Ventilatory response to exercise in subjects breathing CO_2 or HeO_2

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Babb, T. G. Ventilatory response to exercise in subjects breathing CO_2 or HeO_2. *J. Appl. Physiol.* 82(3): 746–754, 1997.—To investigate the effects of mechanical ventilatory limitation on the ventilatory response to exercise, eight older subjects with normal lung function were studied. Each subject performed graded cycle ergometry to exhaustion once while breathing room air; once while breathing 3% CO_2-21% O_2-balance N_2; and once while breathing HeO_2 (79% He and 21% O_2). Minute ventilation ($\dot{V}_E$) and respiratory mechanics were measured continuously during each 1-min increment in work rate (10 or 20 W). Data were analyzed at rest, at ventilatory threshold (VTh), and at maximal exercise. When the subjects were breathing 3% CO_2, there was an increase ($P < 0.001$) in $\dot{V}_E$ at rest and at VTh but not during maximal exercise. When the subjects were breathing HeO_2, $\dot{V}_E$ was increased ($P < 0.05$) only during maximal exercise (24 ± 11%). The ventilatory response to exercise below VTh was greater only when the subjects were breathing 3% CO_2 ($P < 0.05$). Above VTh, the ventilatory response when the subjects were breathing HeO_2 was greater than when breathing 3% CO_2 ($P < 0.01$). Flow limitation, as percent of tidal volume, during maximal exercise was greater ($P < 0.01$) when the subjects were breathing CO_2 (22 ± 12%) than when breathing room air (12 ± 9%) or when breathing HeO_2 (10 ± 7%) ($n = 7$). End-expiratory lung volume during maximal exercise was lower when the subjects were breathing HeO_2 than when breathing room air or when breathing CO_2 ($P < 0.01$). These data indicate that older subjects have little reserve for accommodating an increase in ventilatory demand and suggest that mechanical ventilatory constraints influence both the magnitude of $\dot{V}_E$ during maximal exercise and the regulation of $\dot{V}_E$ and respiratory mechanics during heavy-to-maximal exercise.

mechanical ventilatory limitations to exercise; control of breathing during exercise; exercise in the aged; ventilatory capacity in the aged

RECENTLY, IT WAS OBSERVED that patients with lower maximal expiratory flows have little reserve for accommodating an increase in ventilatory demand when compared with age-matched subjects with higher flows (4). It appeared that, when confronted with an increased ventilatory demand (3% inspired CO_2), these lower flow subjects increased minute 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 affects not only the mechanical limits to ventilatory output but also the regulation of ventilation during heavy-to-maximal 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 was recruited for study. Older subjects were selected because they approach mechanical ventilatory limitations during exercise more so than do younger subjects, but to a lesser degree than patients with mild chronic airflow limitation (12). As part of the study, the subjects were asked to breathe either room air, a gas mixture containing 3% CO_2-21% O_2-balance N_2, or a helium-oxygen mixture (HeO_2; 21% O_2-79% He) during exercise. The purpose of the inspired CO_2 was to increase ventilatory demand during exercise, and the purpose of the HeO_2 mixture was to reduce the resistive load to $\dot{V}_E$, which, in essence, lessens the mechanical ventilatory constraints to $\dot{V}_E$. It was hypothesized that the subjects would not experience an increase in their ventilatory response to heavy-to-maximal exercise when ventilatory demand was augmented by inspired CO_2 but that with resistive unloading of the airways (HeO_2) they would be able to increase their ventilatory response to heavy-to-maximal exercise. These two outcomes, taken together in the same subjects, would demonstrate that, even with an increase in chemical drive, $\dot{V}_E$ could not be increased as much if the system were mechanically unloaded (decreased mechanical ventilatory constraints). Although it has been shown that inspired CO_2 increases $\dot{V}_E$ less as ventilatory demand becomes higher, such as during near-maximal exercise (9, 17), $\dot{V}_E$ has not been shown to be increased more, in the same subjects, when breathing is mechanically unloaded. Furthermore, although it has been suggested that the reason for the progressive flattening of the ventilatory response to increasing concentrations of CO_2 during heavy exercise is related to approaching mechanical ventilatory constraints, respiratory mechanics measurements have not been made in these studies (9, 17). Similarly, although flow-volume limitations have been shown at maximal exercise during inhalation of 4 or 5% CO_2, where $\dot{V}_E$ failed to increase significantly (13, 14), these results were obtained from fit subjects (younger and older), who exercised regularly and who could exercise at very high exercise capacities where higher relative ventilatory demands might be expected, unlike otherwise sedentary subjects, such as the ones recruited for this study. Also, these subjects were not mechanically unloaded to see whether their $\dot{V}_E$ could be increased further.

It was also hypothesized that, during submaximal exercise, when mechanical ventilatory limitations are not usually approached, the ventilatory response to exercise when the subjects were breathing inspired CO_2 would be increased over that when they were breathing room air, but the response when the subjects were breathing HeO_2 would be similar to that of room air. Although it has been suggested that HeO_2 may stimulate breathing during submaximal exercise, this has not been determined both below and above VTh for older subjects who approach mechanical limitations during heavy exercise, nor have respiratory mechanics been measured in the same subjects when they were breathing room air in comparison with breathing CO_2 or HeO_2.

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 for the last 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 alcohol for a least 2 h before exercise testing.

Volunteers were accepted for study if their forced vital capacity and forced expiratory volume in 1 s 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. Of the volunteers, three never smoked, whereas five were former smokers [22 ± 20 (SD) pack·yr, where pack·yr is no. of packs/yr × years of smoking; years since quitting 25 ± 18].

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 (3). Also, American Thoracic Society standards were used to determine normal pulmonary function (2). Predicted values were based on norms by Knudson et al. (15).

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 by using an esophageal balloon placed ~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 in real time (66 Hz) on a personal computer (NEC) for subsequent analysis.

Isovolume pressure-flow curves were constructed from data collected while the subjects performed multiple vital capacities of various efforts (graded flow-volume curves) (18). The minimum pressure necessary to obtain maximal flow (Pcrit) was determined from the isovolume pressure-flow curves at 75, 50, 35, and 25% of forced vital capacity. These data were used in conjunction with maximal expiratory flow-volume curves and exercise tidal flow-volume loops to confirm expiratory flow limitation (see below).

Study protocol. After screening pulmonary function tests, electrocardiogram (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-balance N_2, or a mixture of 21% O_2-79% He. The order of the room air and CO_2 tests was randomized. The HeO_2 test was performed last. However, the subjects were not told what results we expected during the test, but they were told what gas mixture they were breathing.

Gas-exchange measurements. Measurements of O_2 uptake ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) 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 mouth port and were analyzed with a mass spectrometer (Marquette Electronics, model 1100). Calibration of the analyzer was performed by using reference gases before each test. 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-liter 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 was $<1\ cmH_2O \cdot l^{-1} \cdot s$ 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 (6, 24) and a plot of lactic acid vs. work rate, when available. VTh was designated as the work rate that was most congruent among the different threshold-determination methods.

Blood samples. Measurement of arterial blood gases and blood lactate concentrations was made on blood samples drawn from an indwelling arterial catheter. The catheter was placed in the radial artery and connected to extension tubing, which allowed sampling during exercise with minimal disturbance to the subject. Each blood-gas sample was drawn into a heparinized syringe, placed in an ice bath, and taken to the laboratory for analysis. An additional 2-ml sample was drawn for the analysis of lactate concentration. These samples were immediately placed in 2-ml containers containing potassium oxalate and sodium fluoride. The whole blood samples were analyzed with the use of a Yellow Springs blood lactate analyzer (model 2300 Stat plus).

Expiratory and inspiratory flow measurements. To measure both expiratory and inspiratory flow and $\dot{V}E$, tidal volume (VT), and breathing frequency (f_b) 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, model 4813; Validyne pressure transducers, model MP45, $\pm 2\ cmH_2O$, 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 bidirectional 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 by using known flow rates and different gas mixtures. Calibration of volume was checked before each test by using a calibrated syringe. Flow and volume were displayed on a strip-chart recorder (AstroMed, model MT 95000) and sampled in real time (100 Hz) on a computer (486Dx).

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 with a differential pressure transducer (Validyne pressure transducer, model MP45, $\pm 100\ cmH_2O$, and model CD19A amplifiers). Ptp and oral pressure were displayed on a strip-chart recorder (AstroMed, model

MT 95000) and sampled in real time (100 Hz) on a computer (486Dx).

Inspiratory capacity (IC) was measured at rest and during the 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 with maximal static recoil pressure determined at baseline. It was assumed that TLC does not change significantly during exercise (22, 25). 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) × 100]. End-inspiratory lung volume (EILV) was calculated (EILV = EELV + VT) and expressed as a percentage of TLC [(EILV/TLC) × 100].

Inspired-gas mixtures. During rest and exercise, inspired gas was provided from a large inspiratory reservoir. The inspiratory reservoir was 2,300 liters and was made of 4-mm polyethylene that was heat sealed and taped. The bag was filled with either room air or 3% CO_2-21% O_2-balance N_2. The gas was mixed from separate CO_2, O_2, and N_2 gas tanks via a gas partitioner with three individual flowmeters (Cole Parmer, model 34–39). The gas mixture flowed through a heated cascade humidifier (Bennett) into the reservoir. The humidifier 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_2 exercise tests, so that the subjects were blinded to the gas mixture they were breathing. A smaller reservoir was continuously filled with the HeO_2 mixture, which was at room temperature and humidified.

Exercise protocol. All the 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 (MedGraphics, model CPE 2000). Exercise began at 10 W for the women or 20 W for the men and was incremented by 10 or 20 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_2 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. At each work rate, ECG was monitored continuously through the use of 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 taken with the use of the procedures outlined by American College of Sports Medecine (1) and were recorded at each work rate during the exercise test. Arterial blood gases and lactate concentrations were determined at rest, during each work rate, at maximal exertion, and during recovery.

Maximal and tidal 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 whether exercise had induced bronchodilation, which none of the subjects experienced.

Data analysis. VT, f_b, 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 a 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 before the IC. Also calculated was expiratory flow limitation. Expiratory flow limitation was defined as the percentage of VT, where tidal expiratory flow impinged on maximal expiratory flow and where Ptp simultaneously exceeded Pcrit. 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) (16). The work of breathing was then further partitioned into resistive and elastic components. Data were analyzed at rest, at VTh, and during maximal exercise.

The ventilatory response to exercise was determined below and above VTh by least squares regression. The slope of $\dot{V}E$ vs. work rate was calculated on all the points between rest and VTh (4.2 ± 0.8 points for all three tests), and between VTh and maximal exercise (5.8 ± 0.8, 5.5 ± 0.8, and 5.8 ± 0.8 points for the room air, CO_2, and HeO_2 tests, respectively). The average R^2 below VTh was 0.97 ± 0.03, 0.98 ± 0.03, and 0.98 ± 0.03, and above VTh, the average was 0.96 ± 0.02, 0.98 ± 0.02, and 0.94 ± 0.05 for the room air, CO_2, and HeO_2 tests, respectively. 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 $\dot{V}CO_2$ so that comparisons could be made among the room air, CO_2, and HeO_2 tests, where it was not possible to make gas-exchange measurements.

A one-way analysis of variance for repeated measures was used to test for differences among conditions (room air, CO_2, and HeO_2). Multiple contrasts were used to test among the three conditions when significant *F* ratios were detected with the one-way analysis of variance. When the difference between only two means was to be tested (i.e., maximal $\dot{V}O_2$ between room air and CO_2 tests), paired *t*-tests were used. Relationships among physiological variables were analyzed by Pearson correlation coefficients.

RESULTS

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_2, and HeO_2 tests. As stated above, gas-exchange measurements were not possible when the HeO_2 mixture was breathed. All the subjects had a normal exercise capacity based on $\dot{V}O_2$ and heart rate, as expressed as a percentage of predicted. In general, exercise capacity was slightly less when the subjects were breathing 3% CO_2 and slightly increased when they were breathing HeO_2, at least when based on exercise time. Ratings of perceived exertion and ratings of perceived breathlessness were not different at maximal exercise.

Table 1. *Physical characteristics and pulmonary function of subjects*

Age, yr	Height, cm	Weight, kg	FVC, %pred	FEV_1, %pred	FEV_1/FVC, %	MVV, %pred	RV/TLC, %	TLC, %pred	DL_{CO}, %pred
68 ± 2	170 ± 6	69 ± 10	116 ± 20	104 ± 16	72 ± 5	110 ± 14	37 ± 6	114 ± 16	114 ± 17

Values are means ± SD. Subjects were 5 men and 3 women. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity; DL_{CO}, diffusing capacity; %pred, % predicted.

Ventilation at rest, VTh, and maximal exercise. $\dot{V}_E$ at rest, VTh, and maximal exercise when the subjects were breathing room air, 3% CO_2, or HeO_2 are shown in Fig. 1, where $\dot{V}_E$ is plotted against work rate. $\dot{V}_E$ at rest ($P < 0.001$) and at VTh ($P < 0.01$) was significantly higher when the subjects were breathing 3% CO_2 (82 ± 24 and 49 ± 20% increase over room air; mean ± SD, respectively) than when the subjects were breathing room air or HeO_2. During maximal exercise, $\dot{V}_E$ was larger ($P < 0.05$) only when the subjects were breathing the HeO_2 mixture (24 ± 11% increase over room air). Therefore, the subjects were able to increase $\dot{V}_E$ during maximal exercise more with resistive unloading than when they were breathing 3% CO_2 (4 ± 13%). The increase in $\dot{V}_E$ when the subjects were breathing HeO_2 was equally associated with increases in both V_T and f_b (~12% each); however, the increases failed to reach significance ($P > 0.05$). Despite the changes in $\dot{V}_E$, ratings of perceived exertion and ratings of perceived breathlessness were not different among any of the conditions.

Ventilatory response to exercise. The ventilatory response to exercise above VTh (Fig. 1) was significantly greater ($P < 0.01$) when the subjects were breathing HeO_2 (0.89 ± 0.22 $l \cdot min^{-1} \cdot W^{-1}$) than when the subjects were breathing 3% CO_2 (0.66 ± 0.17 $l \cdot min^{-1} \cdot W^{-1}$), but only tended to be greater than when the subjects were breathing room air (0.72 ± 0.18 $l \cdot min^{-1} \cdot W^{-1}$; $P = 0.0574$). The ventilatory response to exercise below VTh when the subjects were breathing 3% CO_2 (0.52 ± 0.17 $l \cdot min^{-1} \cdot W^{-1}$) was significantly greater ($P < 0.05$) than when the subjects were breathing room air (0.39 ± 0.11 $l \cdot min^{-1} \cdot W^{-1}$) but was not greater than when the subjects were breathing HeO_2 (0.48 ± 0.16 $l \cdot min^{-1} \cdot W^{-1}$).

Table 2. *Maximal exercise*

Variable	Test		
	Room air	CO_2	HeO_2
Workload, W	124 ± 42	116 ± 38§	129 ± 41
Time, min	7.4 ± 1.0	7.1 ± 1.1§	7.8 ± 1.0†
$\dot{V}O_2$, %pred	129 ± 22	117 ± 25*	
HR, %pred	98 ± 6	95 ± 7*	98 ± 6§
$\dot{V}_E$/MVV, %	72 ± 9	73 ± 14	
Lactate, mM	7.3 ± 0.6	6.2 ± 1.8	7.7 ± 1.9
VTh, %$\dot{V}O_{2max}$	58 ± 10		
RPE (6–20)	19 ± 1	18 ± 1	18 ± 1
RPB (0–10)	9 ± 2	10 ± 2	9 ± 1
RER	1.27 ± 0.11	1.16 ± 0.08*	

Values are means ± SD; $n = 8$ except for lactate where $n = 5$. $\dot{V}O_2$, O_2 uptake; HR, heart rate; $\dot{V}_E$, minute ventilation; VTh, ventilatory threshold; $\dot{V}O_{2max}$, maximal $\dot{V}O_2$; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; RER, respiratory exchange ratio. *$P < 0.05$ and †$P < 0.01$ denote significant differences from room air test. §$P < 0.01$ denote significant differences between CO_2 and HeO_2 tests.

Arterial P_{CO_2} at rest, VTh, and maximal exercise. It was possible to place arterial catheters in all three conditions in only five of the subjects. These results are shown in Fig. 2. These results were used to indicate the adequacy of ventilation when the subjects were breathing room air, 3% CO_2, or HeO_2 during exercise below and above VTh. There was a significant increase in arterial P_{CO_2} (Pa_{CO_2}) at rest ($P < 0.05$), VTh ($P < 0.001$), and maximal exercise ($P < 0.001$) when the subjects were breathing 3% CO_2. When the subjects were breathing HeO_2, Pa_{CO_2} was similar to that when they were breathing room air, except at maximal exercise when it was significantly less ($P < 0.05$). These data support the tendency for the subjects to maintain a constant Pa_{CO_2} during submaximal exercise but to reduce Pa_{CO_2} during maximal exercise when the subjects were breathing room air. The tendency for Pa_{CO_2} to increase during both submaximal and maximal exercise when the subjects were breathing 3% CO_2 indicates that $\dot{V}_E$ was not increased sufficiently to maintain even the resting level of Pa_{CO_2} during submaximal or maximal exercise. On the other hand, resistive unloading did provide an increased ventilatory output sufficient to lower Pa_{CO_2} during maximal exercise, which was lower than when the subjects were breathing room air.

Although it was not a focus of the study to measure the ventilatory response to CO_2, these calculations were determined at VTh for the subjects who had arterial lines ($n = 5$). The range was 0.88–4.11 $l \cdot min^{-1} \cdot Torr^{-1}$, with a mean value of 2.36 ± 1.27 (SD) $l \cdot min^{-1} \cdot Torr^{-1}$, which is within the expected normal range.

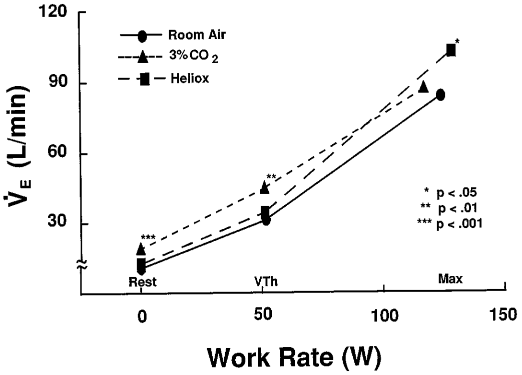


Fig. 1. Ventilatory response to exercise when subjects were breathing room air, 3% CO_2, or HeO_2 (Heliox). $\dot{V}_E$, minute ventilation (l/min); ●, room air; ▲, 3% CO_2-21% O_2-balance N_2; ■, 79% He-21% O_2 at rest, ventilatory threshold (VTh), and maximal exercise (Max). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ denote significant differences from room air condition. Values are means ± SD for, respectively, room air, CO_2, and HeO_2: rest $\dot{V}_E$ = 10 ± 3, 19 ± 5, 11 ± 2 l/min; VTh $\dot{V}_E$ = 31 ± 12, 45 ± 16, 34 ± 10 l/min; maximal $\dot{V}_E$ = 83 ± 21, 87 ± 25, 102 ± 25 l/min; $\dot{V}_{th}$ work rate = 51 ± 25 for all conditions; and maximal work rates = 124 ± 42, 116 ± 38, 129 ± 41 W, respectively.

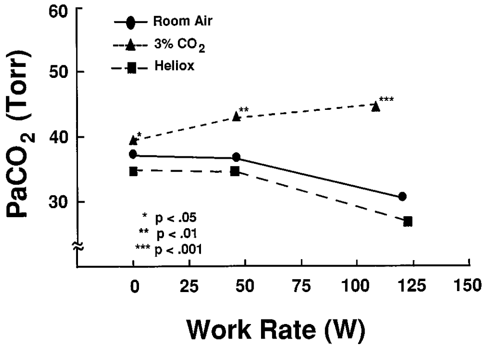


Fig. 2. Plot of arterial CO_2 (Pa_{CO_2}) at rest, VTh, and maximal exercise when subjects were breathing room air (●), 3% CO_2 (▲), and HeO_2 (79% He-21% O_2; ■). $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ denote significant differences from room air condition ($n = 5$).

Breathing mechanics. In Fig. 3, tidal flow-volume loops measured during maximal exercise are shown relative to the maximal flow-volume loop for one subject. Inspection of the exercise tidal flow-volume loops relative to maximal flow-volume loops indicated that the subject had less ventilatory reserve in which to accommodate the augmented ventilatory demand when the subject was breathing CO_2 (Fig. 3*A*), than when breathing the HeO_2 (Fig. 3*B* and *inset*). During maximal exercise when the subject was breathing room air, he did not impinge on his maximal expiratory flow-volume curve; but when he was breathing CO_2, the subject impinged on his maximal expiratory flow-volume curve over roughly 23% of V_T. When the subject was breathing HeO_2 (Fig. 3*B* and *inset*), the subject was able to augment $\dot{V}_E$ during maximal exercise over that possible when he was breathing room air.

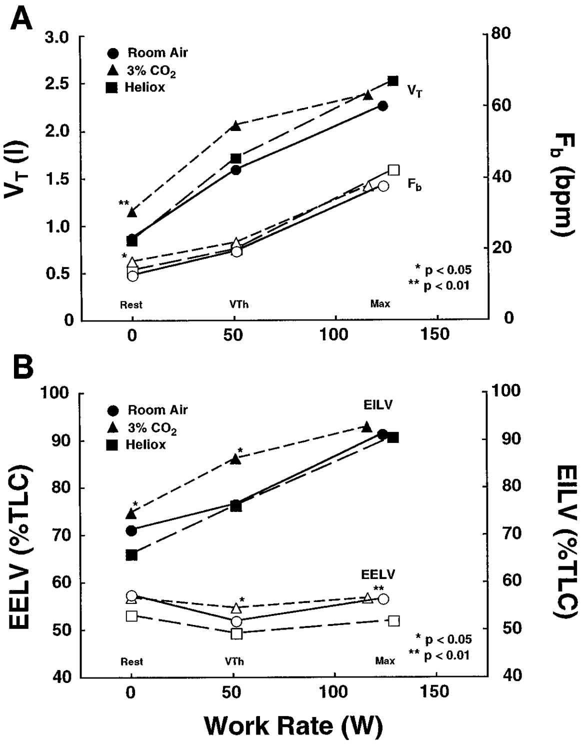
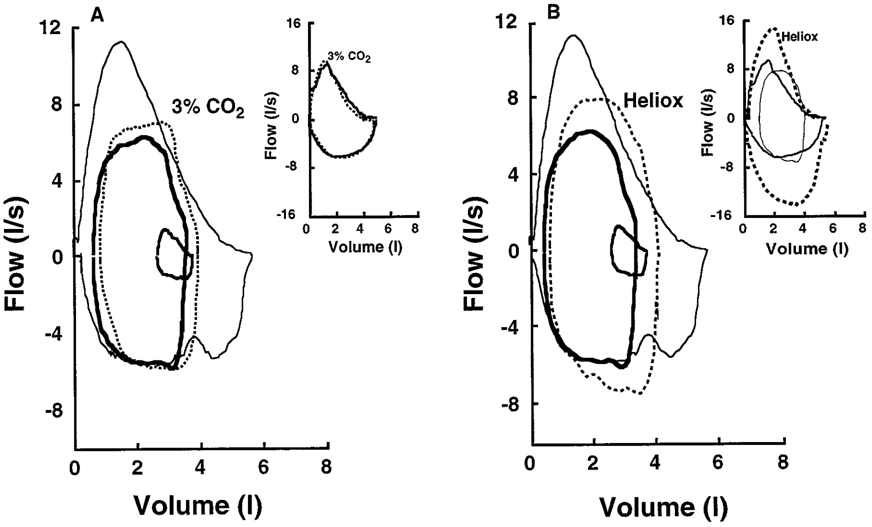


Fig. 4. Breathing pattern (*A*) and lung volumes (*B*) plotted against work rate when subjects were breathing room air (circles and solid lines), 3% CO_2 (triangles and short-dashed lines), or HeO_2 (squares and long-dashed lines) at rest, VTh, and Max. V_T, tidal volume; f_b, breathing frequency in beats/min (bpm); EELV, end-expiratory lung volume; %TLC, %total lung capacity; EILV, end-inspiratory lung volume. $^*P < 0.05$ and $^{**}P < 0.01$ denote significant differences among means.

This subject was less typical than the other subjects, who, on average, had expiratory airflow limitation of 4.3 ± 5.4% of V_T at VTh and 11.7 ± 9.3% of V_T at maximal exercise when they were breathing room air ($n = 7$, see subject in Figs. 6 and 7). When the subjects were breathing HeO_2, they had no expiratory airflow limitation at VTh and only 10.1 ± 7.1% V_T at maximal exercise, which was similar to that at room air, although $\dot{V}_E$ was higher when the subjects were breathing HeO_2. When the subjects were breathing CO_2, 9.1 ± 11.5% V_T had expiratory airflow limitation at VTh and significantly more limitation at maximal exercise than when the subjects were breathing room air ($P < 0.05$) or HeO_2 ($P < 0.01$), with 22.1 ± 12.6% V_T.

Fig. 3. Maximal and tidal flow-volume loops for one subject. Maximal flow loops measured at rest (thinner solid lines, *A* and *B*), and tidal flow-volume loops measured during maximal exercise when subject was breathing room air (thicker solid line), when breathing 3% CO_2 (thicker dashed line, *A*), and when breathing HeO_2 (thicker dashed line in *B* and solid thinner line in *inset* in *B*). Small loops are resting tidal flow-volume loops when subject breathed room air (*A* and *B*). *Insets* in *A* and *B*, *top right*, show preexercise maximal flow-volume loops when subject was breathing room air (solid line), when breathing 3% CO_2 (dashed line), or when breathing HeO_2 (dashed line). Values are for, respectively, room air, CO_2, and HeO_2: $\dot{V}_E$ = 124, 123, 159 l/min; tidal volume = 2.84, 3.06, 3.49 liters; expiratory airflow limitation = 0, 23, 8% of tidal volume; and Pa_{CO_2} = 29, 47, 24 Torr.



V_T and f_b are plotted against work rate in Fig. 4*A*, and EELV and EILV are plotted against work rate in Fig. 4*B*. V_T ($P < 0.01$) and f_b ($P < 0.05$) were significantly higher at rest when the subjects were breathing CO_2. At VTh and maximal exercise, there were no significant differences among the gas mixtures, although there was a tendency for V_T and f_b both to be greater when the subjects were breathing HeO_2. EELV was significantly lower when the subjects were breathing HeO_2 than when breathing CO_2 at VTh ($P < 0.05$) and lower than both when the subjects were breathing room air and when breathing CO_2 at maximal exercise ($P < 0.01$). EILV was significantly higher when the subjects were breathing CO_2 than when breathing HeO_2 at rest ($P < 0.05$) and when the subjects were breathing room air and when breathing CO_2 at VTh ($P < 0.05$). Overall, EELV tended to be lower when the subjects were breathing HeO_2 and higher when breathing CO_2. EILV tended to be increased when the subjects were breathing CO_2. In Table 3, EELV and EILV are presented in liters for all three conditions at rest, VTh, and maximal exercise.

The total work of breathing against the lung is shown in Fig. 5*A*, and the elastic and resistive components of the total work of breathing are shown in Fig. 5, *B* and *C*, respectively. The total work of breathing was increased when the subjects were breathing CO_2, but not when they were breathing HeO_2, although $\dot{V}_E$ was significantly greater ($P < 0.05$) when the subjects were breathing HeO_2. The elastic work of breathing was increased at rest and at VTh when the subjects were breathing CO_2, which is consistent with the tendency to increase V_T when the subjects were breathing CO_2. The resistive work of breathing was increased at rest, VTh, and maximal exercise when the subjects were breathing CO_2, as compared with breathing room air, despite no change in f_b. Therefore, the increase in the resistive work when the subjects were breathing CO_2 is probably related to the increased magnitude of airflow limitation present when the subjects were breathing CO_2. This suggestion is supported by the findings observed when the subjects were breathing HeO_2, when the resistive work of breathing was not significantly different from that when the subjects were breathing room air, although $\dot{V}_E$ was higher when the subjects were breathing HeO_2. The effect of breathing HeO_2 was to unload the system by decreasing the resistance to flow and the amount of airflow limitation, which at a greater $\dot{V}_E$ required the same work of breathing as when the subjects were breathing room air.

Table 3. *Dynamic lung volumes*

	Test		
	Room Air	CO_2	HeO_2
EELV, liters			
Rest	3.6 ± 1.1	3.6 ± 1.0	3.4 ± 0.7
VTh	3.3 ± 0.8	3.5 ± 0.8	3.1 ± 0.6‡
Max	3.6 ± 0.7	3.6 ± 0.6	3.3 ± 0.7*§
EILV, liters			
Rest	4.6 ± 1.1	4.8 ± 1.1	4.2 ± 0.8‡
VTh	4.9 ± 0.9	5.5 ± 1.2†	4.8 ± 0.6‡
Max	5.8 ± 1.1	6.0 ± 1.2	5.8 ± 1.2

Values are means ± SD. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; 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.

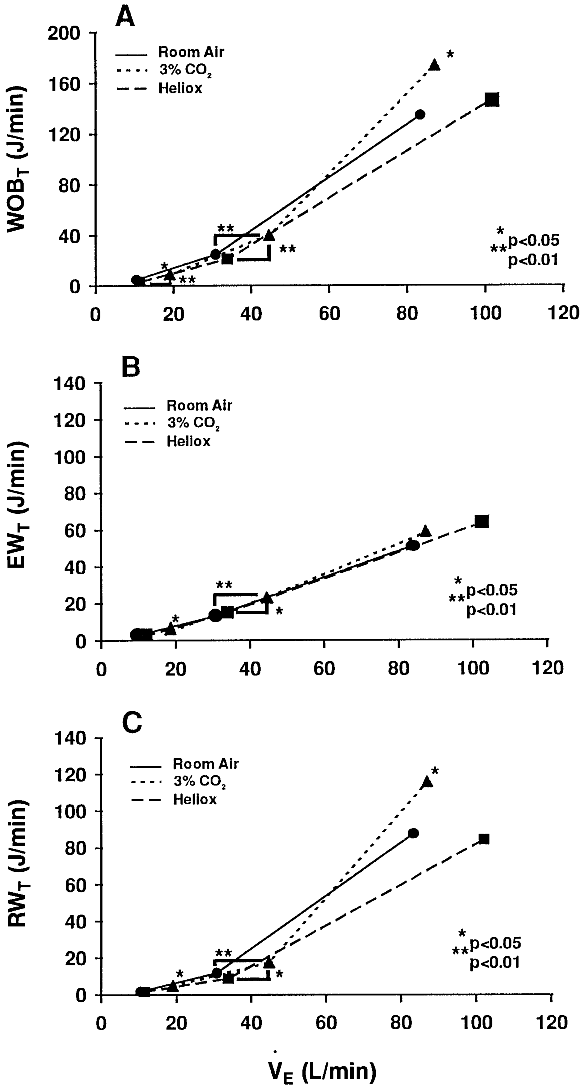


Fig. 5. Total work of breathing per minute (WOB$_T$; *A*), total elastic work of breathing (EW$_T$; *B*), and total resistive work of breathing (RW$_T$; *C*) against lung (J/min) plotted against $\dot{V}_E$ at rest, VTh, and Max when subjects were breathing room air (●), 3% CO_2 (▲), and HeO_2 (■). *$P < 0.05$ and **$P < 0.01$ denote significant differences among means.

To demonstrate the differences in the mechanical loads when the subjects were breathing room air, CO_2, or HeO_2, flow-volume and pressure-volume loops at maximal exercise are plotted for one typical subject for all three gas-mixture conditions (Figs. 6 and 7). In Fig. 6*B*, note that the pressure-volume loops were similar when the subject was breathing room air and when breathing HeO_2; however, as noted in the legend, the $\dot{V}_E$ was greater when the subject was breathing the HeO_2. Also, EELV was lower when the subject was breathing the HeO_2, which was also probably related to the reduced magnitude of airflow limitation, since it

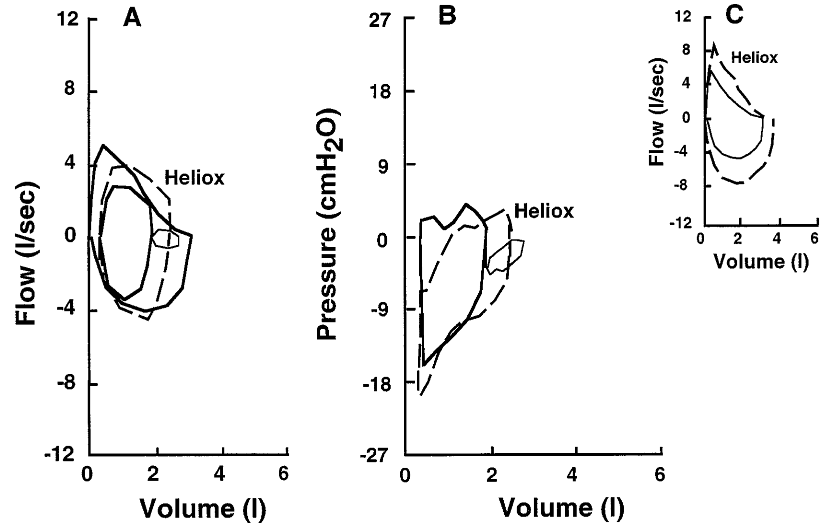


Fig. 6. Maximal and tidal flow-volume and pressure-volume loops for typical subject breathing room air or HeO_2. Maximal-flow loops were measured at rest (*A* and *C*) and tidal flow-volume loops were measured during maximal exercise, when subject was breathing room air (thicker solid line) and when breathing HeO_2 (thicker dashed line, *A*). Tidal pressure-volume loops were measured during maximal exercise, when subject was breathing room air (thicker solid line) and when breathing HeO_2 (thicker dashed line, *B*). Small loops are resting tidal loops when subject was breathing room air (*A* and *B*). Values are for, respectively, room air and HeO_2: V̇E = 58 and 80 l/min; VT = 1.57 and 2.06 liters; total work of breathing = 80 and 91 J/min; and expiratory airflow limitation = 15 and 19% of VT.

has been shown that EELV rises when airflow limitation occurs. When the subject was breathing CO_2, the pressure-volume loops are larger, which appears to be the result of an increase in airflow limitation when compared with breathing room air. This appears correct, especially since f_b is not increased enough to contribute to an increase in breathing resistance. The airflow limitation also tends to influence the EELV and EILV during exercise, which were increased at VTh when the subject was breathing 3% CO_2.

DISCUSSION

The findings of this study indicate that V̇E during maximal exercise can be increased more by resistive unloading than by inspiring 3% CO_2 in older subjects with normal lung function. Furthermore, the ventilatory response to exercise above VTh is also increased by resistive unloading unlike that of CO_2 loading. Respiratory mechanics were also altered by inspired CO_2 and resistive unloading of the airways. Flow limitation during maximal exercise was greater when the subjects were breathing CO_2 than when breathing room air or when breathing HeO_2, and EELV was lower during maximal exercise when the subjects were breathing HeO_2 than when breathing room air or when breathing CO_2. The work of breathing against the lung during maximal exercise was increased when the subjects were breathing CO_2 but not when breathing HeO_2. The increase was mainly related to increased resistive work, which was probably related to the increased magnitude of airflow limitation when the subjects were breathing CO_2.

The implication of these findings is that mechanical ventilatory limitations, even minimal, can attenuate the ventilatory response to heavy-to-maximal exercise when the subjects were breathing room air or when breathing 3% CO_2, despite the large increase in the chemical drive for V̇E. However, the attenuation of V̇E is not sufficient to limit exercise capacity, since all of the subjects had a normal exercise capacity when breathing room air and when breathing 3% CO_2. Nevertheless, exercise time was increased minimally by mechanical unloading of the respiratory system during exercise. This would appear to indicate that at maximal exercise these older subjects have little ventilatory reserve for accommodating an increase in ventilatory demand and

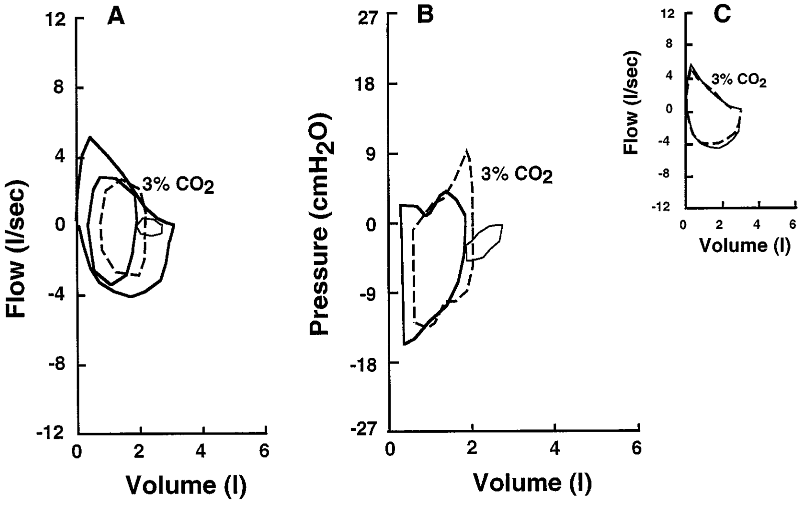


Fig. 7. Maximal and tidal flow-volume and pressure-volume loops for typical subject breathing room air or 3% CO_2. Maximal-flow loops were measured at rest (*A* and *C*), and tidal flow-volume loops were measured during maximal exercise, when subject was breathing room air (thicker solid line) and when breathing 3% CO_2 (thicker dashed line, *A*). Tidal pressure-volume loops were measured during maximal exercise, when subject was breathing room air (thicker solid line) and when breathing 3% CO_2 (thicker dashed line, *B*). Small loops are resting tidal loops, when subject was breathing room air (*A* and *B*). Values are for, respectively, room air and 3% CO_2: V̇E = 58 and 56 l/min; VT = 1.57 and 1.51 liters; total work of breathing = 80 and 87 J/min; expiratory airflow limitation = 15 and 30% of VT; and Pa_{CO_2} = 30 and 45 Torr.

to some minimal degree experience mechanical ventilatory limitations during heavy-to-maximal exercise when breathing room air. Below VTh, the influence of mechanical unloading is absent and the ventilatory response to exercise is increased as expected when breathing 3% CO_2. This finding suggests that, during submaximal exercise, mechanical ventilatory reserves are greater than demand (see Fig. 3 and other respiratory mechanics data) and do not influence the ventilatory response to exercise. Overall, these results further demonstrate that even mild mechanical ventilatory constraints can influence the ventilatory response to heavy-to-maximal exercise, maximum $\dot{V}_E$, and respiratory mechanics.

Although it is not possible to conclude that these subjects were "ventilatory limited" during exercise when breathing room air or when breathing 3% CO_2, as exercise capacity was similar in both cases, it could be concluded that their $\dot{V}_E$ was as high as it could be when they were breathing room air or when breathing 3% CO_2 (see Figs. 3, 6–7). For instance, when the subjects were breathing 3% CO_2, $\dot{V}_E$ was not increased even at the expense of retaining CO_2 and increased airflow limitation, which is a similar finding to that reported for subjects exposed to resistive loading during exercise, where $\dot{V}_E$ is reduced at the expense of an increase in Pa_{CO_2} (7). However, it is probably reasonable to suggest that exercise capacity is slightly influenced by mechanical ventilatory limitations in these subjects. It is only by unloading the mechanical constraints of the respiratory system that $\dot{V}_E$ can be increased slightly and Pa_{CO_2} lowered. Although the subjects have no frank signs of mechanical ventilatory limitation to exercise (retention of CO_2 or reduced exercise capacity), they do approach maximal expiratory flow both when breathing room air and when breathing 3% CO_2 (see Figs. 3, 6, 7), which is consistent with the findings of others (13). If the subjects had a capacity similar to that of unloaded breathing, they could ventilate more at maximal exercise and push Pa_{CO_2} lower. Therefore, it appears that exercise capacity is maintained at the expense of gas exchange when the subjects were breathing room air and when breathing 3% CO_2. This would tend to suggest that measures such as the ventilatory response to heavy-to-maximal exercise, dynamic respiratory mechanics, and Pa_{CO_2} tension are more sensitive to the presence of mechanical ventilatory limitations than exercise capacity or the $\dot{V}_E$-to-maximal voluntary ventilation ratio, which was quite normal for these older subjects.

Although different from the ventilatory response to exercise studied here, it has been demonstrated that the ventilatory response to CO_2 may also be influenced by mechanical ventilatory constraints (8, 9). It has been suggested that the work to increase $\dot{V}_E$ is less tolerable than the rise in Pa_{CO_2} (8, 17, 20). In the present study, the rate of increase in $\dot{V}_E$ during exercise was higher when the subjects were breathing CO_2 during exercise below VTh but tended to be lower above VTh, which suggests that the ventilatory response to exercise when the subjects were breathing 3% CO_2 is probably influenced by mechanical ventilatory constraints just as the ventilatory response to CO_2 is influenced by mechanical limitations. The lack of increase in ventilatory response when mechanical limitations are approached when the subjects were breathing CO_2 during exercise has also been described by other investigators for subjects with normal pulmonary function. This is true for young subjects (9), middle-aged adults (19), and older fit adults (13), 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 regulation of $\dot{V}_E$ during exercise.

The increase in the $\dot{V}_E$ during maximal exercise when the subjects were breathing HeO_2 is consistent with the findings of others (5, 21). Although the increase in the ventilatory response to exercise has not been reported specifically before, the finding is also consistent with the findings of others (11). The mechanism for the increase in $\dot{V}_E$ when the subjects were breathing HeO_2 is unclear from these findings, but there are several possibilities. First, the reduction in mechanical impedance imposed by breathing the low-density gas mixture could have produced the higher $\dot{V}_E$ at the same or lower neural drive (11, 23). Another possibility is that maximal flow rates were increased when the subjects were breathing HeO_2, thereby increasing maximal ventilatory capacity as defined by the maximal flow-volume loop (Fig. 3, *insets*). This increase in capacity could have decreased the mechanical constraints to $\dot{V}_E$ so that the subjects could have increased flow rates independently of the resistive work of breathing. The possibility that breathing HeO_2 increases the drive for $\dot{V}_E$ is probably unlikely, based on the results of Hussain et al. (11) and on the results of this study, in which $\dot{V}_E$ was observed to be unchanged at rest and during exercise at VTh. Furthermore, because the ventilatory response to exercise was increased from VTh to maximum exercise, it suggests that the increase in $\dot{V}_E$ became greater as the ventilatory demand increased above VTh. This would imply that the effect of resistive unloading of the airways became greater at higher flow rates, suggesting that the increase in $\dot{V}_E$ was related to the decreased impedance effect of HeO_2 (decrease in airway resistance and decrease in the magnitude of airflow limitation), on the regulation of $\dot{V}_E$ during exercise. This finding would also be consistent with the observations that $\dot{V}_E$ is decreased when the subjects are breathing a more dense gas such as that imposed by breathing room air at a raised air pressure (10). Again, these findings suggest that mechanical limitations affect not only the physical limits to ventilatory capacity but also the regulation of $\dot{V}_E$ during exercise as well as the $\dot{V}_E$ at maximum exercise and respiratory mechanics.

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