Breathing $He\text{-}O_2$ Increases Ventilation but Does Not Decrease the Work of Breathing during Exercise

T. G. BABB

Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas; and University of Texas Southwestern Medical Center, Dallas, Texas

We previously observed an increase in minute ventilation ($\dot{V}_E$) with resistive unloading ($He\text{-}O_2$ breathing) in healthy elderly subjects with normal pulmonary function. To investigate the effects of resistive unloading in elderly subjects with mild chronic airflow limitation (FEV_1/FVC: 61 ± 4%), we studied 10 elderly men and women 70 ± 3 yr of age. These subjects performed graded cycle ergometry to exhaustion, once breathing room air and once breathing a $He\text{-}O_2$ gas mixture (79% He, 21% O_2). $\dot{V}_E$, pulmonary mechanics, and $P_{ET_{CO_2}}$ were measured during each 1-min increment in work rate. Data were analyzed by paired *t* test at rest, at ventilatory threshold (VTh), and during maximal exercise. $\dot{V}_E$ was significantly ($p < 0.05$) increased at VTh (3.4 ± 4.0 L/min or 12 ± 15% increase) and maximal exercise (15.2 ± 9.7 L/min or 22 ± 13% increase) while breathing $He\text{-}O_2$. Concomitant to the increase in $\dot{V}_E$, $P_{ET_{CO_2}}$ was decreased at all levels ($p < 0.01$), whereas total work of breathing against the lung was not different. We concluded that $\dot{V}_E$ is increased during $He\text{-}O_2$ breathing because of resistive unloading of the airways and the maintenance of the relationship between the work of breathing and exercise work rate.

The mechanisms for a sustained hyperventilatory response (i.e., increased $\dot{V}_E$) to breathing a low density gas mixture of helium and oxygen ($He\text{-}O_2$) during exercise remain unclear. It has been suggested that the increase is related to decreased airflow turbulence at high ventilatory rates (1, 2), to reflex mechanisms (3), to stimulation of irritant receptors (4), and to decreased mechanical ventilatory constraints (5). Recently, it was suggested that only women who experience expiratory flow limitation during exercise have a sustained hyperventilatory response to $He\text{-}O_2$ breathing (6). These new data suggest that the decrease in turbulent airflow and subsequent reduction in pulmonary resistance play a much lesser role on the ventilatory response to $He\text{-}O_2$ breathing than expiratory flow limitation. If removal of expiratory flow limitation is critical to sustained hyperventilation with $He\text{-}O_2$ breathing, we thought that older subjects with mild chronic airflow limitation, who have both age-related and disease-related declines in pulmonary function and substantial ventilatory constraints during exercise (7, 8), including extensive expiratory flow limitation, might show relatively large increases in $\dot{V}_E$ with $He\text{-}O_2$ breathing. Furthermore, we proposed that examination of this population may also provide further insight into the mechanisms by which $\dot{V}_E$ is increased by $He\text{-}O_2$ breathing, if the increase in $\dot{V}_E$ with $He\text{-}O_2$ breathing is dependent on the magnitude of expiratory flow limitation during exercise. Thus, the purpose of the present study was to determine the effect of $He\text{-}O_2$ breathing on $\dot{V}_E$ and respiratory mechanics during exercise in older subjects with mild chronic airflow limitation.

METHODS

Subjects

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 during the previous 6 mo. 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 exercise, food, caffeine, and smoking for at least 2 h prior to exercise testing.

Volunteers were accepted for study if their FEV_1 was < 79% of predicted and/or their FEV_1/FVC ratio was < 74%. No subject had a significant change in spirometry with inhaled bronchodilators. Many of the subjects were unaware of their reductions in pulmonary function until screened for the study, and, therefore, none of the subjects was receiving medications for their breathing. Two subjects were current smokers (1 M, 2 packs/d; 1 W, 1 pack/d), and all 10 subjects had a history of smoking (mean ± SD; 42 ± 13 yr; 65 ± 41 pack-years; 8 ± 8 yr since quitting for eight subjects).

Pulmonary Function

All subjects had standard spirometry, lung volume, and diffusing capacity determinations (Model 6200 body plethysmograph; SensorMedics, Yorba Linda, CA). Pulmonary function was performed according to guidelines of the American Thoracic Society (9). ATS standards were also used for the evaluation of pulmonary impairment (10). Predicted values were based on norms by Knudson and coworkers (11) and Enright and colleagues (12).

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 (SensorMedics 6200). Transpulmonary pressure (Ptp) was estimated using an esophageal balloon placed approximately 45 cm from the nostril (13). Isovolume-pressure flow (IVPF) curves were constructed (14) and used to determine the minimum pressure necessary to obtain maximal flow (Pcrit) as described previously (5). IVPF curves were also determined with $He\text{-}O_2$ breathing with the use of multiple graded vital capacities, which were performed prior to the $He\text{-}O_2$ exercise test. Maximal expiratory flow was increased with $He\text{-}O_2$ breathing, but Pcrit was not significantly different between room air and $He\text{-}O_2$ breathing (data not shown). These Pcrit data were used solely to confirm expiratory flow limitation during exercise (*see below*).

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. However, in the $He\text{-}O_2$ tests, it was not possible to measure gas exchange because of the deleterious effects of helium on mass spectrometer operation. Ventilatory threshold (VTh) was determined from a combination of gas exchange methods (15, 16). VTh was designated as the work rate that was most congruent among the different threshold determination methods. End tidal CO_2 ($P_{ET_{CO_2}}$) was measured when breathing room air as well as when breathing $He\text{-}O_2$ with the use of the Poet TE CO_2 monitor (Model 602/11; Criticare systems Inc., Waukesha, WI).

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Correspondence and requests for reprints should be addressed to T. G. Babb, Ph.D., Institute for Exercise and Environmental Medicine, 7232 Greenville Ave., Dallas, TX 75231. E-mail: tonybabb@TexasHealth.org

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Breathing Mechanics

Expiratory and inspiratory flow was measured continuously during the exercise tests as described previously (5). An esophageal balloon was placed as described above for measurements of Ptp during the second and third maximal exercise tests (5). 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 (5). End-expiratory lung volume (EELV) was estimated from measurement of IC and reported as a percentage of TLC. End-inspiratory lung volume was calculated (EILV = EELV + V_T) and expressed as a percentage of TLC.

Inspired Gas Mixtures

During rest and exercise, inspired gas was provided from a large inspiratory reservoir as described previously (5). The bag was filled with either room air or 21% O_2, and the balance He, which was humidified similar to that of room air as in prior studies (5, 17). External resistance (i.e.; valve, tubing, and pneumotachographs) was matched between the room air and He-O_2 conditions (5, 17). By matching external apparatus resistance, the He-O_2 effect was restricted to the respiratory airways.

Study Protocol

After screening, which included pulmonary function tests, an electrocardiogram, and practice on the cycle ergometer, all subjects performed three maximal exercise tests. The first was a preliminary exercise test to clear subjects for further participation in the study. The second and third tests were performed while they breathed either room air or a gas mixture of 21% O_2 and 79% He. The order of these tests were randomized and the subjects were blinded to which gas mixture they were breathing.

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 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 (Model 3700; Ohmeda, Boulder, CO). Ratings of perceived exertion (Borg 20 point scale) and breathlessness (Borg 10 point scale) were taken with the use of the procedures outlined by the American College of Sports Medicine (18) and were recorded at each work rate during the exercise test.

Data Analysis

V_T, f, $\dot{V}_E$, and exercise tidal flow-volume and pressure-volume loops were determined with the use of an interactive computer program developed in this laboratory, as described previously (5). Pulmonary resistance was computed on a breath-by-breath basis with multiple linear regression by the method of least squares for the whole breath as described in Method 1 by Officer and colleagues (19). Resistance was estimated from Ptp and flow on 5 to 10 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 Ptp-volume loop with addition of that portion of a triangle describing work that fell outside the tidal pressure-volume loop when plotting Ptp and volume (i.e., part of inspiratory elastic work) (20), and then averaged. The work of breathing was then further partitioned into resistive and elastic components. Expiratory flow limitation was defined as the percentage of V_T (%V_T) where tidal expiratory flow impinged on maximal expiratory flow and where Ptp simultaneously exceeded Pcrit. Data were analyzed at rest, at VTh, and during maximal exercise. The slope of $\dot{V}_E$ versus work rate was calculated on all the points between rest and VTh and between VTh and maximal exercise for the room air and He-O_2 exercise tests. If the R^2 was not greater than 0.85 (i.e., indicating the fit of the data by least squares regression), then the subject's data were dropped from the group analysis of ventilatory response. Below VTh, one subject was dropped when breathing room air and two subjects were dropped when breathing He-O_2; above VTh no subjects were dropped from analysis. The individual slopes were then averaged and used as indicators of ventilatory response below and above VTh. Work rate was used in the determination of ventilatory response instead of $\dot{V}CO_2$ as previously described (5, 17) so that comparisons could be made between the room air and the He-O_2 tests, where it was not possible to make gas exchange measurements.

TABLE 1. PULMONARY FUNCTION IN SIX MEN AND FOUR WOMEN*

FVC (*% pred*)	FEV_1 (*% pred*)	FEV_1/FVC (*%*)	MVV (*% pred*)	RV/TLC (*%*)	TLC (*% pred*)	D_{LCO} (*% pred*)
98 ± 11	78 ± 7	61 ± 4	86 ± 11	42 ± 8	108 ± 12	92 ± 21

Definition of abbreviations: D_{LCO} = diffusing capacity; MVV = maximal voluntary ventilation; RV = residual volume.

* Values are mean ± SD.

The difference between means was tested with the use of paired *t* tests at rest, at VTh, and during maximal exercise. Relationships among physiologic variables were analyzed by Pearson's correlation coefficients.

RESULTS

Subjects

There were six men and four women with a mean age of 70 ± 3 yr (mean ± SD) who participated in the study (height, 170 ± 10 cm; weight, 74 ± 14 kg). Pulmonary function data are presented in Table 1, which are consistent with mild chronic airflow limitation. Maximal exercise values are presented in Table 2 for the preliminary graded exercise test, room air, and He-O_2 tests. Exercise capacity was normal in these subjects based on $\dot{V}O_2$ and HR as a percentage of the age- and sex-predicted normal. Also, $\dot{V}_E$/MVV ratio was not noticeably elevated. Exercise capacity was not different with breathing He-O_2. Likewise, RPE and RPB were not different when breathing He-O_2.

Ventilation at Rest, VTh, and Maximal Exercise

$\dot{V}_E$ (L/min) at rest, VTh, and maximal exercise when breathing room air and He-O_2 are shown in Figure 1, where $\dot{V}_E$ is plotted

TABLE 2. MAXIMAL EXERCISE TEST*

Variables	GXT	Room Air	He-O_2
Work load, W	114 ± 40	114 ± 35	116 ± 38
Time, min	7.0 ± 1.0	7.0 ± 1.0	7.1 ± 1.1
$\dot{V}O_2$, % pred	115 ± 24	113 ± 24	—
HR, % pred	92 ± 9	89 ± 11	90 ± 10
$\dot{V}_E$/MVV, %	72 ± 15	71 ± 13	—
VTh, % $\dot{V}O_2$max	64 ± 12	—	—
RPE, 6–20 scale	17 ± 2	18 ± 2	18 ± 2
RPB, 0–10 sclae	8 ± 2	8 ± 2	9 ± 2
RER	1.22 ± 0.09	1.23 ± 0.06	—

Definition of abbreviations: GXT = preliminary graded exercise test; HR = heart rate; MVV = maximal voluntary ventilation; RER = respiratory exchange ratio; RPB = rating of perceived breathlessness; RPE = rating of perceived exertion; $\dot{V}e$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake; VTh = ventilatory threshold; W = watts.

* Values are mean ± SD.

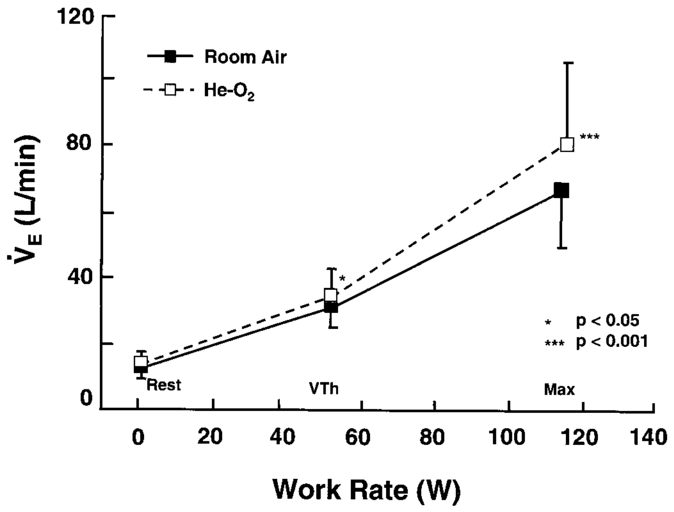

Figure 1. Ventilatory response to exercise when breathing room air or He-O_2. $\dot{V}_E$ = minute ventilation (L/min); *closed squares* and *solid line* = room air, *open squares* and *dashed line* = 79% He and 21% O_2 at rest, ventilatory threshold (VTh), and maximal exercise (max). *$p < 0.05$, and ***$p < 0.001$ denote significant difference from room air condition. Values are in the following order, room air and He-O_2, respectively (mean ± SD): $\dot{V}_E$ at rest = 12 ± 4, 13 ± 4 L/min; $\dot{V}_E$ at VTh = 31 ± 8, 34 ± 8 L/min; $\dot{V}_E$ at max = 66 ± 17, 81 ± 24 L/min. VTh work rate = 52 ± 14 for both conditions. Maximal work rates = 114 ± 35, 116 ± 38 W.

against work rate (W). $\dot{V}_E$ was significantly higher at VTh ($p < 0.05$) and maximal exercise ($p < 0.001$) when breathing He-O_2 (22 ± 13% increase at maximal exercise). The increase in $\dot{V}_E$ during maximal exercise with He-O_2 breathing was due to a significant ($p < 0.01$) increase in V_T (approximately 12% increase) (Table 3). Along with the increase in $\dot{V}_E$ with He-O_2 breathing, there was a significant ($p < 0.001$) decrease in $P_{ET_{CO_2}}$ at rest, VTh, and maximal exercise (Table 3). The decrease in $P_{ET_{CO_2}}$ supports the tendency for sustained hyperventilation when breathing He-O_2, even during maximal exercise.

Ventilatory Response to Exercise

The ventilatory response to exercise below VTh increased from 0.39 ± 0.08 to 0.47 ± 0.11 L/min/W when breathing He-O_2, but failed to reach significance ($p = 0.0521$) (Figure 1). The ventilatory response to exercise above VTh was significantly greater ($p < 0.01$) when breathing He-O_2 (0.74 ± 0.18) as compared with breathing room air (0.60 ± 0.15).

Breathing Mechanics

There was no expiratory airflow limitation at rest with either room air or He-O_2 breathing. At VTh and maximal exercise, expiratory flow limitation was not significantly different between breathing conditions, although $\dot{V}_E$ was significantly higher during maximal exercise with He-O_2 breathing (Table 3). Six subjects had expiratory flow limitation at VTh while seven had expiratory flow limitation at maximal exercise when breathing either room air or He-O_2. EELV was significantly lower when breathing He-O_2 at rest, at VTh, and during maximal exercise (Table 3), which is similar to previous findings and appears to be related to increased maximal expiratory flow and decreased expiratory airflow limitation (5, 17). EILV between room air and He-O_2 was not different at any level (Table 3). Pulmonary resistance (cm H_2O/L/s) was reduced at rest (Δ−0.63 ± 0.92, −15 ± 21%, $p = 0.0583$), VTh (Δ−0.66 ± 0.79, −19 ± 17%, $p < 0.05$), and during maximal exercise (Δ−0.87 ± 0.45, −30 ± 9%, $p < 0.001$) when breathing He-O_2 (Table 3). External resistance as calculated from oral pressure and flow was not different at any level between the room air and He-O_2 tests, which demonstrates that matching of the external resistance between room air and He-O_2 was accomplished (data not shown).

The total work of breathing against the lung was unchanged from that of room air at rest, VTh, and maximal exercise when breathing He-O_2, despite a significantly greater $\dot{V}_E$ at VTh and maximal exercise (Figure 2). Also, at a given absolute work rate (e.g., 20, 40, 60, and 80 W), the total work of breathing against the lung was not changed (data not shown). When the total work of breathing was partitioned into elastic and resistive components at maximal exercise, the elastic work of breathing was increased ($p < 0.05$), probably because of the higher $\dot{V}_E$ and V_T. The resistive work of breathing was not significantly different at maximal exercise. At rest and VTh, neither the elastic nor the resistive work of breathing against the lung were different. Peak expiratory pressure was not changed at rest, VTh, or maximal exercise by breathing He-O_2. It would appear that at a given level of exercise, respiratory effort

TABLE 3. SELECTED VARIABLES FROM ROOM AIR AND He-O_2 tests*

	Room Air			He-O_2		
	Rest	VTh	Maximal	Rest	VTh	Maximal
Work load, W	0	52 ± 14	114 ± 35	0	52 ± 14	116 ± 38
V_T, L	0.91 ± 0.25	1.5 ± 0.51	1.9 ± 0.51	0.94 ± 0.23	1.6 ± 0.54	2.1 ± 0.64‡
f, breaths/min	14 ± 5	22 ± 6	36 ± 6	15 ± 4	22 ± 5	39 ± 6
$P_{ET_{CO_2}}$, mm Hg	36 ± 3	40 ± 4	38 ± 4	32 ± 4§	36 ± 4§	33 ± 3§
EFL, % V_T	0	15 ± 5	24 ± 18	0	13 ± 14†	25 ± 22
EELV, % TLC	57 ± 8	56 ± 7	61 ± 7	54 ± 8‡	52 ± 8†	57 ± 7†
EILV, % TLC	72 ± 7	80 ± 4	90 ± 3	68 ± 8	78 ± 7	90 ± 5
R_L, cm H_2O/L/s	3.34 ± 1.90	2.78 ± 1.49‖	2.91 ± 1.23	2.71 ± 1.40	2.12 ± 0.85‡,‖	2.04 ± 0.90§
RPE, 6–20 scale	0	11 ± 2	18 ± 2	0	11 ± 2	18 ± 2
RPB, 0–10 scale	0	2 ± 2	8 ± 2	0	2 ± 1	9 ± 2
V_T/T_E, L/s	0.33 ± 0.12	0.91 ± 0.23	2.05 ± 0.59	0.37 ± 0.11	0.99 ± 0.24	2.56 ± 0.81§

Definition of abbreviations: EELV = end-expiratory lung volume; EFL = expiratory flow limitation; EILV = end-inspiratory lung volume; f = breathing frequency; $P_{ET_{CO_2}}$ = end tidal P_{CO_2}; R_L = pulmonary resistance; RPB = rating of perceived breathlessness; RPE = rating of perceived exertion; VTh = ventilatory threshold; V_T = tidal volume; V_T/T_E = mean expiratory flow rate; W = watts.

* Values are mean ± SD.

† $p < 0.05$, significantly different from room air.

‡ $p < 0.01$, significantly different from room air.

§ $p < 0.001$, significantly different from room air.

‖ n = 9.

against the lung was unchanged by He-O$_2$ breathing. The similarity of RPE and RPB between room air and He-O$_2$ breathing would also support this observation (Table 3).

Correlations

To determine if the decrease in pulmonary resistance with He-O$_2$ breathing was associated with the increase in V̇E, we correlated the change in resistance at rest with the change in V̇E at maximal exercise. This yielded a poor correlation ($r = -0.18$) but an interesting plot. When this plot was examined further, it was observed that there was a close relationship between the decrease in resistance and the increase in V̇E when men and women were plotted separately (Figure 3) (for the men, $r = -0.82$ and $p < 0.05$; and for the women, $r = -0.997$ and $p < 0.01$). Reporting the change in V̇E with He-O$_2$ breathing as a percent of V̇E during maximal exercise breathing room air did not change these relationships for the men or women, nor did it change the significance of these relationships. Furthermore, numerous attempts to normalize the change in V̇E between the women and men relative to body size, baseline pulmonary function, and exercise tolerance did not yield a significant correlation when the men and women were analyzed as one group. This suggested that there was a difference in the increase in V̇E with He-O$_2$ breathing during exercise between the women and men.

Therefore, we examined V̇E and resistance with He-O$_2$ breathing between the men and women. In the men, the increase in V̇E in L/min was significantly higher only at maximal exercise (20 ± 9 and 7 ± 4 L/min, respectively, $p < 0.05$); although, as a percent change, V̇E at maximal exercise was not significantly different between the men and women (28 ± 13 and 14 ± 9%, respectively). The change in pulmonary resistance at rest, in cm H_2O/L/s or percent change, was not different between the men and women; although, pulmonary resistance in cm H_2O/L/s was significantly higher in the women at rest and during exercise both when breathing room air and He-O$_2$ (data not shown; $p < 0.05$). Thus, the larger increase in V̇E with He-O$_2$ breathing during exercise in the men was probably related to the fact that the men simply had a larger absolute V̇E at maximal exercise than did the women (52 ± 7 versus 76 ± 14 L/min; $p < 0.05$), which is probably related to the fact that the men are larger and have a larger absolute exercise capacity. This seems reasonable since for a larger absolute V̇E there would be greater turbulence and the potential for greater resistive unloading with He-O$_2$ breathing. This possibility is supported when V̇E with room air breathing is correlated with the increase in V̇E with He-O$_2$ breathing over all 30 points (10 subjects at rest, VTh, and maximal exercise; $R^2 = 0.59$, $p < 0.001$). This finding suggests that the increase in V̇E with He-O$_2$ breathing was at least partially related to the magnitude of V̇E when breathing room air, which was greater in the men at maximal exercise.

To further investigate the relationship between the decrease in pulmonary resistance and the increase in V̇E when breathing He-O$_2$, the V̇E when breathing He-O$_2$ was plotted against a predicted V̇E for He-O$_2$ breathing (predicted V̇E He-O$_2$). The predicted V̇E for He-O$_2$ breathing was calculated: Predicted V̇E He-O$_2$ = V̇E room air × ($R_{RA}/R_{He\text{-}O_2}$), where RRA is the breathing circuit resistance at a specified flow rate and $R_{He\text{-}O_2}$ is the breathing circuit resistance at the same specified flow rate. This resistance ratio was calculated from the breathing circuit pressure-flow curves for room air and He-O$_2$ before resistance matching. These curves are shown in Figure 4 for the breathing circuitry (includes tubing, valve, and pneumotachographs). The decreases in resistance were obtained at selected flow rates that were similar to the mean expiratory flow rates (VT/TE, L/s) observed at rest (0.33 L/s), VTh (0.91 L/s), and maximal exercise (2.05 L/s) when breathing room air (*also see* Table 3). At these flow rates, resistance was decreased by 18, 21, and 22%, respectively. Predicted V̇E for He-

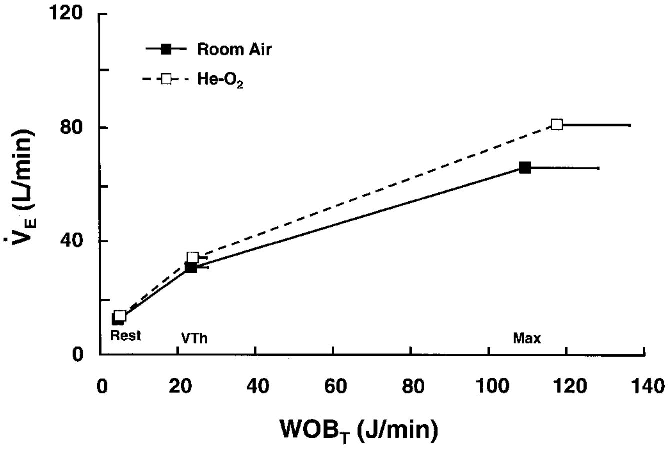

Figure 2. Work of breathing (WOB ± SE) and minute ventilation (V̇E) at rest, ventilatory threshold (VTh), and maximal exercise (max) when breathing room air (*closed squares* and *solid line*) and He-O$_2$ (79% He and 21%O$_2$, *open squares* and *dashed line*).

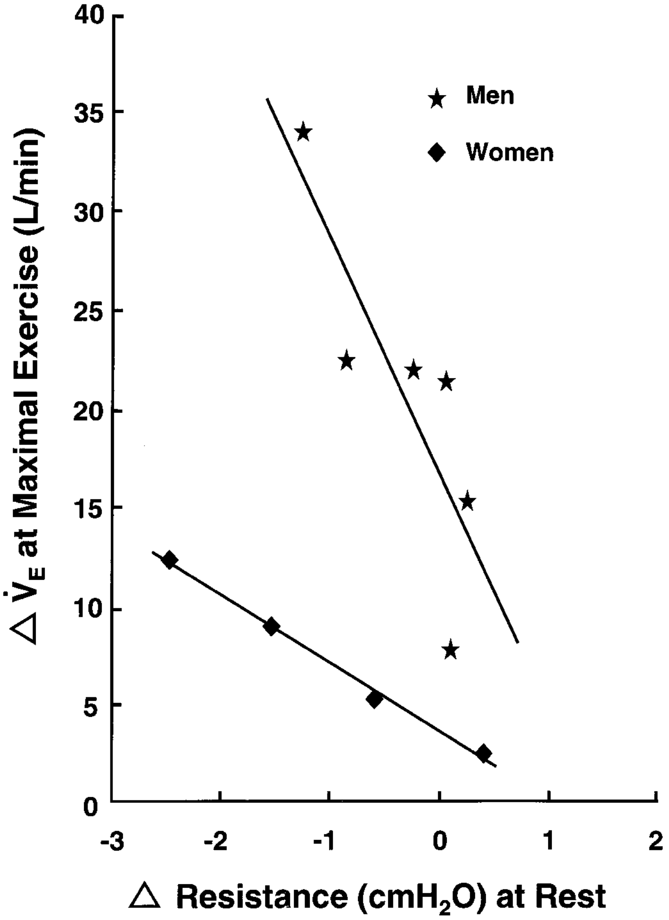

Figure 3. Relationship between the change (Δ) in pulmonary resistance at rest and the change (Δ) in minute ventilation (V̇E) at maximal exercise for men (*stars*) and women (*diamonds*). $R^2 = 0.67$, $p < 0.05$ for the men and $R^2 = 0.99$, $p < 0.001$ for the women.

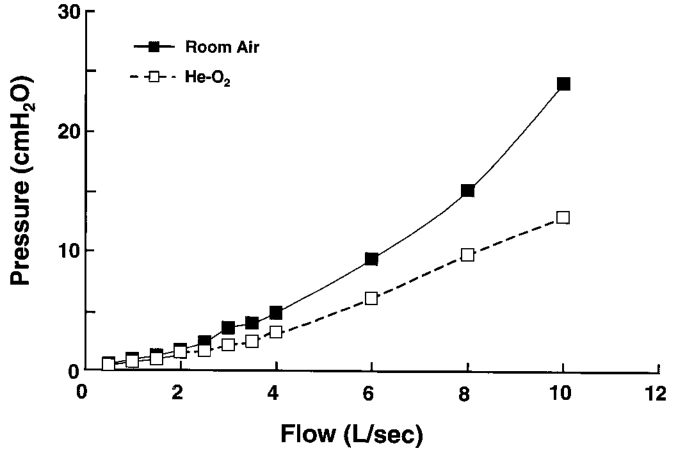

Figure 4. Pressure (cm H_2O)-flow (L/s) curves for breathing circuit (tubing, valve, and pneumotachographs) with room air (*closed squares* and *solid line*) and with He-O_2 (*open squares* and *dashed line*).

O_2 breathing is plotted against observed $\dot{V}_E$ when breathing He-O_2 (Figure 5). The R^2 of this relationship was 0.97 ($p < 0.001$) and there was no significant difference between the means of predicted $\dot{V}_E$ He-O_2 and observed $\dot{V}_E$ He-O_2. This close relationship suggests that the increase in $\dot{V}_E$ with He-O_2 breathing can be predicted by simply knowing the change in pressure-flow characteristics with He-O_2 and the $\dot{V}_E$ when breathing room air.

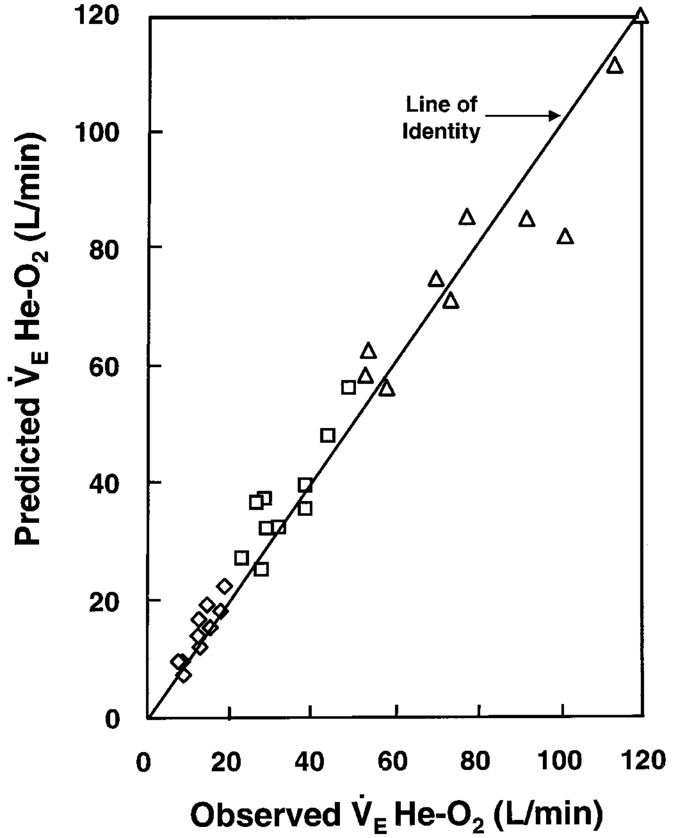

Figure 5. Relationship of observed minute ventilation ($\dot{V}_E$) with He-O_2 breathing (79% He and 21% O_2, L/min) and predicted $\dot{V}_E$ for He-O_2 breathing at rest (*diamonds*), ventilatory threshold, VTh (*squares*), and maximal exercise, max (*triangles*). $R^2 = 0.97$, $p < 0.001$. Mean ± SD, observed $\dot{V}_E$ He-O_2 = 13 ± 4, 34 ± 8, and 81 ± 24, at rest, VTh, and max exercise, respectively; predicted $\dot{V}_E$ He-O_2 = 14 ± 5, 31 ± 9, and 81 ± 21 at rest, VTh, and max exercise respectively. Regression: $y = 0.94x + 3.6$.

In contrast to the decrease in resistance at rest, the magnitude of expiratory flow limitation during maximal exercise when breathing room air was not significantly correlated with the change in $\dot{V}_E$ with He-O_2 breathing. But, when expiratory flow limitation was correlated to the increase in $\dot{V}_E$ over all points (10 subjects at rest, VTh, and maximal exercise, 30 points total), there was a significant ($p < 0.01$) but weak relationship ($R^2 = 0.32$) between the two. This relationship suggests that the magnitude of expiratory flow limitation explains only a small part of the increase in $\dot{V}_E$ with He-O_2 breathing during exercise. Furthermore, expiratory flow limitation tended to be larger in the women at VTh and maximal exercise, although these differences failed to reach significance in such small sample sizes (data not shown). Also, the increases in peak expiratory flow (PEF) 20 ± 5%, $p < 0.01$) and flow at 50% of the forced vital capacity (FVC) (44 ± 11%) when breathing He-O_2 were not significantly correlated with the change in $\dot{V}_E$ at maximal exercise. Nor was the increase in PEF with He-O_2 breathing, or the increase in flow at 50% of the FVC significantly correlated with the change in pulmonary resistance at rest with He-O_2 breathing. This suggests that the increase in $\dot{V}_E$ during maximal exercise when breathing He-O_2 was more related to the decrease in pulmonary resistance at rest than to the increase in maximal expiratory flow.

DISCUSSION

The major findings of this study were twofold. One, the increase in $\dot{V}_E$ when breathing He-O_2 was largely explained by the decrease in pulmonary resistance at rest and could be predicted by the model presented in this study. Two, the total work of breathing against the lung was not decreased at VTh or maximal exercise, although pulmonary resistance was decreased with He-O_2 breathing. This indicates that at a given exercise work rate He-O_2 breathing does not always produce a decrease in the work of breathing against the lung, as commonly assumed, and that respiratory effort against the lung remains constant per work rate with room air and He-O_2 breathing. Contrary to previous findings (6), we observed that expiratory airflow limitation during exercise breathing room air only partially explained the increase in $\dot{V}_E$ with He-O_2 breathing.

Hyperventilatory Response with He-O_2 Breathing

The increase in $\dot{V}_E$ during maximal exercise with He-O_2 breathing was similar to that reported previously by the author (5, 17) and by others (2, 3, 21, 22) for younger and older men and women with normal pulmonary function (24 + 11% increase). Also the increase in percent $\dot{V}_E$ was similar to that reported for patients with severe chronic airflow limitation (23) and for normal subjects at raised atmospheric pressures (24). Thus, the relative increase in $\dot{V}_E$ with He-O_2 breathing appears to be consistent over many populations, including younger and older members with normal pulmonary function and patients with mild-to-severe chronic airflow limitation, as well as in those in different environmental conditions (21, 22). This is important because it suggests that pulmonary function and expiratory flow limitation during exercise are probably not great influences on the ventilatory response to He-O_2 breathing (*see* EXPIRATORY FLOW LIMITATION *below*).

The results of this study also suggest that the increase in $\dot{V}_E$ with He-O_2 breathing is directly proportional to the decrease in resting pulmonary resistance and can be predicted from simple pressure-flow characteristics of $He\text{-}O_2$. The relationship between $\dot{V}_E$ with $He\text{-}O_2$ breathing and predicted $\dot{V}_E$ with $He\text{-}O_2$ breathing is very strong support for this conclusion (Figure 5). The more moderate correlation between the magnitude of $\dot{V}_E$ during maximal exercise when breathing room air and the increase in $\dot{V}_E$ with $He\text{-}O_2$ breathing is further support that the increase in $\dot{V}_E$ during exercise when breathing $He\text{-}O_2$ is the result of resistive unloading of the airways and the magnitude of $\dot{V}_E$ as suggested by others (25).

The slope of the ventilatory response to exercise above VTh with $He\text{-}O_2$ breathing was also increased as previously reported by the author (5) (0.89 ± 0.22 versus 0.74 ± 0.18 L/min/W) and other investigators (1–3) (Figure 1). This increase in slope indicates that the effect of resistive unloading on $\dot{V}_E$ becomes greater as the ventilatory output is increased above VTh. This observation suggests that as ventilatory output is increased, turbulent flow is also increased; and as such, the effect of resistive unloading becomes greater, which has been suggested by others (25). Below VTh, where ventilatory output is lower, $\dot{V}_E$ was increased very little, which is consistent with the above statements and with the findings of others as well (2, 3, 5, 17). Also, for the subjects with chronic airflow limitation in the present study, the ventilatory response to exercise below VTh, before marked flow limitation, was similar to that of other subjects 65 to 75 yr of age with normal pulmonary function (Figure 6A). Above VTh, when expiratory flow limitation was pronounced, their ventilatory response to exercise when breathing room air was slightly lower as compared with the ventilatory response of other subjects 65 to 75 yr of age with normal pulmonary function (Figure 6A). But with $He\text{-}O_2$ breathing, the present subjects' ventilatory response to exercise above VTh was restored to a level similar to that of those 65 to 75 yr of age with normal lung function breathing room air (Figure 6B). This supports the contention that increased mechanical ventilatory constraints attenuate the ventilatory response to exercise above VTh, as suggested previously by the author (5) and by others (6, 26).

Furthermore, our data suggest that the increase in $\dot{V}_E$ with $He\text{-}O_2$ breathing is less in women than in men at maximal exercise. However, there are too few men and women to adequately address the findings related to sex, and they are reported with caution. However, the percent increase in $\dot{V}_E$ with $He\text{-}O_2$ breathing in the older women with mild chronic airflow limitation studied here was similar to that reported by McClaran and colleagues (6) for younger women with normal pulmonary function.

Work of Breathing

The total work of breathing against the lung was not decreased at rest, VTh, or maximal exercise with $He\text{-}O_2$ breathing. This observation is consistent with previous work in older subjects with normal pulmonary function (5). Others have assumed that the work of breathing against the lung was reduced with $He\text{-}O_2$ breathing during exercise, but few have actually measured the work of breathing (27). The results of the present study suggest that respiratory effort against the lung, as reflected by the total mechanical work of breathing against the lung, remained unchanged for a given exercise work rate; and as a result of the decreased pulmonary resistance, $\dot{V}_E$ was increased progressively as the unloading effect of $He\text{-}O_2$ became greater with heavy-to-maximal exercise. Thus, for a given level of exercise, it appears to be more important to maintain the same level of work of breathing against the lung than to maintain a specific level of $\dot{V}_E$, or for that matter, $P_{ET_{CO_2}}$. This is in agreement with the conclusions of others (27–29), and appears true for subjects with mild chronic airflow limitation as well as for younger and older subjects with normal pulmonary function.

Expiratory Flow Limitation

It has been suggested that the increase in $\dot{V}_E$ with $He\text{-}O_2$ breathing occurs only when flow limitation is present, at least in young women (6). McClaran and colleagues (6) reported that in a study of women, only those with flow limitation during room air exercise increased their $\dot{V}_E$ during exercise with $He\text{-}O_2$ breathing. This finding would suggest that ventilatory capacity was increased, as defined by an increase of the maximal expiratory flow-volume envelope, to such an extent that the women were able to increase $\dot{V}_E$ during maximal exercise by as much as 14% while incurring less flow limitation than obtained during exercise with room air breathing (6). Of the 10 subjects in the present study, seven had expiratory flow limitation during maximal exercise when breathing room air (34 ± 4%V_T) and breathing $He\text{-}O_2$ (36 ± 6%V_T). They had an average increase in $\dot{V}_E$ of 26 ± 13% with $He\text{-}O_2$ breathing. Three subjects with no flow limitation had an average increase in $\dot{V}_E$ of 14 ± 11% during maximal exercise with $He\text{-}O_2$ breathing. When examined relative for the women (data not shown), it

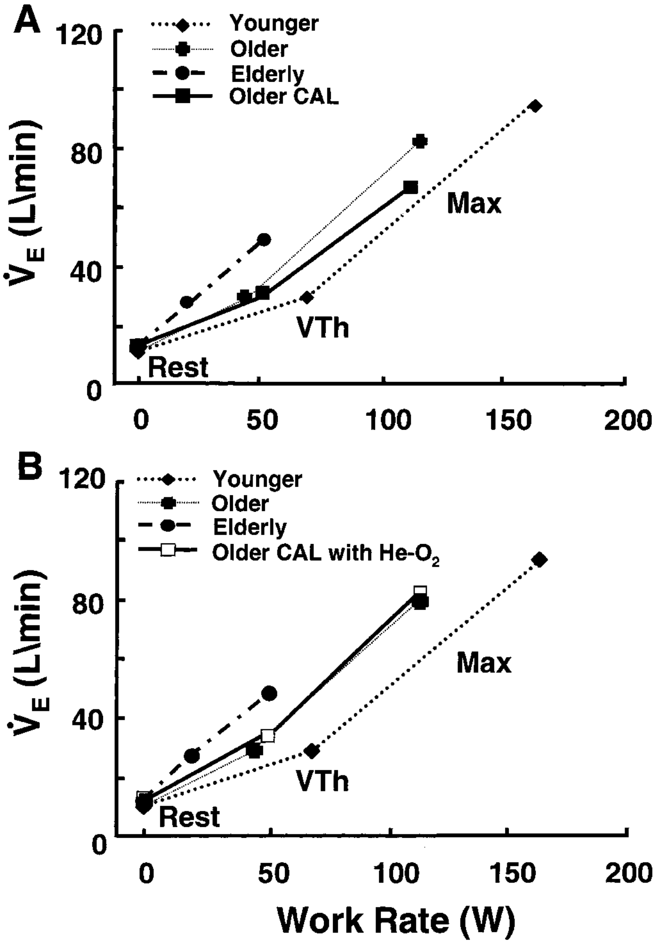

Figure 6. Ventilatory responses to exercise among younger (35 to 45 yr), older (65 to 75 yr), and elderly (85 to 95 yr) men and women with normal lung function, and that of older (65 to 75 yr) men and women with chronic airflow limitation (CAL). Work rate as a percent of predicted maximal exercise is plotted against minute ventilation ($\dot{V}_E$) in L/min at rest, ventilatory threshold (VTh), and maximal exercise (max) in both *Panels A* and *B*. *Panel A*: responses breathing room air, younger subjects = *diamonds* and *dotted line*, older subjects = *plus sign* and *dashed line*, elderly subjects = *circles* and *dashed/dotted line*, and older CAL subjects = *squares* and *solid lines*. *Panel B*: CAL subjects breathing $He\text{-}O_2$ (*longer dashed lines* with *open squares*), compared with younger, older, and elderly subjects.

was found that the increase in $\dot{V}_E$ (14 ± 9%) with He-O_2 breathing and the magnitude of expiratory flow limitation (27 ± 18%V_T) with room air was similar to that reported by McClaran and colleagues (6) for young women with normal pulmonary function. However, there was no significant correlation between the magnitude of expiratory flow limitation during the room air test and the increase in $\dot{V}_E$ during the He-O_2 test. Also, there was no difference in the increase in maximal expiratory flow with He-O_2 breathing between the flow-limited and non-flow-limited subjects. Overall, the subjects in the present study increased both maximal expiratory flow and $\dot{V}_E$ with He-O_2 breathing, and expiratory flow limitation stayed approximately the same with He-O_2 breathing as with room air breathing, which has been reported previously in both younger and older men and women with normal pulmonary function (5, 17) and is now reported for men and women with mild chronic airflow limitation. Unfortunately, there are very few studies that have measured expiratory flow limitation with He-O_2 breathing in which to compare these results.

Influence of Mechanical Constraints

On the basis of the results of the present study, it remains unclear how important mechanical ventilatory constraints, specifically expiratory flow limitation, are to the increase of $\dot{V}_E$ with He-O_2 breathing. It is certainly possible that decreasing expiratory flow limitation could cause some reflex modulation of expiration, and, as a result, produce an increase in $\dot{V}_E$ when maximal expiratory flow is increased with He-O_2 breathing (3, 30, 31). Alternatively, as in the present study, the increase in $\dot{V}_E$ could be related to the reduction in pulmonary resistance, which resulted in increases in $\dot{V}_E$ in both flow-limited and non-flow-limited subjects in this study. Nevertheless, it is reasonable, and in agreement with McClaran and colleagues (6), that expiratory flow limitation could potentially "inhibit" $\dot{V}_E$ during heavy exercise, just as increased pulmonary resistance appeared to attenuate $\dot{V}_E$ in the present study. However, rather than by inhibitory feedback to a highly integrated controller mechanism, expiratory flow limitation and increased pulmonary resistance could simply impede $\dot{V}_E$ while ventilatory regulation (i.e., respiratory drive) remained the same (28). The finding that the relationship between the work of breathing and exercise work rate was unchanged by resistive unloading of the airways suggests that the regulation of $\dot{V}_E$ is unchanged by He-O_2 breathing. Thus, the increase in $\dot{V}_E$ with He-O_2 breathing is simply the result of decreased respiratory impedance, which becomes greater as $\dot{V}_E$ becomes higher. It also suggests that the drive for breathing during exercise is more related to the intensity of exercise and to the work of breathing (i.e., feed forward control and peripheral feedback from the exercising limbs) than $\dot{V}_E$ or pulmonary gas exchange (i.e., $P_{ET_{CO_2}}$), which can be altered by changes in respiratory impedance. These results have important implications for patients with pulmonary disease regarding the possible mechanisms by which the ventilatory response to exercise may be increased or decreased during exercise.

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