99 ± 9
$\dot{V}_E$ /MVV (%)	68 ± 17	78 ± 17 <sup>a</sup>	–	–	–
VTh (% $\dot{V}O_2$ max)	66 ± 5	66 ± 6	–	–	–
RPE (6–20)	16 ± 2	17 ± 2 <sup>a</sup>	18 ± 2 <sup>a</sup>	17 ± 3 <sup>a</sup>	16 ± 3 <sup>b</sup>
RPB (0–10)	6 ± 3	6 ± 3 <sup>a</sup>	6 ± 4 <sup>a</sup>	7 ± 3 <sup>a</sup>	6 ± 4 <sup>b</sup>
RER	1.32 ± 0.12	1.34 ± 0.10 <sup>a</sup>	–	–	–

Values mean ± S.D. Preliminary exercise test, graded exercise test (GXT). He–O<sub>2</sub>, exercise while breathing 21% O<sub>2</sub> and 79% He; He–O<sub>2</sub>+R<sub>E</sub>, exercise while breathing He–O<sub>2</sub> plus imposed external expiratory resistance; He–O<sub>2</sub>+R<sub>I</sub>, exercise while breathing He–O<sub>2</sub> plus imposed external inspiratory resistance; W, watts;  $\dot{V}O_2$ , oxygen uptake; %Pred, percent predicted; HR, heart rate;  $\dot{V}_E$ , minute ventilation; MVV, maximal voluntary ventilation; VTh, ventilatory threshold; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; and RER, respiratory exchange ratio.

<sup>a</sup>  $n = 9$ .

<sup>b</sup>  $n = 8$ .

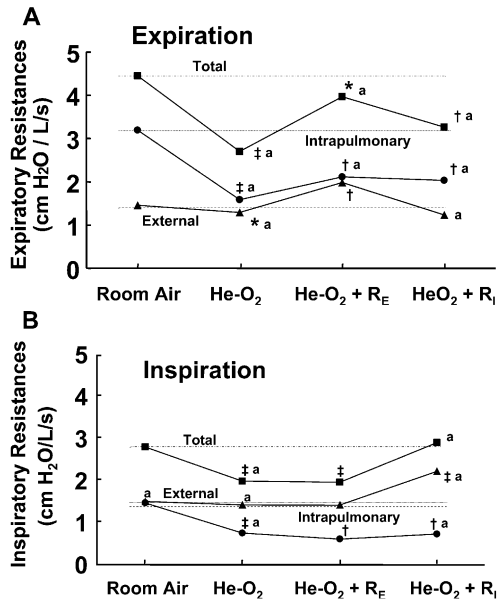


Fig. 3. Panel A: expiratory pulmonary resistance ( $P_{TP}$ ), external resistance ( $P_o$ ), and total resistance ( $P_{PL}$ ) during peak exercise breathing room air, He–O<sub>2</sub>, He–O<sub>2</sub>+R<sub>E</sub> (imposed expiratory resistance), and He–O<sub>2</sub>+R<sub>I</sub> (imposed inspiratory resistance). Lines equal control resistance levels (i.e. room air breathing). Panel B: inspiratory pulmonary resistance ( $P_{TP}$ ), external resistance ( $P_o$ ), and total resistance ( $P_{PL}$ ) during peak exercise breathing room air, He–O<sub>2</sub>, He–O<sub>2</sub>+R<sub>E</sub> (imposed expiratory resistance), and He–O<sub>2</sub>+R<sub>I</sub> (imposed inspiratory resistance). Lines equal control resistance levels (i.e. room air breathing). \*,  $P < 0.05$ ; †,  $P < 0.01$ , and ‡,  $P < 0.001$  denote significant differences from room air; <sup>a</sup>,  $n = 9$ .

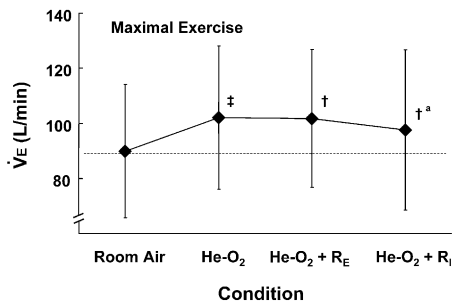


Fig. 4. Ventilation ( $\dot{V}_E$ ) at peak exercise when breathing room air (control), He–O<sub>2</sub>, He–O<sub>2</sub>+R<sub>E</sub> (increased expiratory resistance), and He–O<sub>2</sub>+R<sub>I</sub> (increased inspiratory resistance). Dashed line equals control  $\dot{V}_E$  (i.e. breathing room air). †,  $P < 0.01$  and ‡,  $P < 0.001$  denote significant difference from room air; <sup>a</sup>,  $n = 9$ .

volume ( $V_T$ ,  $P < 0.05$ ), although this difference failed to reach significance with He–O<sub>2</sub> breathing alone. There was a significant ( $P < 0.01$ ) decrease in  $P_{ETCO_2}$  at rest,  $V_{Th}$ , and peak exercise when breathing He–O<sub>2</sub> (Tables 3 and 4). The decrease in  $P_{ETCO_2}$  supports the tendency for hyperventilation when breathing He–O<sub>2</sub>, despite the increase in external inspiratory and expiratory resistance.

### 3.4. Mechanics

Total resistance over the entire breath (i.e. inspiration and expiration) was roughly 12% higher with He–O<sub>2</sub>+R<sub>I</sub> and 14% higher with He–O<sub>2</sub>+R<sub>E</sub> than with He–O<sub>2</sub> breathing alone. Thus, over the whole breath respiratory impedance was increased only modestly while during expiration or inspiration resistance was increased significantly as planned.

The total mechanical work of breathing against the lung was unchanged from that of room air at rest (data not shown),  $V_{Th}$  (data not shown), and peak exercise (Fig. 5) when breathing He–O<sub>2</sub> despite a significantly greater  $\dot{V}_E$  at  $V_{Th}$  and peak exercise. Also, at a given absolute work rate (i.e. 20, 40, and 60 W), the total work of breathing against the lung was not changed (Fig. 5). Peak expiratory pressure was not changed either at rest,  $V_{Th}$ , or peak exercise by breathing He–O<sub>2</sub> (data not shown). The total mechanical work of breathing against the lung and external resistance, as calculated by  $P_{PL}$  and flow, was also unchanged at peak exercise ( $221 \pm 101$ ,  $210 \pm 115$ ,  $235 \pm 110$ , and  $219 \pm 122$  J/min, respectively). It would appear that at a given level of exercise, respiratory effort against the lung (i.e. as reflected by mechanical work and peak expiratory pressure) was unchanged by He–O<sub>2</sub> breathing. The similarity of RPE and RPB between room air and He–O<sub>2</sub> breathing would also support this observation (Tables 3 and 4).

There was no expiratory airflow limitation at rest with either room air or He–O<sub>2</sub> breathing. At  $V_{Th}$  and peak exercise, expiratory flow limitation was not significantly different between breathing conditions, despite the significant increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing (Tables 3 and 4). One subject had flow limitation at  $V_{Th}$  while seven

Table 3  
Selected variables from room air and He–O<sub>2</sub> tests

Variables	Room air			He–O <sub>2</sub>		
	Rest	VTh	Peak	Rest	VTh	Peak
Workload (W)	0	61 ± 30	128 ± 50	0	61 ± 30	131 ± 50
$\dot{V}_E$ (L/min)	17.81 ± 7.24	37.34 ± 10.86	89.90 ± 24.17	17.12 ± 10.48	43.05 ± 14.15†	102.06 ± 26.00‡
V <sub>T</sub> (L)	1.19 ± 0.56	1.78 ± 0.63	2.30 ± 0.65	1.08 ± 0.50	1.80 ± 0.64	2.51 ± 0.79
f <sub>b</sub> (bpm)	16 ± 3	22 ± 4	40 ± 7	16 ± 4	25 ± 5	42 ± 7
P <sub>ETCO<sub>2</sub></sub> (Torr)	32 ± 8	38 ± 4 <sup>a</sup>	32 ± 4 <sup>a</sup>	29 ± 7†	34 ± 5‡	28 ± 4†
FL (% $\dot{V}_T$ )	0	3 ± 10	15 ± 13	0	2 ± 8	12 ± 10
EELV (%TLC)	50 ± 8	50 ± 7	52 ± 7	47 ± 10*	46 ± 8†	47 ± 7*
EILV (%TLC)	69 ± 10	78 ± 7	88 ± 4	64 ± 9*	74 ± 10*	86 ± 5
R <sub>L</sub> (cmH <sub>2</sub> O/L per sec)	2.08 ± 0.60	2.11 ± 0.51	2.29 ± 0.63 <sup>a</sup>	1.84 ± 0.53 <sup>a</sup>	1.34 ± 0.46‡ <sup>b</sup>	1.39 ± 0.56‡ <sup>b</sup>
RPE (6–20)	0	10 ± 1	17 ± 2 <sup>a</sup>	0	11 ± 1 <sup>a</sup>	18 ± 2 <sup>a</sup>
RPB (0–10)	0	2 ± 1	6 ± 3 <sup>a</sup>	0	2 ± 2 <sup>a</sup>	6 ± 4 <sup>a</sup>
V <sub>T</sub> /T <sub>E</sub> (L/sec)	0.53 ± 0.25	1.12 ± 0.33	2.85 ± 0.74	0.50 ± 0.35	1.31 ± 0.44†	3.30 ± 0.78‡
V <sub>T</sub> /T <sub>I</sub> (L/sec)	0.70 ± 0.23	1.39 ± 0.39	3.17 ± 0.89	0.72 ± 0.33	1.61 ± 0.55*	3.55 ± 1.08*

Values mean ± S.D. Room air, exercise while breathing room air; He–O<sub>2</sub>, exercise while breathing 21% O<sub>2</sub> and 79% He; VTh, ventilatory threshold; peak, peak exercise; W, watts;  $\dot{V}_E$ , ventilation; V<sub>T</sub>, tidal volume; f<sub>b</sub>, breathing frequency; P<sub>ETCO<sub>2</sub></sub>, end tidal CO<sub>2</sub>; FL, expiratory flow limitation; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; TLC, total lung capacity; R<sub>L</sub>, pulmonary resistance for the whole breath; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; V<sub>T</sub>/T<sub>E</sub>, mean expiratory flow rate; and V<sub>T</sub>/T<sub>I</sub>, mean inspiratory flow rate. \*,  $P < 0.05$ ; †,  $P < 0.01$ ; ‡,  $P < 0.001$  significant difference from breathing room air.

<sup>a</sup>  $n = 9$ .

<sup>b</sup>  $n = 8$ .

had flow limitation at peak exercise when breathing either room air or He–O<sub>2</sub>. EELV was decreased at VTh and peak exercise when breathing He–O<sub>2</sub> (Tables 3 and 4).

#### 4. Discussion

This study demonstrated that offsetting the decrease in intrapulmonary resistance during He–O<sub>2</sub> breathing with separately applied inspiratory or expiratory external resistance does not limit the increase in  $\dot{V}_E$  at VTh and peak exercise. This finding suggests that inspiratory resistive unloading is no more important than expiratory resistive unloading to the ventilatory response to He–O<sub>2</sub> breathing during peak exercise.

##### 4.1. Hyperventilatory response with He–O<sub>2</sub> breathing

The increase in  $\dot{V}_E$  during peak exercise with He–O<sub>2</sub> breathing alone was similar to that reported previously by the author (Babb, 1997a,b) and by others (Hussain et al., 1985; Brice and Welch, 1983; Esposito and Ferretti, 1997; Wilson and Welch, 1980; Spitler et al., 1980; Ward et al., 1982). This includes studies on both younger and older men and women with normal pulmonary function. Furthermore, the percent increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing in this study was also similar to that reported for patients with mild (Babb, 2001) or severe chronic airflow limitation (Oelberg et al., 1998; Raimondi et al., 1970). The increase in  $\dot{V}_E$  was likewise, similar to the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing reported for normal subjects at raised atmospheric pressures (Fagraeus, 1974). Thus, the ventilatory response to He–O<sub>2</sub>

Table 4  
Selected variables for He–O<sub>2</sub> tests with superimposed external resistance

Variables	He–O <sub>2</sub> +R <sub>E</sub>			He–O <sub>2</sub> +R <sub>I</sub> <sup>a</sup>		
	Rest	VTh	Peak	Rest	VTh	Peak
Workload (W)	0	61 ± 30	131 ± 48	0	59 ± 30	127 ± 54
$\dot{V}_E$ (L/min)	17.75 ± 9.23	42.55 ± 13.28†	101.00 ± 0.72‡	17.30 ± 11.32	41.71 ± 13.37†	97.59 ± 29.10†
V <sub>T</sub> (L)	1.14 ± 0.47	1.88 ± 0.68	2.62 ± 0.78†	1.05 ± 0.66	1.83 ± 0.88	2.52 ± 0.87*
f <sub>b</sub> (bpm)	17 ± 5	24 ± 5	40 ± 7	17 ± 6	25 ± 6	40 ± 8
PET <sub>CO<sub>2</sub></sub> (Torr)	28 ± 7*	34 ± 6‡	29 ± 6†	28 ± 6* <sup>b</sup>	34 ± 6‡	29 ± 6‡
FL (% $\dot{V}_T$ )	0	2 ± 8	10 ± 11	0	0	6 ± 7
EELV (%TLC)	49 ± 10	46 ± 8†	47 ± 8†	51 ± 10	46 ± 8†	48 ± 8†
EILV (% TLC)	67 ± 9	75 ± 9	88 ± 5	67 ± 11	75 ± 10	87 ± 4
R <sub>L</sub> (cmH <sub>2</sub> O/L per sec)	1.61 ± 0.50	1.36 ± 0.42†	1.36 ± 0.45‡ <sup>a</sup>	1.55 ± 0.48 <sup>b</sup>	1.45 ± 0.39† <sup>a</sup>	1.41 ± 0.41‡ <sup>a</sup>
RPE (6–20)	0	10 ± 2 <sup>a</sup>	17 ± 3 <sup>a</sup>	0	10 ± 2 <sup>b</sup>	16 ± 3 <sup>b</sup>
RPB (0–10)	0	2 ± 1 <sup>a</sup>	7 ± 3 <sup>a</sup>	0	2 ± 1 <sup>b</sup>	6 ± 4 <sup>b</sup>
V <sub>T</sub> /T <sub>E</sub> (L/sec)	0.51 ± 0.33	1.26 ± 0.42*	3.09 ± 0.74	0.50 ± 0.38	1.29 ± 0.45†	3.26 ± 0.98†
V <sub>T</sub> /T <sub>I</sub> (L/sec)	0.72 ± 0.28	1.63 ± 0.50*	3.78 ± 1.02‡	0.69 ± 0.36	1.51 ± 0.43*	3.28 ± 0.98†

Values mean ± S.D. He–O<sub>2</sub>+R<sub>E</sub>, exercise while breathing 21% O<sub>2</sub> and 79% He plus imposed external expiratory resistance; He–O<sub>2</sub>+R<sub>I</sub>, exercise while breathing He–O<sub>2</sub> plus imposed external inspiratory resistance; VTh, ventilatory threshold; peak, peak exercise; W, watts;  $\dot{V}_E$ , ventilation; V<sub>T</sub>, tidal volume; f<sub>b</sub>, breathing frequency; PET<sub>CO<sub>2</sub></sub>, end tidal CO<sub>2</sub>; FL, expiratory flow limitation; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; TLC, total lung capacity; R<sub>L</sub>, pulmonary resistance for the whole breath; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; V<sub>T</sub>/T<sub>E</sub>, mean expiratory flow rate; and V<sub>T</sub>/T<sub>I</sub>, mean inspiratory flow rate. \*, *P* < 0.05; †, *P* < 0.01; ‡, *P* < 0.001 significantly different than breathing room air.

<sup>a</sup> *n* = 9.

<sup>b</sup> *n* = 8.

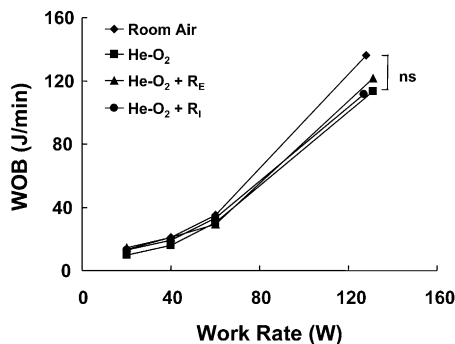


Fig. 5. Work of breathing (WOB) plotted against work rate (W) at 20, 40, 60 W, and peak exercise when breathing room air He–O<sub>2</sub>, He–O<sub>2</sub>+R<sub>E</sub> (increased expiratory resistance), and He–O<sub>2</sub>+R<sub>I</sub> (increased inspiratory resistance). ns, Nonsignificant difference from room air.

breathing appears to be fairly robust and consistent among individuals with normal and abnormal lung function, although the mechanism remains unclear and controversial (Krishnan et al., 1997; Forster et al., 1994).

## 4.2. Effects of imposed external resistance

Increases in inspiratory or expiratory resistance to offset for the decrease in intrapulmonary resistance did not limit the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing at VTh and during peak exercise. Potential mechanisms for the increase in the  $\dot{V}_E$  with He–O<sub>2</sub> breathing include: (1) altered expiratory airways mechanics, (2) effects of expiratory flow limitation, (3) reflex effect of He–O<sub>2</sub> breathing, (4) effects of respiratory muscle unloading, and (5) decreased total respiratory resistance over the entire breathing cycle.

### 4.2.1. Altered expiratory airway mechanics

With He–O<sub>2</sub> breathing, altered airway mechanics could change flow patterns, including local maximal expiratory flow and/or dynamic compression, which could stimulate vagal afferent receptors sensitive to flow, pressure, and even temperature. These afferents could influence respiratory control and produce hyperventilation during exercise (Krishnan et al., 1997; Coleridge

and Coleridge, 1991; Widdicombe, 2001). Because the determinants of maximal expiratory flow are so different from that of inspiratory flow, we thought that expiratory airway mechanics could be more sensitive to the effects of He–O<sub>2</sub>+R breathing.

When external resistance loads are imposed, like that used in this study, P<sub>TP</sub> and intrapulmonary resistance are similar to that of He–O<sub>2</sub> breathing alone, while P<sub>PL</sub> and total resistance are increased in response to the external resistor. Therefore, the imposed loads tend to offset some of the resistive unloading effects of He–O<sub>2</sub> breathing. The increase in total resistance imposed in this study, during either expiration or inspiration, did not appear to significantly affect the ventilatory response to He–O<sub>2</sub> breathing during exercise. Thus, inspiratory resistive unloading is no more important than expiratory resistive unloading to the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing during heavy and peak exercise.

#### 4.2.2. Effects of expiratory flow limitation

The results of this study suggest that the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing was not related to expiratory flow limitation, since flow limitation was minimal with room air and He–O<sub>2</sub> breathing. This finding is in agreement with our prior work in younger (Babb, 1997b), older (Babb, 1997a), and older men and women with chronic airflow limitation (Babb, 2001). In these reports, the increase in  $\dot{V}_E$  was not related to expiratory flow limitation and expiratory flow limitation was the same with and without He–O<sub>2</sub> breathing. However, these findings are in contrast to the findings of others (McClaran et al., 1998, 1999) who studied young fit women during treadmill exercise.

#### 4.2.3. Reflex effect of He–O<sub>2</sub> breathing

It has been suggested that He may stimulate rapidly adapting irritant receptors in the airways (Sant'Ambrogio and Widdicombe, 2001) and evoke an increase in  $\dot{V}_E$  during exercise (Ward et al., 1982). Others have also suggested a reflex effect of He (Hussain et al., 1985). These mechanisms have been proposed because breathing He–O<sub>2</sub> can increase  $\dot{V}_E$  in the first few breaths of He–

O<sub>2</sub> breathing (Forster et al., 1994; Krishnan et al., 1997; Ward et al., 1982). Furthermore, topical and inhaled aerosol blockade of vagally mediated afferents of the upper extrathoracic airways and the major intrathoracic airways can attenuate the first breath transients in  $\dot{V}_E$  but not the overall increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing during exercise (Krishnan et al., 1997). Although we consider He stimulation of irritant receptors as an unlikely mechanism for the increase in  $\dot{V}_E$  during exercise, this potential mechanism can not be excluded by this study, where external expiratory and inspiratory loads were imposed separately.

#### 4.2.4. Effects of respiratory muscle unloading

Consistent with previous data (Babb, 1997a, 2001), the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing does not appear to be related to unloading of the respiratory muscles because the work of breathing was not changed with He–O<sub>2</sub> breathing. Even with the imposition of inspiratory or expiratory resistance the work of breathing was not significantly altered. Furthermore, others have reported that decreasing the load on the inspiratory respiratory muscles has little effect on  $\dot{V}_E$  in humans (Krishnan et al., 1996; Gallagher and Younes, 1989; Harms et al., 1997) and animals (Forster et al., 1994; Pan et al., 1987). The data from this study suggest that the imposition of inspiratory or expiratory resistance with He–O<sub>2</sub> breathing was not great enough to significantly increase the work of breathing over the entire breath, especially at a given level of exercise. Thus, it seems more important to the respiratory controller to maintain the same mechanical work of breathing per work rate than to maintain a specific level of  $\dot{V}_E$ , or for that matter, P<sub>ETCO<sub>2</sub></sub>. This is in agreement with the conclusions of others as well (Eldridge and Davis, 1959; Milic-Emili and Tyler, 1963; Nattie and Tenney, 1970).

#### 4.2.5. Total resistance over the entire breathing cycle

In previous work, we observed that the increase in  $\dot{V}_E$  with He–O<sub>2</sub> breathing during peak exercise was closely associated with the decrease in total pulmonary resistance (Babb, 2001). While inspira-

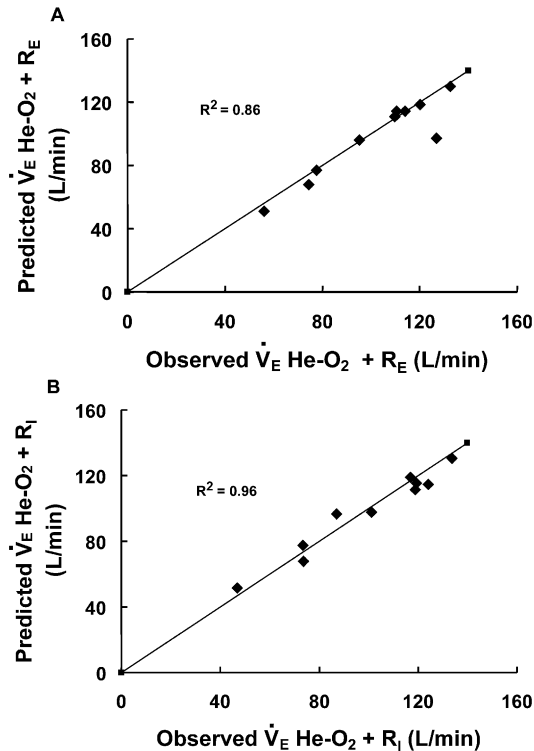


Fig. 6. Panel A: relationship of observed minute ventilation ( $\dot{V}_E$ ) with He-O<sub>2</sub> breathing+imposed expiratory resistance (R<sub>E</sub>) during peak exercise and predicted  $\dot{V}_E$  for He-O<sub>2</sub> breathing+R<sub>E</sub> during peak exercise. Solid line is line of identity.  $R^2 = 0.86$ ,  $P < 0.0001$ . Mean  $\pm$  S.D., observed  $\dot{V}_E$  He-O<sub>2</sub>+R<sub>E</sub> =  $102 \pm 25$  and predicted  $\dot{V}_E$  He-O<sub>2</sub>+R<sub>E</sub> =  $98 \pm 25$  ( $P > 0.05$ ). Panel B: relationship of observed  $\dot{V}_E$  with He-O<sub>2</sub> breathing imposed inspiratory resistance (R<sub>I</sub>) during peak exercise and predicted  $\dot{V}_E$  for He-O<sub>2</sub> breathing+R<sub>I</sub> during peak exercise. Solid line is line of identity.  $R^2 = 0.96$ ,  $P < 0.0001$ . Mean  $\pm$  S.D., observed  $\dot{V}_E$  He-O<sub>2</sub>+R<sub>I</sub> =  $100 \pm 28$  and predicted  $\dot{V}_E$  He-O<sub>2</sub>+R<sub>I</sub> =  $98 \pm 25$  ( $P > 0.05$ ).

tory or expiratory resistance loading produced a phase-specific increase in total resistance that was similar to that of breathing room air, total resistance for the entire breath was only modestly increased over that of breathing He-O<sub>2</sub> alone, and it was less than breathing room air (data not shown). This small increase in total resistance may not have been sufficient to significantly limit the increase in  $\dot{V}_E$  during peak exercise with imposed external loading (Hesser and Lind, 1984). In fact, if we predicted the change in  $\dot{V}_E$  with the imposed external resistances and He-O<sub>2</sub> breathing, much

of the observed results could be explained (Fig. 6). This predicted  $\dot{V}_E$  He-O<sub>2</sub> was based on changes in breathing circuit resistance and the pressure-flow relationships as shown in Fig. 1. This method has been described previously (Babb, 2001). Briefly, if loading increased the overall resistance of the breathing circuit by 36% during He-O<sub>2</sub>+R<sub>E</sub> and 32% during He-O<sub>2</sub>+R<sub>I</sub>, then it would be predicted that the increase in  $\dot{V}_E$  with He-O<sub>2</sub> breathing would be reduced by 36 and 32%, respectively. The data presented in Fig. 6 tend to demonstrate that the reduction in  $\dot{V}_E$  with separate loading could be predicted, and suggests that the increase in  $\dot{V}_E$  with He-O<sub>2</sub> breathing is closely associated with changes in resistance. However, separate loading of inspiratory or expiratory circuitry appears to make no difference.

The simultaneous imposition of expiratory and inspiratory external resistance was not attempted in this study. In hindsight, this may have yielded further information. However, our goal was to examine the effects of offsetting the decrease in intrapulmonary resistance on  $\dot{V}_E$  during He-O<sub>2</sub> breathing with separate expiratory and inspiratory resistive loading. In this regard, we believe that the loads imposed in this study were sufficient to determine that imposed inspiratory or expiratory resistance produced similar ventilatory outcomes during exercise. Based on the data shown in Fig. 6, we would expect the increase in  $\dot{V}_E$  to be diminished if both inspiratory and expiratory external resistances were applied simultaneously.

## 5. Conclusion

In summary, superimposing separate inspiratory and expiratory external resistance on He-O<sub>2</sub> breathing during inspiration and expiration did not diminish the ventilatory response to exercise. Thus, we conclude that inspiratory resistive unloading is no more important than expiratory resistive unloading to the increase in  $\dot{V}_E$  with He-O<sub>2</sub> breathing during peak exercise. These findings suggest that the changes in respiratory impedance encountered over the entire breathing cycle is the major contributing factor for hyperventilation with He-O<sub>2</sub> breathing during peak

exercise, not changes in load on the respiratory muscles.

### Acknowledgements

The authors wish to thank Brenda L. Wyrick and Penny P. Gardner for their assistance throughout the various stages of this project. The authors also wish to acknowledge their appreciation to Dr Benjamin D. Levine for the medical assistance with this project. This work was supported by NIH grant: NIA-AG11805.

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