

# Ventilation and respiratory mechanics during exercise in younger subjects breathing CO<sub>2</sub> or HeO<sub>2</sub>

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## Abstract

To determine if ventilation ( $\dot{V}_E$ ) during maximal exercise would be increased as much by 3% CO<sub>2</sub> loading as by resistive unloading of the airways, we studied seven subjects ( $39 \pm 5$  years; mean  $\pm$  S.D.) during graded cycle ergometry to exhaustion while breathing: (1) room air (RA); (2) 3% CO<sub>2</sub>, 21% O<sub>2</sub>, and 76% N<sub>2</sub>; or (3) 79% He and 21% O<sub>2</sub>.  $\dot{V}_E$  and respiratory mechanics were measured during each 1-min increment (20 or 30 W) in work rate.  $\dot{V}_E$  during maximal exercise was increased  $21 \pm 17\%$  when breathing 3% CO<sub>2</sub> and  $23 \pm 16\%$  when breathing HeO<sub>2</sub> ( $P < 0.01$ ). Further, the ventilatory response to exercise above ventilatory threshold (VTh) was increased ( $P < 0.05$ ) when breathing HeO<sub>2</sub> ( $0.89 \pm 0.26$  L/min/W) as compared with breathing RA ( $0.65 \pm 0.12$ ). When breathing HeO<sub>2</sub>, end-expiratory lung volume (%total lung capacity, TLC) was lower during maximal exercise ( $46 \pm 7$ ) when compared with RA ( $53 \pm 6$ ,  $P < 0.01$ ). In conclusion,  $\dot{V}_E$  during maximal exercise can be augmented equally by 3% CO<sub>2</sub> loading as by resistive unloading of the airways in younger subjects. This suggests that in younger subjects with normal lung function there are minimal mechanical ventilatory constraints on  $\dot{V}_E$  during maximal exercise. © 1997 Elsevier Science B.V.

**Keywords:** Carbon dioxide, ventilation; Control of breathing, CO<sub>2</sub>, resistive unloading; Exercise, ventilation; Mammals, humans; Ventilation, CO<sub>2</sub> loading vs. resistive unloading

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## 1. Introduction

It was observed that subjects with lower maximal expiratory flows have little reserve for accommodating an increase in ventilatory demand during exercise when compared with age-matched

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subjects with higher maximal expiratory flows (Babb et al., 1994). When confronted with an increased ventilatory demand (3% inspired  $\text{CO}_2$ ), these subjects with lower maximal expiratory flows increased ventilation ( $\dot{V}_E$ ) sparingly above ventilatory threshold (VTh) in proportion to their maximal expiratory flow. As a result, it was concluded that the presence of mechanical limitations during exercise affect not only the limits to  $\dot{V}_E$  but also the control of  $\dot{V}_E$  during heavy-to-maximal exercise (the ventilatory response to exercise).

To better understand the effects of mechanical ventilatory limitations on  $\dot{V}_E$ , the ventilatory response to exercise, and respiratory mechanics, a group of older subjects with normal pulmonary function were studied ( $68 \pm 2$  years, mean  $\pm$  S.D.) (Babb, 1997). Older subjects were selected because they approach mechanical ventilatory limitations during exercise more so than younger subjects, but to a lesser degree than patients with mild chronic airflow limitation (Johnson and Dempsey, 1991). As part of the study (Babb, 1997), the older subjects were asked to breathe either room air, a gas mixture containing 3%  $\text{CO}_2$ , 21%  $\text{O}_2$ , and balance  $\text{N}_2$ , or 21%  $\text{O}_2$  and 79% He ( $\text{HeO}_2$ ) during exercise. The objective of the inspired  $\text{CO}_2$  was to increase ventilatory demand during exercise and the objective of the  $\text{HeO}_2$  mixture was to reduce the resistive load to  $\dot{V}_E$ , which in essence lessens the mechanical ventilatory constraints to  $\dot{V}_E$ . These older subjects were not able to increase their ventilatory response to heavy-to-maximal exercise when ventilatory demand was augmented by inspired  $\text{CO}_2$ . But when breathing  $\text{HeO}_2$ , they were able to increase their ventilatory response to heavy-to-maximal exercise. These two outcomes, taken in combination, in the same subjects, demonstrated that even with an increase in chemical drive,  $\dot{V}_E$  could not be increased as much as when the system was mechanically unloaded (decreased mechanical ventilatory constraints). These data indicated that older subjects have little reserve for accommodating an increase in ventilatory demand similar to that of the lower flow patients while resistive unloading allows for an augmentation of  $\dot{V}_E$  during

maximal exercise. This suggested that mechanical ventilatory constraints influence both the magnitude of  $\dot{V}_E$  during maximal exercise and the control of  $\dot{V}_E$  during heavy-to-maximal exercise in these subjects.

The purpose of the current study was to determine if  $\dot{V}_E$  during maximal exercise could be increased as much by  $\text{CO}_2$  loading as by resistive unloading of the airways in younger subjects. Younger subjects were selected because they do not usually approach mechanical ventilatory constraints during maximal exercise unlike that of older subjects (Babb, 1997). Also,  $\dot{V}_E$  at maximal exercise has not been compared between  $\text{CO}_2$  loading and  $\text{HeO}_2$  unloading in the same younger relatively sedentary subjects. However, Ward et al. (1982) did study subjects during submaximal constant load exercise (90% of anaerobic threshold), when breathing  $\text{HeO}_2$  and with the addition of  $\text{CO}_2$ . They observed  $\dot{V}_E$  to be increased further when  $\text{CO}_2$  was added to the  $\text{HeO}_2$  gas mixture ( $\text{HeO}_2$  plus  $\text{CO}_2$ ). Respiratory mechanics were not measured in the study by Ward et al. (1982), but they concluded that airway resistance appeared to impose a constraint on the magnitude of hyperpnea during submaximal exercise. The investigator's previous findings in patients with mild-to-moderate chronic airflow limitation (Babb et al., 1994) as well as older subjects (Babb, 1997) are in agreement with those of Ward et al. (1982). Also, in other studies, flow-volume limitations have been shown at maximal exercise during inhalation of 4 or 5%  $\text{CO}_2$ , where  $\dot{V}_E$  failed to increase significantly (Johnson et al., 1991, 1992). However, these studies utilized *fit* subjects (younger and older) who could exercise at very high exercise capacities where higher absolute ventilatory demands might be expected than in the sedentary subjects recruited for this study. Also, these subjects were not mechanically unloaded to see if their  $\dot{V}_E$  could be increased further. Nonetheless, it remains unclear if resistive unloading of the airways has the same affect on  $\dot{V}_E$  as  $\text{CO}_2$  loading in younger subjects with normal lung function, who usually do not approach mechanical ventilatory limitations during heavy-to-maximal exercise.

## 2. Methods

### 2.1. 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 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 a cycle ergometer and instructed to avoid exercise, food, and caffeine for a least 2 h prior to exercise testing.

Volunteers were accepted for study if their forced vital capacity (FVC) and forced expiratory volume in 1 sec ( $FEV_1$ ) were  $\geq 80\%$  of predicted and their total lung capacity (TLC) was  $\geq 90\%$  of predicted. Subjects not meeting these guidelines were excluded as well as individuals with respiratory symptoms. None of the subjects had a significant change in spirometry with inhaled bronchodilators. None of the volunteers had ever smoked.

### 2.2. Pulmonary function

All subjects had standard spirometry, lung volume, and diffusing capacity determinations (SensorMedics 6200 body plethysmograph). Pulmonary function was performed according to guidelines of the American Thoracic Society (1987). Also, American Thoracic Society standards were used to determine normal pulmonary function (American Thoracic Society, 1986). Predicted values were based on norms by Knudson et al. (1976).

Resting 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 by subtracting airway opening pressure from esophageal pressure (Celesco), which was measured using an esophageal balloon

placed approximately 45 cm from the nostril. Validity of the balloon pressure was checked by having the subjects blow through a small orifice; if PTP remained constant while oral pressure increased, placement was considered appropriate. Flow, volume, and PTP were displayed and sampled real-time (66 Hz) on a PC computer (NEC) for subsequent analysis.

Isovolume-pressure flow (IVPF) curves were constructed from data collected while the subjects performed multiple vital capacities of various efforts (graded flow-volume curves) in the body plethysmograph (Olafsson et al., 1969). The minimum pressure necessary to obtain maximal flow ( $P_{crit}$ ) was determined from the IVPF curves at 75, 50, 35, and 25% of FVC. These data were used in conjunction with maximal expiratory flow-volume curves and exercise tidal flow-volume loops to establish whether or not there was evidence of expiratory airflow limitation (see below).

### 2.3. Study protocol

After obtaining the screening pulmonary function tests, resting ECG, and practice on the cycle ergometer, all subjects performed four maximal exercise tests. The first was a screening test to clear subjects for further participation in the study. The second, third, and fourth maximal exercise tests were performed while breathing either room air, a gas mixture of 3%  $CO_2$ , 21%  $O_2$ , and balance  $N_2$ , or a mixture of 21%  $O_2$  and 79% Helium. The order of the room air and  $CO_2$  tests were randomized. The  $HeO_2$  test was performed last. However, the subjects were *not* told what we expected during the test, but they were told what gas mixture they were breathing.

### 2.4. Gas exchange measurements

Measurements of oxygen uptake ( $\dot{V}_{O_2}$ ) and carbon dioxide output ( $\dot{V}_{CO_2}$ ) were made with the use of a custom gas exchange system that was computerized (NEC 486DX). Gas samples were drawn continuously at 60 ml/min from the mouthport and were analyzed with a mass spectrometer (Marquette Electronics, model 1100). Calibration of the analyzer was performed before

each test with the use of standard reference gases. Expired volume was measured at the mouth with a turbine flow device (Interface Associates), which was calibrated before each test with the use of a 3-L calibration syringe. The subjects breathed through a mouthpiece attached to the flow device via saliva trap (Interface Associates), which was affixed proximally to a Hans Rudolph valve (model 2700). Total system dead space was 170 ml and system resistance (valve, pneumotachograph, and tubing) was  $< 1$  cmH<sub>2</sub>O per L/s through 6 L/s for expiration. A noseclip was worn during rest and exercise data collections.

VTh was determined from a combination of gas exchange methods (Caiozzo et al., 1982; Wasserman et al., 1987). VTh was designated as the work rate that was most congruent among the different threshold determination methods. VTh was defined in terms of work rate instead of  $\dot{V}_{O_2}$  so that comparisons could be made between the room air, CO<sub>2</sub> and the HeO<sub>2</sub> tests, where it was not possible to make gas exchange measurements.

### 2.5. Expiratory and inspiratory flow measurements

To measure both expiratory and inspiratory flow and  $\dot{V}_E$ , tidal volume ( $V_T$ ), and breathing frequency (fb) continuously during the maximal exercise test, the Hans Rudolph valve was connected to separate inspiratory and expiratory pneumotachographs via large bore breathing tubes (Hans Rudolph pneumotachographs, model 4813; Validyne pressure transducers, model MP45,  $\pm 2$  cmH<sub>2</sub>O and model CD19A amplifiers). The expired pneumotachograph was heated (Hans Rudolph, model 3850A). The separate expiratory and inspiratory flow signals were joined to give one bi-directional flow signal (Validyne Buffer Amplifier, model BA112) and volume was determined from the digital integration of the single flow signal. The pneumotachographs were checked for linearity before the study using known flow rates and different gas mixtures. Calibration of volume was checked before each test using a calibrated syringe. Flow and volume were displayed on a strip chart recorder (AstroMed, model MT 95000) and sampled real-time (100 Hz) on a computer (NEC 486Dx).

### 2.6. Breathing mechanics

An esophageal balloon was placed for measurements of PTP during the second, third, and fourth maximal exercise tests. Balloon volume and placement were checked as outlined above before baseline measurements were made. PTP was determined using a differential pressure transducer (Validyne pressure transducer, model MP45,  $\pm 100$  cmH<sub>2</sub>O and model CD19A amplifiers). PTP and oral pressure were displayed on a strip chart recorder (AstroMed, Model MT 95000) and sampled real-time (100 Hz) on a computer (NEC 486Dx).

Inspiratory capacity (IC) was measured at rest and during exercise to determine placement of tidal flow-volume loops within the maximal flow-volume loop. Measurement of IC was performed by having the subjects, on cue from the investigator, inhale maximally to TLC. A maximal inspiratory effort was confirmed by comparing maximal PTP during the IC maneuver to maximal static recoil pressure determined at baseline. It was assumed that TLC does not change significantly during exercise (Stubbing et al., 1980; Younes and Kivinen, 1984). The subjects in this study were able to perform the procedure without difficulty.

End-expiratory lung volume (EELV) was estimated from measurement of IC ( $EELV = TLC - IC$ ) and reported as a percentage of TLC ( $[EELV/TLC] \times 100$ ). End-inspiratory lung volume was calculated ( $EILV = EELV + V_T$ ) and expressed as a percentage of TLC ( $[EILV/TLC] \times 100$ ).

### 2.7. Inspired gas mixtures

During rest and exercise, inspired gas was provided from a large inspiratory reservoir. The inspiratory reservoir was 2300 L and made of 4-mm polyethylene, which was heat sealed and taped. The bag was filled with either room air or 3% CO<sub>2</sub>, 21% O<sub>2</sub>, and balance N<sub>2</sub>. The gas was mixed from separate CO<sub>2</sub>, O<sub>2</sub>, and N<sub>2</sub> gas tanks via a gas partitioner with three individual flow meters (Cole Parmer, model 34-39). The gas mixture flowed through a heated cascade humidifier (Bennett) into the reservoir, which was set to humidify the

gas mixture similar to that of room air. Room air was blown into the bag with the use of a standard vacuum used for inspired gases only. The reservoir was used during the room air and CO<sub>2</sub> exercise tests so that the subjects were blinded to the gas mixture they were breathing. A smaller reservoir was continuously filled with the HeO<sub>2</sub> mixture, which was at room temperature and humidified. Also, inspiratory and expiratory system resistance was balanced to match that present during the room air test.

### 2.8. Exercise protocol

All exercise tests followed the same 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 (Med-Graphics, model CPE 2000). Exercise began at 20 W for the women or 30 W for the men and was incremented by 20 or 30 W every minute until the subjects stopped because of exhaustion. Gas exchange measurements were made during each increment in work rate, except in the HeO<sub>2</sub> tests where it was not possible to measure gas exchange during the test. IC was measured during the last 20 s of each exercise increment and tidal flow-volume and pressure-volume loops were measured continuously. Heart rate and rhythm was monitored continuously at each work rate via a 12-lead ECG (Schiller CS-100), and blood pressure was monitored with the use of an automated system (Suntech 4240). Arterial saturation was monitored at rest and continuously throughout the first exercise test by pulse oximetry (Ohmeda model 3700). Ratings of perceived exertion (Borg 20 point scale) and breathlessness (Borg 10-point scale) were obtained according to procedures outlined by American College of Sports Medicine (1991) and were recorded at each work rate during the exercise test.

Maximal and tidal flow-volume and pressure-volume loops were determined at rest, while the subjects were seated on the cycle ergometer breathing the specific test gas mixture (room air, CO<sub>2</sub>, or HeO<sub>2</sub>), just before the baseline measure-

ments, and within 2 min after terminating exercise to determine if exercise had induced bronchodilation, which none of the subjects experienced.

### 2.9. Data analysis

V<sub>T</sub>, f<sub>B</sub>, and  $\dot{V}_E$  were calculated from the dual pneumotachograph volume signal by an interactive computer program developed in this laboratory. Also, the interactive computer program was used to generate exercise tidal flow-volume and pressure-volume loops, which were then placed within the maximal flow-volume or maximal pressure-volume loop, respectively. A typical tidal flow-volume and corresponding pressure-volume loop were chosen from the breaths preceding the maximal inspiration and were positioned within the maximal flow-volume or pressure-volume loop according to the measured IC. A breath was considered typical if it had similar volume and flow characteristics as the other breaths prior to the IC. Also estimated was expiratory airflow limitation. Expiratory airflow limitation was defined as the percentage of V<sub>T</sub> (%V<sub>T</sub>) where tidal expiratory flow impinged on maximal expiratory flow and where P<sub>TP</sub> simultaneously matched or exceeded P<sub>crit</sub>. By overlaying the maximal pressure-volume loop and the exercise pressure-volume loops, pressure characteristics could be compared between baseline and exercise. Also, the work of breathing against the lung was estimated per breath from the area of the tidal pressure-volume loop with the addition of that portion of a triangle describing work that fell outside the tidal pressure-volume loop (part of elastic work) (McGregor and Becklake, 1961). The work of breathing was then further partitioned into resistive and elastic components. Data were analyzed at rest, at V<sub>Th</sub>, and during maximal exercise.

The ventilatory response to exercise was determined below and above V<sub>Th</sub> by least-squares regression for each subject. The slope of  $\dot{V}_E$  versus work rate was calculated on all the points between rest and V<sub>Th</sub> ( $4 \pm 1$  points for all three tests), and between V<sub>Th</sub> and maximal exercise ( $4.6 \pm 0.5$ ,  $4.3 \pm 0.8$ , and  $4.6 \pm 0.5$  points for the room air, CO<sub>2</sub>, and HeO<sub>2</sub> tests, respectively). The average  $R^2$  below V<sub>Th</sub> was  $0.95 \pm 0.06$ ,  $0.96 \pm$

Table 1  
Physical characteristics and pulmonary function (mean  $\pm$  S.D.) of subjects

Subjects	Age (years)	Height (cm)	Weight (kg)	FVC (%pred)	FEV <sub>1</sub> (%pred)	FEV <sub>1</sub> /FVC (%)	MVV (%Pred)	RV/TLC (%)	TLC (%pred)	D <sub>LCO</sub> (%pred)
(2M,5W)	39 $\pm$ 5	166 $\pm$ 12	65 $\pm$ 14	107 $\pm$ 12	98 $\pm$ 12	77 $\pm$ 5	107 $\pm$ 13	26 $\pm$ 4	99 $\pm$ 17	104 $\pm$ 17

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>LCO</sub>, diffusing capacity; and (%pred), percent of predicted.

0.02, and  $0.97 \pm 0.03$ , and above VTh the average was  $0.96 \pm 0.03$ ,  $0.97 \pm 0.03$ , and  $0.94 \pm 0.02$  for the room air, CO<sub>2</sub>, and HeO<sub>2</sub> tests, respectively. The individual slopes were then averaged and used as indicators of ventilatory response to exercise below and above VTh. Work rate was used in the determination of ventilatory response instead of  $\dot{V}_{\text{CO}_2}$  so that comparisons could be made between the room air, CO<sub>2</sub> and the HeO<sub>2</sub> tests, where it was not possible to make gas exchange measurements.

A one-way ANOVA for repeated measures was used to test for differences between conditions (room air, CO<sub>2</sub>, and HeO<sub>2</sub>). Multiple contrasts were used to test among the three conditions when significant *F* ratios were detected with the one-way ANOVA. When the difference between only two means was to be tested (i.e.,  $\dot{V}_{\text{O}_2\text{max}}$  between room air and CO<sub>2</sub> tests), paired *t*-tests were used. Relationships among physiological variables were analyzed by Pearson correlation coefficients.

### 3. Results

#### 3.1. Subjects

Physical characteristics and pulmonary function data are presented in Table 1. Maximal exercise values are presented in Table 2 for the room air, CO<sub>2</sub>, and HeO<sub>2</sub> tests. As stated before, gas exchange measurements were not possible when breathing the HeO<sub>2</sub> mixture. All subjects had a normal exercise capacity based on  $\dot{V}_{\text{O}_2}$  and HR as expressed as a percentage of predicted. In general, exercise capacity was slightly less when breathing 3% CO<sub>2</sub> based on exercise time ( $P < 0.05$ ).  $\dot{V}_E/\text{MVV}$  was increased when breathing 3% CO<sub>2</sub> ( $P < 0.01$ ). RPE and RPB were not different at maximal exercise among any of the breathing mixtures.

#### 3.2. Ventilation at rest, VTh, and maximal exercise

$\dot{V}_E$  at rest, VTh, and maximal exercise when breathing room air, 3% CO<sub>2</sub>, or HeO<sub>2</sub> are shown

in Fig. 1, where  $\dot{V}_E$  is plotted against work rate.  $\dot{V}_E$  at rest ( $P < 0.001$ ), at VTh ( $P < 0.01$ ), and during maximal exercise ( $P < 0.01$ ) was significantly higher when breathing 3% CO<sub>2</sub> than when breathing room air ( $52 \pm 24$ ,  $48 \pm 25$ , and  $21 \pm 17\%$  increase over room air, mean  $\pm$  SD, respectively). When breathing the HeO<sub>2</sub> mixture,  $\dot{V}_E$  was increased ( $P < 0.01$ ) over that when breathing room air only during maximal exercise ( $23 \pm 16\%$ ). Therefore, the subjects were able to increase  $\dot{V}_E$  during maximal exercise equally with resistive unloading (HeO<sub>2</sub>) as with breathing 3% inspired CO<sub>2</sub>. Despite the differences in  $\dot{V}_E$ , RPE and RPB were not different among any of the conditions at VTh.

#### 3.3. Ventilatory response to exercise

The ventilatory response to exercise above VTh (Fig. 1) was greater ( $P < 0.05$ ) when breathing HeO<sub>2</sub> ( $0.89 \pm 0.26$  L/min/W) than when breathing room air ( $0.65 \pm 0.12$ ), but only tended to be greater than when breathing 3% CO<sub>2</sub> ( $0.78 \pm 0.23$ ,  $P = 0.10$ ). There was no difference in the ventilatory response to exercise when breathing room air or CO<sub>2</sub>. The ventilatory response to exercise be-

Table 2  
Maximal exercise

Variable	Test		
	Room air	CO <sub>2</sub>	HeO <sub>2</sub>
Workload (W)	151 $\pm$ 49	146 $\pm$ 54	151 $\pm$ 49
Time (min)	6.3 $\pm$ 1.0	6.0 $\pm$ 1.0*	6.3 $\pm$ 1.0 <sup>+</sup>
$\dot{V}_{\text{O}_2}$ (%pred)	89 $\pm$ 10	82 $\pm$ 12	—
HR (%pred)	97 $\pm$ 5	96 $\pm$ 4	95 $\pm$ 9
$\dot{V}_E/\text{MVV}$ (%)	66 $\pm$ 6	79 $\pm$ 11**	—
VTh (% $\dot{V}_{\text{O}_2\text{max}}$ )	69 $\pm$ 28	—	—
RPE (6–20)	18 $\pm$ 3	18 $\pm$ 2	19 $\pm$ 2
RPB (0–10)	8 $\pm$ 3	9 $\pm$ 3	8 $\pm$ 3
RER	1.33 $\pm$ 0.09	1.24 $\pm$ 0.06**	—

Values are mean  $\pm$  S.D. W, watts;  $\dot{V}_{\text{O}_2}$ , oxygen uptake; HR, heart rate;  $\dot{V}_E$ , ventilation; MVV, maximal voluntary ventilation; VTh, ventilatory threshold; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; and RER, respiratory exchange ratio.

\* $P < 0.05$  and \*\* $P < 0.01$  denote significant difference from room air test. <sup>+</sup> $P < 0.05$  denotes significant difference between CO<sub>2</sub> and HeO<sub>2</sub> tests.

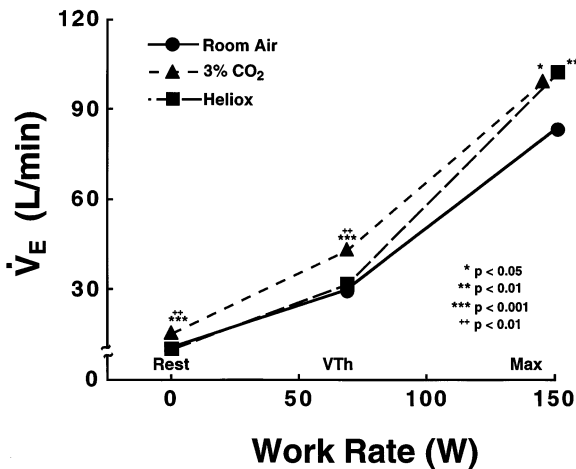


Fig. 1. Ventilatory response to exercise when subjects were breathing room air, 3% CO<sub>2</sub>, or HeO<sub>2</sub>.  $\dot{V}_E$  = ventilation (L/min); circles and solid line, room air; triangles and shorter dashed line, 3% CO<sub>2</sub>, 21% O<sub>2</sub>, and N<sub>2</sub>; and squares and longer dashed line, 79% He and 21% O<sub>2</sub> at rest, ventilatory threshold (VTh), and maximal exercise (max). \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$  denote significance from room air condition. ++ $P < 0.01$  denotes significance between CO<sub>2</sub> and HeO<sub>2</sub> conditions. Values are in the following order, room air, CO<sub>2</sub>, and HeO<sub>2</sub>, respectively (mean  $\pm$  S.D.): rest,  $\dot{V}_E = 10 \pm 2$ ,  $16 \pm 3$ ,  $10 \pm 2$  L/min; VTh,  $\dot{V}_E = 29 \pm 7$ ,  $43 \pm 10$ ,  $32 \pm 9$  L/min; max,  $\dot{V}_E = 83 \pm 24$ ,  $99 \pm 27$ ,  $102 \pm 29$  L/min. VTh work rate,  $68 \pm 28$  W for all conditions; and max work rates,  $151 \pm 49$ ,  $146 \pm 54$ ,  $151 \pm 49$  W.

low VTh was not different among any of the gas mixtures (room air =  $0.30 \pm 0.06$ , 3% CO<sub>2</sub> =  $0.37 \pm 0.06$  and HeO<sub>2</sub> =  $0.32 \pm 0.06$  L/min/W).

### 3.4. Breathing mechanics

In Figs. 2 (room air vs. 3% CO<sub>2</sub>) and 3 (room air vs. HeO<sub>2</sub>), tidal flow-volume loops measured during rest and maximal exercise are shown relative to the maximal flow-volume loop for a typical subject (left panels). Tidal pressure-volume loops measured at rest and during maximal exercise are also shown in Figs. 2 and 3 (right panels). Visual inspection of the exercise tidal flow-volume loops relative to the maximal flow-volume loop indicated that the subject had ventilatory reserve in which to accommodate the augmented ventilatory demand when breathing CO<sub>2</sub> (Fig. 2, left panel). When breathing room air, the subject did not

impinge on her maximal expiratory flow-volume curve (0% expiratory airflow limitation); but when breathing CO<sub>2</sub>, she impinged on her maximal expiratory flow-volume curve over roughly 16% of VT. The effect of the airflow limitation is evident from the increase in the pressure-volume loop when breathing CO<sub>2</sub> (right panel, Fig. 2). When breathing HeO<sub>2</sub> (Fig. 3, left panel), the subject was able to augment  $\dot{V}_E$  during exercise to a greater extent than when breathing room air (also see upper insert right panel). Also, her pressure-volume loops were similar between room air and HeO<sub>2</sub> (Fig. 3, right panel), although  $\dot{V}_E$  was increased by approximately 36 L/min.

The subjects, on average ( $n = 5$ , in two subjects we were unable to confirm expiratory airflow limitation without esophageal pressure measurements in all three conditions), had expiratory airflow limitation of  $1.8 \pm 4\%V_T$  at VTh and  $4.6 \pm 7\%V_T$  at maximal exercise when breathing room air. When breathing HeO<sub>2</sub>, they had  $1.6 \pm 4\%V_T$  expiratory airflow limitation at VTh and  $5.0 \pm 7\%V_T$  at maximal exercise, which was similar to that at room air.  $\dot{V}_E$  was higher when breathing HeO<sub>2</sub> than when breathing room air. When breathing CO<sub>2</sub>, they had  $1.8 \pm 4\%V_T$  expiratory airflow limitation at VTh and significantly more limitation at maximal exercise than when breathing room air ( $P < 0.01$ ), or HeO<sub>2</sub> ( $P < 0.01$ ),  $16.2 \pm 4\%V_T$ .

In Fig. 4  $V_T$  and  $f_B$  are plotted against work rate in the top panel and, EELV and EILV are plotted against work rate in the bottom panel (see also Table 3). The increase in  $\dot{V}_E$  when breathing CO<sub>2</sub> was associated with an increase in  $V_T$  at VTh and maximal exercise more so than  $f_B$  (top panel) ( $P < 0.001$  and  $P < 0.05$ ). The increase in  $\dot{V}_E$  when breathing HeO<sub>2</sub> during maximal exercise was equally associated with small increases in both  $V_T$  and  $f_B$ , however the increases failed to reach significance ( $P > 0.05$ ). EELV was significantly lower when breathing HeO<sub>2</sub> than when breathing room air at VTh ( $P < 0.05$ ) and at maximal exercise ( $P < 0.01$ ). EELV tended to be lower when breathing HeO<sub>2</sub> than when breathing CO<sub>2</sub> at maximal exercise ( $P = 0.062$ ). EILV was significantly higher when breathing CO<sub>2</sub> than when breathing room air ( $P < 0.001$ ) or when

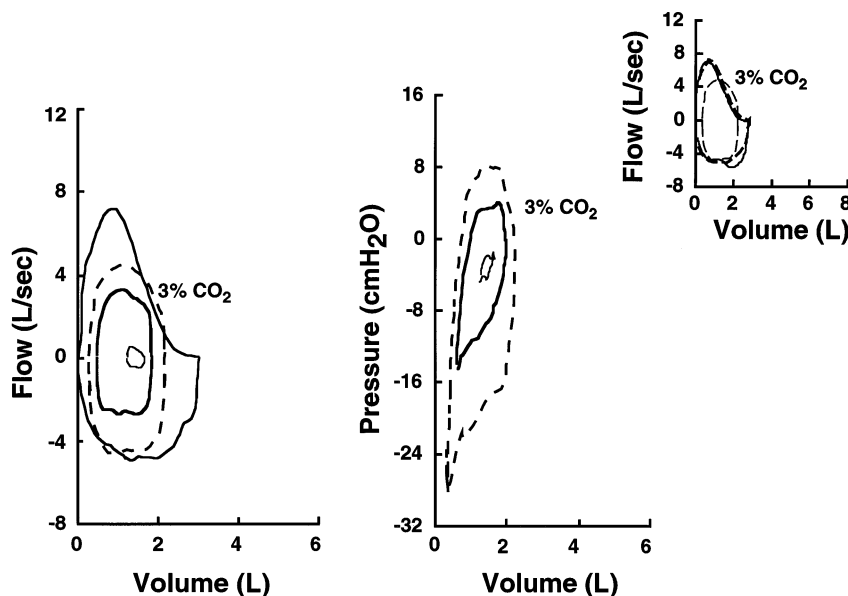


Fig. 2. Maximal and tidal flow-volume loops, and tidal pressure-volume loops for one typical subject. Maximal flow-loop measured while breathing room air (thinner solid line, left panel and right panel insert) and tidal flow-volume and pressure-volume loops measured at rest and during maximal exercise when breathing room air (thicker solid lines) and when breathing 3% CO<sub>2</sub> (thicker dashed line). The insert in the upper right hand corner of the right panel shows pre-exercise maximal flow-volume loops when breathing room air (solid line) and when breathing 3% CO<sub>2</sub> (dashed line). Average values for this subject at maximal exercise when breathing room air and CO<sub>2</sub>, respectively: ventilation, 68 and 95 L/min; tidal volume, 1.35 and 1.81 L; breathing frequency, 51 and 52 BPM; total work of breathing against the lung, 78 and 197 J/min; end-expiratory lung volume, 51 and 45% of total lung volume; and expiratory airflow limitation, 0 and 16% of tidal volume.

breathing HeO<sub>2</sub> ( $P < 0.01$ ) at V<sub>Th</sub>. At maximal exercise, EILV was greater when breathing CO<sub>2</sub> than when breathing HeO<sub>2</sub> ( $P < 0.05$ ). Overall, EELV tended to be lower when breathing HeO<sub>2</sub> than when breathing room air. However, expiratory airflow limitation when breathing HeO<sub>2</sub> was not less than when breathing room air, although  $\dot{V}_E$  was increased when breathing HeO<sub>2</sub>. EILV tended to be increased, as was expiratory airflow limitation, when breathing CO<sub>2</sub>.

The total work of breathing against the lung is shown in panel A of Fig. 5 and the elastic and resistive components of the total work of breathing against the lung are shown in panels B and C of Fig. 5, respectively. These values are based on the data of five subjects because two subjects did not have esophageal balloons in all tests. At rest, the total work of breathing was increased when breathing HeO<sub>2</sub> ( $P < 0.05$ ) as compared with breathing room air ( $3.2 \pm 1.6$  vs.  $3.6 \pm 2.1$  J/min),

but lower ( $P < 0.01$ ) than when breathing CO<sub>2</sub> ( $5.6 \pm 1.6$ ). At V<sub>Th</sub>, the total work of breathing was increased ( $P < 0.05$ ) when breathing CO<sub>2</sub> ( $42 \pm 17$ ) and lower ( $P < 0.01$ ) when breathing HeO<sub>2</sub> ( $20 \pm 9$ ) than when breathing room air ( $22 \pm 9$ ). At maximal exercise, the total work of breathing was greater both for CO<sub>2</sub> ( $P < 0.05$ ,  $280 \pm 129$ ) and HeO<sub>2</sub> ( $P < 0.01$ ,  $175 \pm 87$ ) when compared with room air ( $160 \pm 78$ ). The work was much larger when breathing CO<sub>2</sub> ( $P < 0.01$ ) than when breathing HeO<sub>2</sub> at maximal exercise.

In general, the elastic work of breathing was increased when breathing CO<sub>2</sub> (Fig. 5, panel B), which is consistent with the increase in V<sub>T</sub> and EILV when breathing CO<sub>2</sub> (Fig. 4). At maximal exercise the elastic work of breathing was increased when breathing HeO<sub>2</sub> as compared with breathing room air, which was probably related to the tendency to increase V<sub>T</sub>, although this would be in contrast to the lower EILV and EELV when

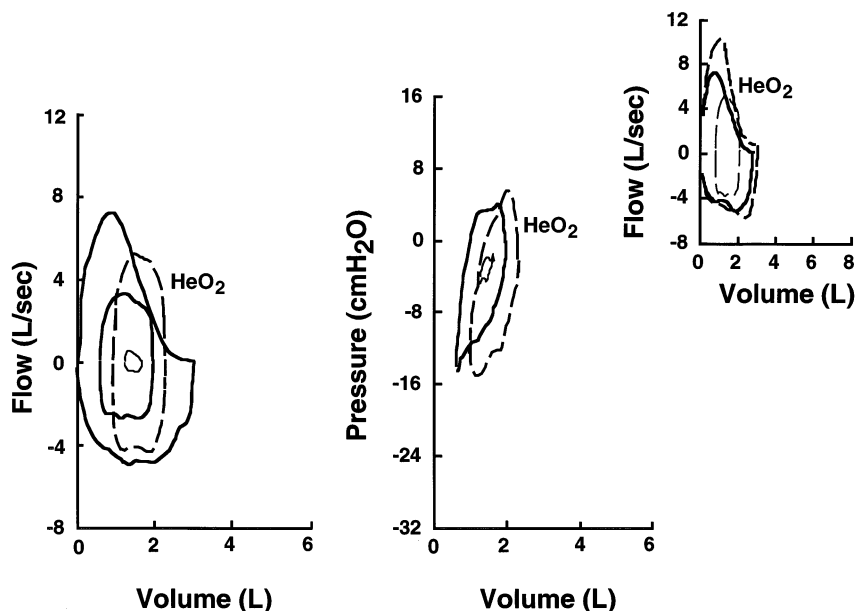


Fig. 3. Maximal and tidal flow-volume loops, and tidal pressure-volume loops for one typical subject. Maximal flow-loop measured while breathing room air (thinner solid line, left panel and right panel insert) and tidal flow-volume and pressure-volume loops measured at rest and during maximal exercise when breathing room air (thicker solid lines) and when breathing HeO<sub>2</sub> (thicker dashed line, thinner longer-dashed line in upper insert of right panel). The insert in the upper right hand corner of the right panel shows pre-exercise maximal flow-volume loops when breathing room air (solid line) and when breathing HeO<sub>2</sub> (dashed line). Average values for this subject at maximal exercise when breathing room air and HeO<sub>2</sub>, respectively: ventilation, 68 and 105 L/min; tidal volume, 1.35 and 1.36 L; breathing frequency, 51 and 77 bpm; total work of breathing against the lung, 78 and 144 J/min; end-expiratory lung volume, 51 and 44% of total lung volume; and expiratory airflow limitation, 0 and 0% of tidal volume.

breathing HeO<sub>2</sub> (Fig. 4). Even though EILV and EELV were lower when breathing HeO<sub>2</sub>, V<sub>T</sub> occurred over the linear portion of the lung pressure-volume curve, in contrast to that when breathing CO<sub>2</sub>. The resistive work of breathing tended to be greater when breathing CO<sub>2</sub> as compared with breathing room air, despite no change in f<sub>B</sub>. The tendency for greater resistive work when breathing CO<sub>2</sub> was consistent with the increase in expiratory airflow limitation when breathing CO<sub>2</sub>. Resistive work was less when breathing HeO<sub>2</sub> than when breathing room air, although  $\dot{V}_E$  was greater at maximal exercise (Fig. 5, panel C).

#### 4. Discussion

The findings of this study indicate that  $\dot{V}_E$  during maximal exercise can be increased as much

by resistive unloading (23%) as by inspiring 3% CO<sub>2</sub> (21%) in younger, relatively sedentary, subjects with normal lung function. Further, the ventilatory response to exercise above V<sub>Th</sub> can be increased by resistive unloading when compared with breathing room air, unlike that of CO<sub>2</sub> loading. This indicates that while both CO<sub>2</sub> (loading) and HeO<sub>2</sub> (resistive unloading of the airways) can increase  $\dot{V}_E$  during maximal exercise, the increase in  $\dot{V}_E$  when breathing HeO<sub>2</sub> is greater as ventilatory demand becomes greater (increase of 1.24 L at V<sub>Th</sub> and 19.1 L increase at maximal exercise). In contrast, breathing 3% inspired CO<sub>2</sub> increases  $\dot{V}_E$  similarly at V<sub>Th</sub> (14.6 L) as during maximal exercise (17.7 L), with the ventilatory response to exercise remaining similar to that when breathing room air. Therefore, CO<sub>2</sub> acts as an offset in ventilatory demand while HeO<sub>2</sub> changes the gain of the ventilatory response to heavy-to-maximal exercise. The implication of these findings is that

mechanical ventilatory constraints, even minimal, influence the gain of the ventilatory response to heavy-to-maximal exercise.

Below  $V_{Th}$ , the influence of mechanical unloading is absent in these subjects and the ventilatory response to exercise is increased as expected when breathing 3%  $CO_2$ . This finding suggests that, during subthreshold exercise, mechanical ventilatory reserves are greater than demand and do not influence the ventilatory response to exercise.

The increase in the  $\dot{V}_E$  during maximal exercise when breathing  $HeO_2$  is consistent with the find-

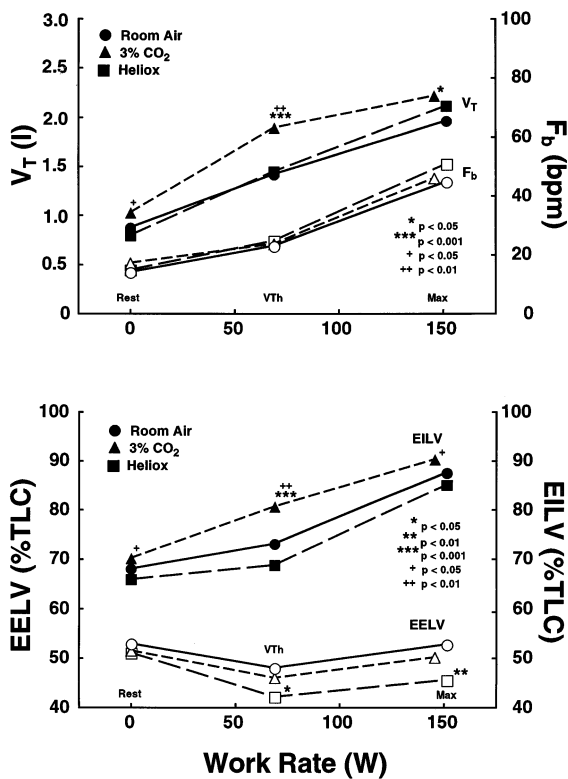


Fig. 4. Breathing pattern (A) and lung volumes (b) plotted against work rate (W) when the subjects were breathing room air (solid lines), 3%  $CO_2$  (shorter dashed lines), or  $HeO_2$  (longer dashed lines) at rest, ventilatory threshold ( $V_{Th}$ ), and maximal exercise (max). \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$  denote significant difference from room air condition. + $P < 0.05$  and ++ $P < 0.01$  denotes significance between  $CO_2$  and  $HeO_2$  conditions.  $V_T$ , tidal volume; fb, breathing frequency; EELV, end-expiratory lung volume (%TLC); EILV, end-inspiratory lung volume (%TLC).

Table 3  
Dynamic lung volumes

Variable	Test		
	Room air	$CO_2$	$HeO_2$
EELV (l)			
Rest	$2.9 \pm 0.8$	$2.8 \pm 0.8$	$2.9 \pm 0.9$
$V_{Th}$	$2.6 \pm 0.8$	$2.5 \pm 0.9$	$2.4 \pm 0.9^*$
Max	$2.8 \pm 0.7$	$2.7 \pm 0.9$	$2.6 \pm 1.0$
EILV (l)			
Rest	$3.7 \pm 1.1$	$3.8 \pm 1.0$	$3.7 \pm 1.1$
$V_{Th}$	$4.0 \pm 1.1$	$4.4 \pm 1.2^{**}$	$3.9 \pm 1.3^{++}$
Max	$4.8 \pm 1.3$	$5.0 \pm 1.4$	$4.7 \pm 1.5^+$

Values are mean  $\pm$  S.D. EELV, end expiratory lung volume; EILV, end inspiratory lung volume;  $V_{Th}$ , ventilatory threshold; Max, maximal exercise.

\* $P < 0.05$  significant difference from room air. \*\* $P < 0.01$  significant difference from room air. + $P < 0.05$  significant difference between  $CO_2$  and  $HeO_2$ . ++ $P < 0.01$  significant difference between  $CO_2$  and  $HeO_2$ .

ings of others (Spitler et al., 1980; Hussain et al., 1985; Brice et al., 1991). However, the increase in the ventilatory response to exercise has not been reported specifically before. The mechanism for the increase in  $\dot{V}_E$  when breathing  $HeO_2$  is unclear from these findings, but the findings of this study are in agreement with the findings of Ward et al. (1982) and the investigator's previous findings in older subjects (Babb, 1997). Because the ventilatory response to exercise was increased from  $V_{Th}$  to maximum exercise, it suggests that the increase in  $\dot{V}_E$  became greater as the ventilatory demand increased above  $V_{Th}$ . This would imply that the effect of resistive unloading of the airways becomes greater at higher flow rates, suggesting that the increase in  $\dot{V}_E$  with unloading is proportional to the decrease in mechanical impedance (decrease in airway resistance). This finding would also be consistent with the observations that  $\dot{V}_E$  is decreased when breathing a more dense gas such as that imposed by breathing room air at a raised air pressure (Hesser and Lind, 1984), or when breathing against an increased external resistance (Cerretelli et al., 1969). Again, these findings suggest that mechanical ventilatory constraints affect not only the physical limits to ventilatory capacity but also the control of  $\dot{V}_E$  during exercise as well as  $\dot{V}_E$  at maximum exercise.

The influence on  $\dot{V}_E$  by loading and unloading was not sufficient to limit exercise capacity, since all of the subjects had a normal exercise capacity when breathing room air,  $\text{CO}_2$ , or  $\text{HeO}_2$ . For these younger subjects, aerobic capacity appears

to be less than ventilatory capacity. This would appear to be in contrast to the findings in the older subjects studied previously (Babb, 1997), who at maximal exercise had more ventilatory constraints when breathing room air and, therefore, less reserve for accommodating an increase in ventilatory demand. It was only by unloading the mechanical constraints of the respiratory system that  $\dot{V}_E$  could be increased slightly in the older subjects. Although the older subjects had no frank signs of mechanical ventilatory limitation to exercise (retention of  $\text{CO}_2$  or reduced exercise capacity), they did approach maximal expiratory flow both when breathing room air and when breathing 3%  $\text{CO}_2$ . In either case (younger or older), it is probably reasonable to suggest that exercise capacity is influenced by mechanical ventilatory factors, or to suggest that at least  $\dot{V}_E$  at maximal exercise is affected by respiratory mechanical constraints. The mechanism by which this influence is mediated is unclear.

Respiratory mechanics measurements were also altered by inspired  $\text{CO}_2$  and resistive unloading of the airways. Flow limitation during maximal exercise was greater when breathing  $\text{CO}_2$  than when breathing room air or when breathing  $\text{HeO}_2$ , and EELV was lower during maximal exercise when breathing  $\text{HeO}_2$  than when breathing room air or when breathing  $\text{CO}_2$ . The work of breathing against the lung during maximal exercise was increased when breathing  $\text{CO}_2$  and when breathing  $\text{HeO}_2$ , although the increase in work was much greater when breathing  $\text{CO}_2$  than when breathing  $\text{HeO}_2$ . The increase in the work of breathing was mainly related to increased resistive work, which was related to the increased magnitude of airflow limitation when breathing  $\text{CO}_2$ . However, the elastic work of breathing was increased when breathing  $\text{CO}_2$ , which was related to both the increase in  $V_T$  and in EILV. These results indicate that mechanical ventilatory constraints influence the regulation of respiratory mechanics (lung volume, flow, and pressure) during exercise even in younger subjects with normal lung function, who have minimal if no mechanical ventilatory limitations during maximal exercise. The mechanism for this influence is unclear but appears to be associated with the magnitude of

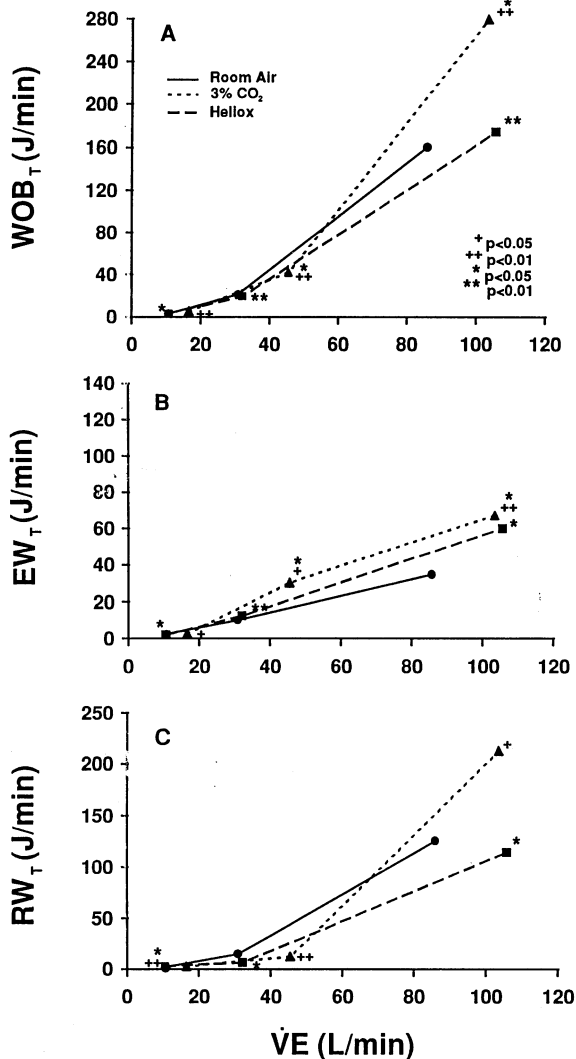


Fig. 5. Total work of breathing against the lung per min ( $\text{WOB}_T$ , A), total elastic work of breathing ( $\text{EW}_T$ , B), and total resistive work of breathing ( $\text{RW}_T$ , C) plotted against ventilation ( $\dot{V}_E$ ) at rest, ventilatory threshold ( $V_{Th}$ ), and maximal exercise (max), when breathing room air (solid lines), 3%  $\text{CO}_2$  (dashed lines), and  $\text{HeO}_2$  (longer dashed lines).  $n = 5$ , \* $P < 0.05$  and \*\* $P < 0.01$  denote significant difference from room air condition. + $P < 0.05$  and ++ $P < 0.01$  denote significance between  $\text{CO}_2$  and  $\text{HeO}_2$  conditions.

expiratory airflow limitation, which is actually related to the amount by which expiratory pressure approaches or exceeds the minimal pressure for maximal expiratory flow ( $P_{crit}$ ). However, the mechanism may also be related to the work of breathing and indirectly to the respiratory impedance to  $\dot{V}_E$ . However, recent work by Krishnan et al. (1996) suggests that mechanically unloading the respiratory muscles has little effect on the control of  $\dot{V}_E$  during heavy exercise unlike that of breathing  $HeO_2$ .

The increase in  $\dot{V}_E$  during exercise when breathing  $CO_2$  is consistent with the findings of others also (Clark et al., 1980; Poon, 1992).  $\dot{V}_E$  was shown to be increased as much when breathing 3%  $CO_2$  as when breathing was mechanically unloaded. Also, the ventilatory response to heavy-to-maximal exercise tended to be increased when breathing 3%  $CO_2$  and was increased when breathing was unloaded. However, in the older subjects studied previously (Babb, 1997) the ventilatory response to exercise when breathing 3%  $CO_2$  was not increased over that of room air (0.66 vs. 0.72 L/min/W, respectively), which is in agreement with the findings of others when comparing younger and older subjects (Poon, 1992).  $\dot{V}_E$  at maximal exercise was not increased either in the older subjects. Also, in subjects with lower maximal expiratory flows, it was observed that the ventilatory response to exercise above  $V_{Th}$  was decreased when breathing 3%  $CO_2$  (0.40 breathing  $CO_2$  and 0.57 breathing room air, L/min/W). It has been shown that inspired  $CO_2$  increases  $\dot{V}_E$  less as ventilatory demand becomes higher, such as during near maximal exercise (Milic-Emili and Tyler, 1963; Clark et al., 1980). It would appear that the reason for the progressive flattening of the ventilatory response to heavy-to-maximal exercise or increasing concentrations of  $CO_2$  during heavy exercise is related to approaching mechanical ventilatory constraints. In the present study, however, respiratory mechanics were only minimally approached, at least in regard to expiratory airflow limitation and EILV. This may explain why the subjects were able to increase  $\dot{V}_E$  and the ventilatory response to exercise above  $V_{Th}$  when breathing 3%  $CO_2$ . The data from this study, and that of earlier studies, support the conclusion that

the ventilatory response to exercise, as well as that to  $CO_2$ , can be affected by mechanical ventilatory constraints, if ventilation reaches a level where mechanical limits are minimally approached. This includes older individuals and individuals with mildly reduced maximal expiratory flows. This is in agreement with the findings of others (Milic-Emili and Tyler, 1963; Clark et al., 1980; Poon, 1992). This appears to be true for young subjects (Clark et al., 1980), middle-aged adults (Poon, 1992), and older fit adults (Johnson et al., 1991), depending on the magnitude of the load and the level of pulmonary function. The mechanism for the attenuation of the ventilatory response to exercise remains unclear as the present study provides no mechanistic insight. However, it does suggest that mechanical limitations affect not only the physical limits to ventilatory capacity but also the control of  $\dot{V}_E$  during exercise. This may be related to the magnitude of tidal expiratory airflow limitation, the lung volume adopted during exercise, the dynamic demand on respiratory muscles, and/or the work of breathing.

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