

Ventilatory response to exercise in aged runners breathing He-O₂ or inspired CO₂

T. G. BABB, DARREN S. DeLOREY, AND BRENDA L. WYRICK

Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas and The University of Texas Southwestern Medical Center, Dallas, Texas 77231

Submitted 14 March 2002; accepted in final form 9 October 2002

Babb, T. G., Darren S. DeLorey, and Brenda L. Wyrick. Ventilatory response to exercise in aged runners breathing He-O₂ or inspired CO₂. *J Appl Physiol* 94: 685–693, 2003; 10.1152/jappphysiol.00214.2002.—The ventilatory response to exercise below ventilatory threshold (VTh) increases with aging, whereas above VTh the ventilatory response declines only slightly. We wondered whether this same ventilatory response would be observed in older runners. We also wondered whether their ventilatory response to exercise while breathing He-O₂ or inspired CO₂ would be different. To investigate, we studied 12 seniors (63 ± 4 yr; 10 men, 2 women) who exercised regularly (5 ± 1 days/wk, 29 ± 11 mi/wk, 16 ± 6 yr). Each subject performed graded cycle ergometry to exhaustion on 3 separate days, breathing either room air, 3% inspired CO₂, or a heliox mixture (79% He and 21% O₂). The ventilatory response to exercise below VTh was 0.35 ± 0.06 l·min⁻¹·W⁻¹ and above VTh was 0.66 ± 0.10 l·min⁻¹·W⁻¹. He-O₂ breathing increased (*P* < 0.05) the ventilatory response to exercise both below (0.40 ± 0.12 l·min⁻¹·W⁻¹) and above VTh (0.81 ± 0.10 l·min⁻¹·W⁻¹). Inspired CO₂ increased (*P* < 0.001) the ventilatory response to exercise only below VTh (0.44 ± 0.10 l·min⁻¹·W⁻¹). The ventilatory responses to exercise with room air, He-O₂, and CO₂ breathing of these fit runners were similar to those observed earlier in older sedentary individuals. These data suggest that the ventilatory response to exercise of these senior runners is adequate to support their greater exercise capacity and that exercise training does not alter the ventilatory response to exercise with He-O₂ or inspired CO₂ breathing.

control of breathing during exercise; ventilatory responses to loaded and unloaded breathing; work of breathing during exercise

IN SEDENTARY AND FIT OLDER adults, the mechanical ventilatory constraints imposed on ventilation (\dot{V}_E) at peak exercise have been well described (5, 23–25, 29). Rather than focusing on \dot{V}_E at peak exercise only, we recently described the effect of age on the overall ventilatory response to incremental exercise (12), that is, the ventilatory response during submaximal exercise as well as during heavy exercise. To this end, the ventilatory response to exercise was described in terms of the response of \dot{V}_E below ventilatory threshold (VTh) and the response of \dot{V}_E above VTh for healthy seden-

tary individuals ranging from 35 to 95 yr of age (12). We had proposed that the age-related changes in maximal expiratory flow and lung volume could affect the ventilatory response to exercise differently, depending on the intensity of exercise. It was observed that the ventilatory response to exercise below VTh increased with aging, whereas the ventilatory response to exercise above VTh declined only slightly (12). This small decline was surprising when the marked mechanical ventilatory constraints that were observed with normal aging were considered. However, the ventilatory response is dependent on the balance among many factors, including ventilatory constraints, ventilatory load, and ventilatory demand, which vary across populations, exercise protocol, and individual motivation levels (22).

Thus we wondered what the overall ventilatory response to exercise for older runners would be below and above VTh. The overall ventilatory response to exercise for older runners has not been addressed in previous work. We hypothesized that, because of their greater exercise capacity, strong motivation, and substantially higher ventilatory demand at peak exercise (25, 29), they could be predisposed to greater mechanical ventilatory constraints and that their slope of \dot{V}_E above VTh could be reduced. That is, \dot{V}_E could be attenuated before they reached their peak exercise capacity. It was proposed that, below VTh where ventilatory capacity is greater than ventilatory demands, their slope would be similar to that measured previously for sedentary older adults (5, 12). Also, to investigate the effects of mechanical ventilatory constraints on the overall ventilatory response to exercise in runners further, airway resistance was decreased by giving them He-O₂ to breathe, or ventilatory demand was increased by giving them 3% CO₂ to breathe.

In our studies in aged sedentary subjects, we previously found that the ventilatory response below VTh was not altered by He-O₂ breathing but increased above VTh (5), which is similar to the results of others (8, 21, 43, 46). However, it was also observed that the increase in ventilatory response to exercise with He-O₂ breathing was similar among younger subjects (4),

Address for reprint requests and other correspondence: T. G. Babb, Institute for Exercise and Environmental Medicine, 7232 Greenville Ave., Dallas, TX 75231 (E-mail: TonyBabb@TexasHealth.org).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

older subjects (5), and older men and women with mild chronic airflow limitation (6). This suggested that the ventilatory response to He-O₂ breathing is independent of the magnitude of ventilatory demand or the extent of mechanical ventilatory constraints, which indicates that the response in runners may be no different from that in sedentary older adults. This is in contrast to data reported for younger fit women (30, 31). The effect of He-O₂ breathing on the overall ventilatory response in older trained adults has not been tested. We hypothesized that \dot{V}_E would be increased just as previously observed for sedentary subjects, despite the runners' high ventilatory demand and high potential for increased ventilatory constraints.

In older sedentary subjects breathing 3% inspired CO₂ during exercise (5, 6), \dot{V}_E was increased only below VTh. In contrast, the ventilatory response to exercise was increased in younger subjects breathing 3% inspired CO₂ (4), both below and above VTh. Thus it has been suggested that the ability to increase \dot{V}_E is limited in the aged only at peak exercise. Although others have shown that \dot{V}_E cannot be increased in fit younger (26) or fit older men (25) at peak exercise, the effect of CO₂ on the overall ventilatory response has not been studied in older runners. We wondered whether the overall ventilatory response to exercise for older runners might be altered with CO₂ breathing, because runners have such high ventilatory demands during exercise. It was hypothesized that the runners would not be able to increase their ventilatory response to exercise above VTh with inspired CO₂ because of limited ventilatory reserves and that exercise capacity may actually be decreased because ventilatory reserves may be low in exercise-trained older adults.

To investigate the overall ventilatory response to exercise in trained aged adults, 12 seniors (10 men, 2 women) who exercised regularly (5 ± 1 days/wk) were studied.

METHODS

Subjects. Volunteers were recruited through local advertisements. None of the subjects had a history of asthma, cardiovascular disease, or diabetes. All of the subjects participated in regular vigorous exercise and had been competing in road races, which ranged in distance from 5 km to ultramarathons. 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 with exercise on the cycle ergometer and instructed to avoid food and caffeine for at least 2 h before exercise testing. They were also instructed to limit their exercise to easy runs 24 h before testing. None of the subjects was a smoker, but eight subjects had a history of cigarette smoking (mean \pm SD; 26 ± 31 pack·yr). As a group, it had been 27 ± 12 yr since they quit smoking. Volunteers were accepted for study if their pulmonary function was considered normal.

Pulmonary function. All subjects had standard spirometry, lung volume, and diffusing capacity determinations (model 6200 body plethysmograph, SensorMedics, Yorba Linda, CA). Pulmonary function was performed according to guidelines of the American Thoracic Society (3). Predicted values were

based on norms by Knudson et al. (27), Enright et al. (13), Goldman and Becklake (16), and Burrows et al. (9).

Resting respiratory mechanics. Maximal flow-volume loops and pressure-volume loops were measured in a pressure-corrected volume-displacement body plethysmograph to eliminate the gas compression artifact (SensorMedics 6200). Transpulmonary pressure (Ptp) was estimated by using an esophageal balloon placed ~ 45 cm from the nostril (33). Isovolume pressure-flow curves were constructed (37) and subsequently used to determine the minimum pressure necessary to obtain maximal flow [critical pressure (Pcrit)] as previously described (5). These Pcrit data were used solely to confirm expiratory flow limitation during exercise (see below).

Gas exchange measurements. Measurements of oxygen uptake (\dot{V}_{O_2}) and carbon dioxide production (\dot{V}_{CO_2}) were made with the use of a custom gas-exchange system that was computerized. It was not possible to use the gas-exchange system when the subjects were breathing He-O₂ because of the deleterious effects of helium on mass spectrometer operation. VTh was determined from the comparison of gas exchange indexes (10) and the V-slope method (45, 47). VTh was designated as the work rate that was most congruent among the different threshold determination methods. End-tidal PCO₂ (PETCO₂) was measured when the subjects were breathing room air, as well as when they were breathing He-O₂ and CO₂, with the use of the Poet TE CO₂ monitor (model 602/11, Criticare Systems, Waukesha, WI).

Breathing mechanics. Expiratory and inspiratory flow were measured continuously during the exercise tests, as described previously (5). An esophageal balloon was placed as described above for continuous measurements of Ptp during the second through fourth maximal exercise tests (5). Maximal flow-volume and pressure-volume loops were determined at rest, while the subjects were seated on the cycle ergometer just before the baseline measurements, and within 2 min after exercise was terminated, to determine whether exercise had induced bronchodilation or bronchoconstriction, which none of the subjects experienced.

Inspiratory capacity (IC) was measured at rest and during exercise to determine placement of tidal flow-volume loops within the maximal flow-volume loop, as described previously (5). End-expiratory lung volume (EELV) was estimated from measurement of IC (EELV = TLC - IC, where TLC is total lung capacity) and reported as a percentage of TLC. End-inspiratory lung volume (EILV) was calculated (EILV = EELV + VT, where VT is tidal volume) and expressed as a percentage of TLC. IC was measured during the last 20 s of each exercise increment, and tidal flow-volume and pressure-volume loops were measured continuously.

Inspired gas mixtures. During rest and exercise, inspired gas was provided from a large inspiratory reservoir, as described previously (4, 5). The bag was filled with either room air, 3% CO₂ in 21% O₂ and 76% N₂, or 21% O₂ and balance He (He-O₂), which was humidified similar to that of room air as in prior studies (4, 5). External resistance (i.e., valve, tubing, and pneumotachographs) was matched between the room air and He-O₂ conditions. By matching external apparatus resistance, the He-O₂ effect was restricted to the respiratory airways. The subjects were blinded in each case to the content of the gas mixture.

Study protocol. After screening, all subjects performed four maximal exercise tests. The first test was a preliminary exercise test to clear subjects for further participation in the study. The next three tests were performed breathing either room air, CO₂, or He-O₂. The order was randomized. Subsequent randomized repeat testing demonstrated no effect of test order (data not shown).

Exercise protocol. All of the exercise tests followed the same sequence of procedures. Testing began with the subjects seated on the cycle ergometer while baseline measurements were obtained. After 3 min of baseline measurements, the subjects performed graded cycle ergometry on an electronically braked cycle ergometer (model CPE 2000, MedGraphics, St. Paul, MN). Exercise began at 15 W for the women, or 30 W for the men, and was incremented by 15 or 30 W, respectively, every minute. The test continued until the subjects stopped because of exhaustion, or the test was stopped because they could not keep the pedal rate at a frequency >50 rpm. Heart rate was monitored continuously through the use of a 12-lead electrocardiogram (model CS-100, Schiller, Baar, Switzerland), and blood pressure was monitored with the use of an automated system (model 4240, Suntech, Raleigh, NC). Arterial saturation was monitored at rest and continuously throughout the first exercise test by pulse oximetry (model 3700, Ohmeda, Louisville, CO). Ratings of perceived exertion (RPE) (Borg 20-point scale) and perceived breathlessness (RPB) (Borg 10-point scale) were taken with the use of the procedures outlined by the American College of Sports Medicine (2) and were recorded at each work rate during the exercise test.

We tested these runners on the cycle ergometer instead of the treadmill because all of our previous data were collected during cycling. Thus, to compare results between this study and our earlier studies, we used the cycle (4–6, 12). Also, it is much easier to make our mechanics measurements while subjects are cycling than running. Nevertheless, we do not believe this negated the effects of training in this group; however, their measured peak $\dot{V}O_2$ would have probably been higher during running.

Data analysis. An interactive computer program developed in this laboratory, as previously described (4, 5), was used to determine V_T , breathing frequency, \dot{V}_E , and exercise tidal flow-volume and pressure-volume loops. Pulmonary resistance was computed on a breath-by-breath basis with multiple linear regression by the method of least squares for the whole breath, as described in method one by Officer and colleagues (36). Resistance was estimated from P_{tp} and flow on 5–10 breaths preceding the measurement of IC and then averaged. The mechanical work of breathing against the lung was estimated per breath from the area enclosed by the dynamic tidal pressure-volume loop (i.e., using P_{tp}), with the addition of that portion of a triangle describing work that fell outside the tidal pressure-volume loop (i.e., part of inspiratory elastic work) (32), and then averaged. Expiratory flow limitation was defined as the percentage of V_T in which tidal expiratory flow impinged on maximal expiratory flow and in which P_{tp} simultaneously exceeded P_{crit} , as described previously (4, 5). Briefly, the beginning and end of expiratory flow limitation were confirmed by determining where P_{tp} met or exceeded P_{crit} rather than by the use of expiratory flow curves. Data were analyzed at rest, at V_{Th} , and during peak exercise.

The relationship between \dot{V}_E and work rate was used to describe the overall ventilatory response to exercise. This

method has been described previously (4–6). Briefly, \dot{V}_E was plotted against work rate, and slopes were calculated for each individual by using all of the points between rest and V_{Th} or all of the points between V_{Th} and peak exercise. Thus the overall ventilatory response was described as the ventilatory response below and above V_{Th} . The individual slopes were averaged and then used as indicators of ventilatory response below and above V_{Th} . If an individual's R^2 for \dot{V}_E vs. work rate was not >0.85 (i.e., indicating a poor fit of the data by linear least squares regression), then that particular slope was not included in the group analysis of ventilatory response. However, in almost all of these individuals as well as in other studies, linear analysis has been able to describe the ventilatory response accurately, both below and above V_{Th} (4–6). We maintained this method because we wanted to be able to compare these results with our previous studies in the aged (4–6, 12). Also, this method was not dependent on attaining the same peak exercise work rate in all conditions, because we were determining the slope of the response, not the peak end point. Work rate was used in the determination of ventilatory response instead of $\dot{V}O_2$ or $\dot{V}CO_2$ so that comparisons could be made with the He- O_2 tests, where it was not possible to make gas-exchange measurements. Also, \dot{V}_E was not compared with PET_{CO_2} because PET_{CO_2} does not rise during heavy exercise with room air or He- O_2 breathing as in tests with inspired CO_2 .

The difference between means across all conditions was tested with the use of a one-way ANOVA for repeated measures at rest, V_{Th} , and peak exercise. In some cases, the difference between means was tested with the use of paired t -tests. Relationships among physiological variables were analyzed by Pearson correlation coefficients.

RESULTS

Subjects. Ten men and two women participated in the study. Their characteristics are presented in Table 1. As expected, peak exercise capacity was above normal, on the basis of $\dot{V}O_2$ as a percentage of age- and gender-corrected norms. As a result, their \dot{V}_E at peak exercise was much higher than observed previously in older (70 ± 3 yr) sedentary men and women (12). \dot{V}_E as a percentage of maximal voluntary ventilation was $74 \pm 14\%$. Pulmonary function data are presented in Table 2 and are consistent with normal lung function. Only diffusing capacity appeared to be higher than expected compared with that in sedentary aged men and women (12).

\dot{V}_E at rest, V_{Th} , and peak exercise. \dot{V}_E (l/min) at rest, V_{Th} , and peak exercise when breathing room air, CO_2 , and He- O_2 are shown in Fig. 1, where \dot{V}_E is plotted against work rate (W). \dot{V}_E was significantly higher at rest and V_{Th} ($P < 0.001$) when breathing CO_2 . When breathing He- O_2 , \dot{V}_E was significantly higher at V_{Th} ($P < 0.01$) and peak exercise ($P < 0.001$). The increase

Table 1. Subject characteristics

Age, yr	Height, cm	Weight, kg	Smoking History,* pk·yr	Peak $\dot{V}O_2$, %predicted	Exercise, yr	Compete, yr	Training Summer, miles/wk	Training Winter, miles/wk	Peak $\dot{V}O_2$, ml/kg
63 ± 4	175 ± 10	72 ± 10	26 ± 31	146 ± 27	20 ± 8	16 ± 6	30 ± 11	32 ± 14	35 ± 6

Values are means ± SD; * $n = 8$. $\dot{V}O_2$, oxygen uptake; Compete, no. of years participating in running races; Training Summer, average no. of training miles per week in the summer months; Training Winter, average no. of training miles per week in the winter months.

Table 2. Pulmonary function

FVC, %predicted	FEV ₁ , %predicted	FEV ₁ /FVC, %	MVV, %predicted	RV/TLC, %	TLC, %predicted	DL _{CO} , %predicted
108 ± 7	102 ± 14	75 ± 6	118 ± 14	33 ± 4	106 ± 6	130 ± 22

Values are means ± SD. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity; DL_{CO}, diffusing capacity.

in \dot{V}_E with CO₂ and He-O₂ breathing was due mainly to an increase in V_T (Tables 3 and 4). In association with the increase in \dot{V}_E with He-O₂ breathing, there was a significant ($P < 0.001$) decrease in PETCO₂ at rest, VTh, and peak exercise (Table 3). In contrast, there was an increase in PETCO₂ with CO₂ breathing (Table 4). The decrease in PETCO₂ with He-O₂ breathing supports the tendency for hyperventilation when breathing He-O₂, even during peak exercise.

Ventilatory response to exercise. The ventilatory response to exercise below VTh increased from $0.35 \pm 0.06 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ ($n = 10$) when breathing room air to $0.44 \pm 0.11 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ when breathing CO₂ ($P < 0.001$; Fig. 2). In contrast, the ventilatory response to exercise above VTh was lower with CO₂ breathing ($0.59 \pm 0.12 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) compared with room air breathing ($0.66 \pm 0.10 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$), but the difference failed to reach significance. With He-O₂ breathing, the ventilatory response to exercise below VTh ($0.40 \pm 0.12 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) and above VTh ($0.81 \pm 0.10 \text{ l} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) was significantly greater ($P < 0.05$) compared with room air breathing.

Two subjects had an $R^2 < 0.85$ for \dot{V}_E vs. work rate below VTh when breathing room air, which indicates that linear regression did not adequately describe their data. Thus only 10 subjects were used in the analysis for room air below VTh. Above VTh, despite a lower peak work rate when breathing CO₂, an average of 4.00 ± 1.13 points was used in the linear regression vs. 4.58 ± 1.31 points when breathing room air. However, the fit of the data by linear regression was very good, as

indicated by high R^2 values during all three exercise tests.

Other variables. Selected variables are presented in Tables 3 and 4 for room air, He-O₂, and CO₂ breathing at rest, VTh, and peak exercise. Peak exercise time and work rate were not different with He-O₂ breathing (Table 3). In contrast, exercise time, work rate, and heart rate were slightly, but significantly, decreased at peak exercise with CO₂ breathing (Table 4). RPE and RPB at peak exercise were not different with CO₂ or He-O₂ breathing. Pulmonary resistance ($\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$) and EELV were significantly reduced, whereas the total mechanical work of breathing against the lung was unchanged from that of room air when breathing He-O₂, despite a significantly greater \dot{V}_E at VTh and peak exercise (Table 3). Expiratory airflow limitation was decreased ($P < 0.05$) with He-O₂ breathing (Table 3) but increased ($P < 0.05$) at peak exercise with CO₂ breathing (Table 4). The mechanical work of breathing is plotted against work rate in Fig. 3 and shown in Tables 3 and 4. Only at rest and VTh with CO₂ breathing was the work of breathing significantly increased ($P < 0.001$). There was no difference at peak exercise with any gas mixture.

DISCUSSION

The major finding of this study was that aged runners have a ventilatory response to exercise, both above and below VTh, that is similar to that previously observed for sedentary senior men and women (12). Furthermore, they increased their ventilatory response when breathing He-O₂ during exercise, which was also similar to that observed previously for sedentary older men and women (5). The aged runners, however, were unable to significantly increase their ventilatory response to exercise above VTh with CO₂ breathing, which was also similar to that observed previously for older sedentary men and women (5). Thus older runners respond to exercise, He-O₂ breathing, and CO₂ breathing in a manner that is similar to that of older sedentary men and women, despite the runners' higher exercise capacity and increased ventilatory requirement at peak exercise. These data also suggest that the ventilatory response to exercise of these aged runners is adequate to support their greater exercise capacity and that the larger ventilatory demand does not result in limiting mechanical ventilatory constraints (25). Furthermore, these findings suggest that exercise training does not alter the ventilatory response to exercise with He-O₂ or inspired CO₂ breathing in aged runners.

Population studied. The subjects for this study were recruited on the basis of their reported exercise train-

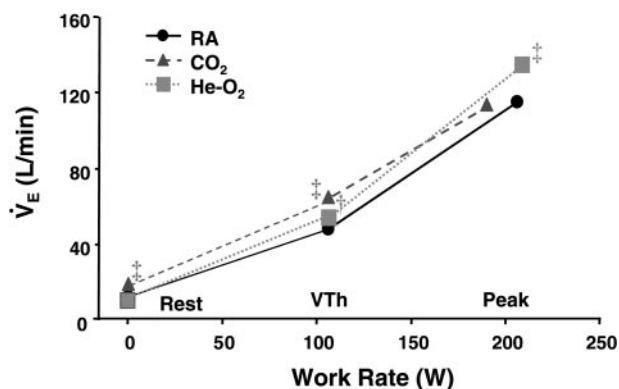


Fig. 1. Minute ventilation (\dot{V}_E) during exercise when breathing room air (RA), CO₂, and He-O₂ (79% He and 21% O₂). Comparisons were made at rest, ventilatory threshold (VTh), and peak exercise. Values are means ± SD. \dot{V}_E at rest: 12 ± 2 , 19 ± 3 , and 12 ± 4 l/min; \dot{V}_E at VTh: 48 ± 11 , 65 ± 12 , and 54 ± 14 l/min; \dot{V}_E at peak: 115 ± 30 , 135 ± 27 , and 135 ± 27 l/min for RA, CO₂, and He-O₂, respectively. VTh work rate = 106 ± 38 W for all conditions. Peak work rates = 206 ± 54 , 190 ± 48 , and 209 ± 48 W, respectively. † $P < 0.01$ and ‡ $P < 0.001$, significant difference from RA condition.

Table 3. Selected variables for room air and He-O₂ tests

Variable	Room Air			He-O ₂		
	Rest	VTh	Peak	Rest	VTh	Peak
Workload, W	0	106 ± 38	206 ± 54	0	106 ± 38	209 ± 48
Time, min	0	3.9 ± 1.2	7.2 ± 1.2	0	3.9 ± 1.2	7.2 ± 1.2
HR, %predicted	39 ± 6	68 ± 10	95 ± 8	38 ± 6	67 ± 10	93 ± 6
V _T , liters	0.93 ± 0.21	1.9 ± 0.49	2.40 ± 0.45	0.93 ± 0.27	2.04 ± 0.60	2.62 ± 0.56*
f _b , breaths/min	14 ± 4	25 ± 3	48 ± 11	14 ± 3	27 ± 4*	53 ± 10
P _{ETCO₂} , Torr	37 ± 5	42 ± 4	34 ± 5	32 ± 5†	36 ± 3‡	28 ± 4‡
EFL, %V _T	0	0.4 ± 1.2 ^a	9 ± 13 ^a	0	0	5 ± 10 ^{a*}
EELV, %TLC	56 ± 4	54 ± 3	56 ± 4	55 ± 5	49 ± 5‡	53 ± 4*
EILV, %TLC	70 ± 6	83 ± 6	91 ± 3	69 ± 6	80 ± 9*	91 ± 5
RL, cmH ₂ O · l ⁻¹ · s	1.90 ± 0.84 ^c	1.80 ± 0.78 ^a	2.46 ± 1.00 ^a	1.38 ± 0.48 ^{d*}	1.10 ± 0.34 ^{b†}	1.30 ± 0.31 ^{a‡}
WOB, J/min	4 ± 1 ^a	40 ± 28 ^a	236 ± 85 ^a	3 ± 1 ^a	41 ± 23 ^a	194 ± 61 ^a
RPE (6–20 scale)	0	12 ± 3	18 ± 2	0	12 ± 2	18 ± 2 ^a
RPB (0–10 scale)	0	4 ± 3	9 ± 2	0	4 ± 2	9 ± 2 ^a
V _T /T _E , l/s	0.34 ± 0.09	1.53 ± 0.33	3.83 ± 1.12	0.32 ± 0.11	1.72 ± 0.43†	4.38 ± 0.96†

Values are mean ± SD (^an = 11, ^bn = 10, ^cn = 9, and ^dn = 8 subjects). VTh, ventilatory threshold; HR, heart rate; V_T, tidal volume; f_b, breathing frequency; P_{ETCO₂}, end-tidal PCO₂; EFL, expiratory flow limitation; EELV, end-expiratory lung volume; TLC, total lung capacity; EILV, end-inspiratory lung volume; RL, pulmonary resistance; WOB, mechanical work of breathing against the lung; RPE, rating of perceived exertion; RPB, rating of perceived breathlessness; V_T/T_E, mean expiratory flow rate. *P < 0.05, †P < 0.01, and ‡P < 0.001.

ing routines and participation in running events. We had no preconceived requirement regarding how much flow limitation they might obtain at peak exercise. Although their measures of ventilatory constraints were less than anticipated, their mechanical constraints to \dot{V}_E could be representative of a large number of very active older adults who are not necessarily highly competitive athletes. In this way, these data may be more typical than data collected on high-endurance masters athletes. Also, although only 9 ± 13% (range of 0–40%) of their V_T met or exceeded maximal expiratory flow, this is not trivial. Their \dot{V}_E -to-maximal voluntary ventilation ratio was 74 ± 14%, which is on the high side of normal, and EILV was over 91% of TLC. If it were not for their above-average spirometry, they would have had more ventilatory limitation. Nevertheless, this does not make this group of runners an exception, but just the opposite. They are probably very typical of older runners, and their results seem very reasonable. Furthermore, their response to He-O₂ breathing was just as we would have anticipated. They

increased their \dot{V}_E by >20%, which is a similar and robust finding across many normal and patient populations (5, 6). The magnitude of expiratory flow limitation appears to make little difference in the level of ventilatory response to He-O₂ breathing. Their response to inspired CO₂ was as anticipated as well.

Ventilatory response to exercise with aging and exercise training. The ventilatory slopes for the runners in this study are shown compared with sedentary men and women from earlier studies in Fig. 4 (12). Their ventilatory response to exercise was similar to that of men and women 65–75 yr of age. Also, their ventilatory levels at rest, VTh, and peak exercise are compared with senior sedentary men and women (65–75 yr) in Fig. 5. In agreement with the findings of others (25), this figure shows how much greater their exercise capacity and ventilatory demand were, which had no effect on their ventilatory responses. Thus, even for older runners, who have a substantially higher ventilatory demand during maximal exercise, the ventilatory response to exercise below VTh increases with

Table 4. Selected variables for room air and CO₂ tests

Variable	Room Air			CO ₂		
	Rest	VTh	Peak	Rest	VTh	Peak
Workload, W	0	106 ± 38	206 ± 54	0	106 ± 38	190 ± 48*
Time, min	0	3.9 ± 1.2	7.2 ± 1.2	0	3.9 ± 1.2	6.6 ± 1.2†
HR, %predicted	39 ± 6	68 ± 10	95 ± 8	36 ± 5	68 ± 9	90 ± 6*
V _T , liters	0.93 ± 0.21	1.9 ± 0.49	2.40 ± 0.45	1.23 ± 0.19†	2.39 ± 0.50‡	2.48 ± 0.53
f _b , breaths/min	14 ± 4	25 ± 3	48 ± 11	16 ± 2	28 ± 4*	47 ± 9
P _{ETCO₂} , Torr	37 ± 5	42 ± 4	34 ± 5	43 ± 4‡	49 ± 5‡	49 ± 4‡
EFL, %V _T	0	0.4 ± 1.2 ^a	9 ± 13 ^a	0	1.0 ± 3.2 ^b	13 ± 14 ^{a*}
EELV, %TLC	56 ± 4	54 ± 3	56 ± 4	58 ± 6	54 ± 4	56 ± 3
EILV, %TLC	70 ± 6	83 ± 6	91 ± 3	77 ± 4†	89 ± 4‡	93 ± 3
RL, cmH ₂ O · l ⁻¹ · s	1.90 ± 0.84 ^c	1.80 ± 0.78 ^a	2.46 ± 1.00 ^a	1.70 ± 0.79 ^{b†}	1.78 ± 0.59 ^b	2.42 ± 1.14 ^a
WOB, J/min	4 ± 1 ^a	40 ± 28 ^a	236 ± 85 ^a	7 ± 2 ^{a‡}	72 ± 31 ^{a‡}	214 ± 46
RPE (6–20 scale)	0	12 ± 3	18 ± 2	0	13 ± 3	19 ± 1
RPB (0–10 scale)	0	4 ± 3	9 ± 2	0	4 ± 2	9 ± 1
V _T /T _E , l/s	0.34 ± 0.09	1.53 ± 0.33	3.83 ± 1.12	0.55 ± 0.12‡	2.06 ± 0.36‡	3.67 ± 0.74

Values are means ± SD (^an = 11, ^bn = 10, ^cn = 9, and ^dn = 8 subjects). *P < 0.05, †P < 0.01, and ‡P < 0.001.

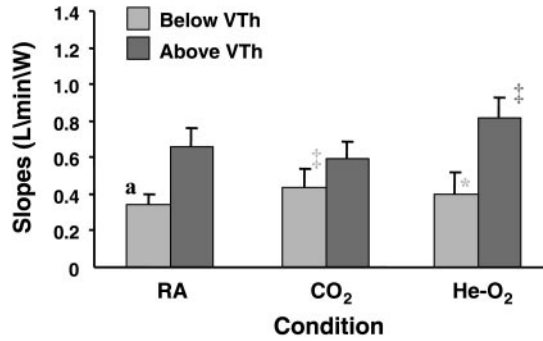


Fig. 2. Ventilatory response to exercise in liters per minute per watt below and above VTh when breathing RA, CO₂, and He-O₂ in older runners (60–75 yr). Values are means ± SD. ^an = 10 Subjects. *P < 0.05 and ‡P < 0.001, significant difference from RA condition.

aging, whereas the ventilatory response above VTh changes little (12). These runners, although slightly younger, had comparable pulmonary function, a slightly lower aerobic capacity, a similar \dot{V}_E at peak exercise, and a similar EILV (%TLC), but a lower degree of expiratory flow limitation (9 ± 13 vs. 27% of V_T) than the runners (all men) studied by Johnson et al. (25).

Ventilatory response to exercise with He-O₂ breathing. The increase in \dot{V}_E with He-O₂ breathing was similar to that reported in the literature (8, 14, 21, 43, 46, 48). We also found the runners' ventilatory response to exercise while breathing He-O₂ to be the same as observed earlier for younger subjects (4), older subjects (5), and older men and women with mild chronic airflow limitation (6). Thus, older runners, despite their higher exercise capacity and ventilatory demand, do not respond any differently to He-O₂ breathing than do sedentary older men and women.

Despite the runners' increase in \dot{V}_E with He-O₂ breathing, their exercise capacity was not increased, just as observed in previous studies (4–6). This finding agrees with the findings of others (14, 21, 43) and contrasts with the findings of some (7, 48). These differences among studies are most likely due to differences in subject ages, the variables used to measure

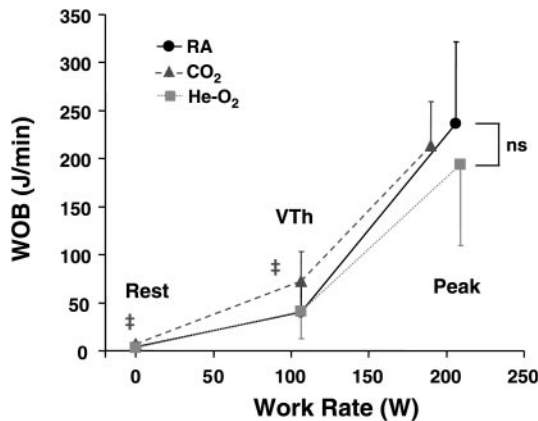


Fig. 3. Mechanical work of breathing (WOB) plotted against work rate (W) at rest, VTh, and peak exercise when breathing RA, CO₂, and He-O₂. ns, Not significant. ‡P < 0.001.

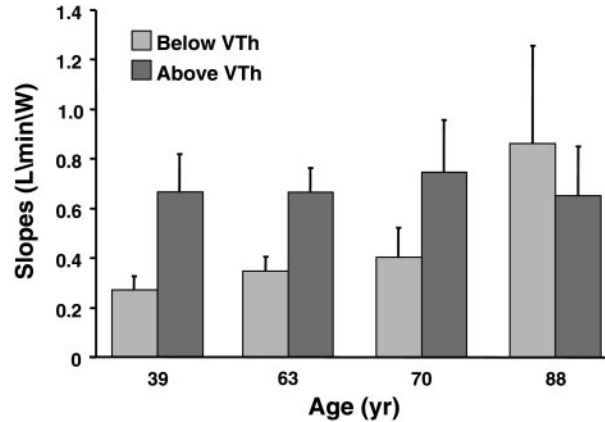


Fig. 4. Ventilatory response to exercise in liters per minute per watt below and above VTh plotted against age. Values are means ± SD. Age = 39 ± 4 yr for n = 20, 70 ± 3 yr for n = 14, and 88 ± 2 yr for n = 11 (12).

exercise capacity (i.e., work rate and exercise time vs. \dot{V}_{O_2}), and the exercise protocols used to determine exercise capacity. However, it was possible, given the runners' greater exercise capacity and substantially higher ventilatory demand at peak exercise, that they could have been predisposed to greater mechanical ventilatory constraints, and their exercise tolerance might have been improved by a lower respiratory impedance. This was not the case, nor does it seem to be the case in lung patients who have marked ventilatory limitations to exercise (6, 35, 41). At this point, the importance of the increase in \dot{V}_E with He-O₂ breathing must be more carefully evaluated, as others have suggested previously (28, 46).

Finally, breathing He-O₂ in the aged runners did not alter the relationship between the mechanical work of breathing and work rate. Whereas pulmonary resistance and respiratory impedance may be lower, the work of breathing of the lung is not lower for a given exercise work rate, even in these aged runners. Nor

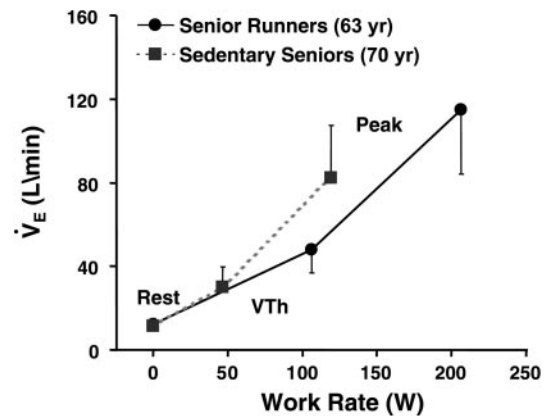


Fig. 5. \dot{V}_E during exercise at rest, VTh, and peak exercise in older runners (60–75 yr; senior runners) and sedentary seniors (65–75 yr). Values are means ± SD for senior runners (n = 12) and sedentary seniors (n = 14). Work rate at VTh = 106 ± 38 and 47 ± 21 W; at peak = 206 ± 54 and 119 ± 42 W for runners and seniors, respectively (12).

was this relationship different from that observed in previous work in sedentary older men and women (5, 6). These findings support the contention that the ventilatory response to exercise can be altered by resistive unloading without affecting the relationship between the work of breathing and exercise capacity. This relationship appears to be more finely controlled during exercise than \dot{V}_E or gas-exchange indicators such as P_{ETCO_2} .

These findings with He-O₂ breathing also help to explain some of the differences observed between He-O₂ breathing and respiratory unloading with inspiratory assist (i.e., positive-pressure breathing). In He-O₂ breathing, \dot{V}_E is increased during exercise, but, with inspiratory pressure assist, \dot{V}_E is not increased (15, 28, 40). Our findings suggest that this difference is due to the fact that the mechanical work of breathing is not altered with He-O₂ breathing, whereas with inspiratory assist, the mechanical work of breathing is actually decreased for a given work rate. This may be why investigators have found exercise tolerance to be increased with inspiratory assist (20) and why we have found no change in exercise capacity with He-O₂ breathing.

Ventilatory response to exercise with CO₂ breathing. We found the runners' ventilatory response to exercise while breathing inspired CO₂ to be the same as observed in earlier work in sedentary older men and women (5, 6). The runners, just like older sedentary subjects, were unable to increase their ventilatory response above V_{Th} with CO₂ breathing (5, 6). This is similar to the findings of others who reported that older fit men could not significantly increase \dot{V}_E at peak exercise with CO₂ breathing (25). These are the first data in older runners to assess the ventilatory response to CO₂ breathing on all work rates above V_{Th} .

In contrast to these data and prior published results, a relatively small group of older sedentary subjects have been shown to have a parallel shift in \dot{V}_E throughout all phases of exercise with inspired CO₂ (22). These results differ not only from the results in fit older subjects in this study and others (25) but also from prior data observed in sedentary men and women (5, 6). This dissimilarity could reflect differences in factors such as exercise protocol (e.g., incremental vs. steady state), exercise mode (e.g., cycling vs. treadmill), and even subject motivation (see below for other alternatives), to mention a few possibilities, but ventilatory constraints were not markedly different. On the basis of our prior results and the results of this study, the ventilatory response to inspired CO₂ is not notably different between older fit and sedentary men and women during graded cycle ergometry to exhaustion.

The majority of findings in older adults are in contrast to those in younger adults, who could increase their ventilatory response to CO₂ above V_{Th} (4, 11), but similar to those in younger endurance athletes, who could not increase \dot{V}_E at peak exercise with CO₂ breathing (26). It has been assumed that failure to increase \dot{V}_E with CO₂ breathing is an indicator of the limitations imposed by mechanical ventilatory con-

straints (i.e., expiratory flow limitation and lung volume). It may not be that simple. Even in young subjects, \dot{V}_E cannot be increased as much when the inspired CO₂ concentration goes >6% (11). In these circumstances, it is difficult to determine whether \dot{V}_E is limited because of decreased CO₂ responsiveness, mechanical ventilatory limitations, or an interaction between respiratory impedance and CO₂ responsiveness (11, 17). It has been shown that the ventilatory response to exercise with CO₂ breathing is incompletely defended when breathing impedance is imposed; however, the ventilatory response to exercise with increased breathing impedance alone is usually not affected (17, 39). Thus it is difficult to explain a lack of response based on just mechanical limitations alone. It could be proposed that, with inspired CO₂, the ventilatory response to exercise might be determined by the respiratory controller's balance between CO₂ drive and the propensity of the controller to minimize respiratory effort (34, 38). Recent data on the importance of respiratory work and diaphragm fatigue in the control of vascular blood flow or cardiac output during exercise certainly support this concept (18–20, 42, 44). Also, it is possible that sedentary or trained older adults are less responsive to ventilatory input (1), especially input that might increase the work of breathing during exercise. The relationship between the work of breathing and exercise intensity appears to be defended strongly, even at the cost of attenuating \dot{V}_E or exercise capacity in sedentary elderly (5, 6) and now the elderly runner.

In further support, CO₂ breathing in the runners resulted in a slight, but significant decrease in exercise capacity, which is in contrast to that observed in sedentary younger and older men and women (4, 5). This may be due to the fact that the runners, because of their higher exercise capacity and greater ventilatory demand, have a lower ventilatory reserve. However, \dot{V}_E was the same as when room air was breathed, as were mechanical ventilatory constraints. Also, RPE and RPB were also similar to room air breathing, although the mechanical work of breathing was increased with CO₂ breathing. This increase in the mechanical work of breathing was similar to that observed previously in older and younger sedentary men and women (4, 5). As proposed above, it may be that CO₂ breathing cannot alter the ventilatory response during heavy exercise in the elderly because of the increase in the mechanical work of breathing, which appears to affect exercise capacity.

Conclusion. In conclusion, the ventilatory responses to exercise with room air, He-O₂, and CO₂ breathing of these fit runners were similar to those observed earlier in older sedentary individuals. These data also suggest that the ventilatory response to exercise of these senior runners is adequate to support their greater exercise capacity and that exercise training does not alter the ventilatory response to exercise with He-O₂ or inspired CO₂ breathing. Furthermore, these findings on exercise capacity with CO₂ and He-O₂ breathing suggest that \dot{V}_E plays a less important role in exercise capacity than conventionally thought. This appears true despite

modest changes in P_{ETCO_2} and mechanical ventilatory constraints, which can also be modulated without affecting exercise capacity. The work of breathing, however, seems to be rather important to exercise capacity, as it does to the responsiveness of the elderly to ventilatory input during exercise.

The authors thank Penny P. Gardner and Lizanne Brandt for assistance throughout the various stages of this project. The authors also express appreciation to Dr. Benjamin D. Levine for medical assistance with this project.

This work was supported by National Institute on Aging Grant AG-11805.

REFERENCES

1. **Akiyama Y, Nishimura M, Kobayashi S, Yamamoto M, Miyamoto K, and Kawakami Y.** Effects of aging on respiratory load compensation and dyspnea sensation. *Am Rev Respir Dis* 148: 1586–1591, 1993.
2. **American College of Sports Medicine.** Guidelines for exercise test administration. In: *Guidelines for Exercise Testing and Prescription*. Philadelphia, PA: Lea & Febiger, 1991, p. 69–71.
3. **American Thoracic Society.** Standardization of spirometry—1987 update. Statement of the American Thoracic Society. *Am Rev Respir Dis* 136: 1285–1298, 1987.
4. **Babb TG.** Ventilation and respiratory mechanics during exercise in younger subjects breathing CO_2 or HeO_2 . *Respir Physiol* 109: 15–28, 1997.
5. **Babb TG.** Ventilatory response to exercise in subjects breathing CO_2 or HeO_2 . *J Appl Physiol* 82: 746–754, 1997.
6. **Babb TG.** Breathing HeO_2 increases ventilation but does not decrease the work of breathing during exercise. *Am J Respir Crit Care Med* 163: 1128–1134, 2001.
7. **Brice AG, Forster HV, Pan LG, Lowry TF, Murphy CL, and Mead J.** Effects of increased end-expiratory lung volume on breathing in awake ponies. *J Appl Physiol* 70: 715–725, 1991.
8. **Brice AG and Welch HG.** Metabolic and cardiorespiratory responses to HeO_2 breathing during exercise. *J Appl Physiol* 54: 387–392, 1983.
9. **Burrows B, Kasik JE, Niden AH, and Barclay WR.** Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis* 84: 789–806, 1961.
10. **Caiozzo VJ, Davis JA, Ellis JF, Azus JL, Vandagriff R, and Prietto CA.** A comparison of gas exchange indices used to detect the anaerobic threshold. *J Appl Physiol* 53: 1184–1189, 1982.
11. **Clark JM, Sinclair RD, and Lenox JB.** Chemical and nonchemical components of ventilation during hypercapnic exercise in man. *J Appl Physiol* 48: 1065–1076, 1980.
12. **DeLorey DS and Babb TG.** Progressive mechanical ventilatory constraints with aging. *Am J Respir Crit Care Med* 160: 169–177, 1999.
13. **Enright PL, Kronmal RA, Higgins MW, Schenker MB, and Haponik EF.** Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. *Am Rev Respir Dis* 147: 125–133, 1993.
14. **Esposito F and Ferretti G.** The effects of breathing HeO_2 mixtures on maximal oxygen consumption in normoxic and hypoxic men. *J Physiol* 503: 215–221, 1997.
15. **Gallagher CG and Younes M.** Effect of pressure assist on ventilation and respiratory mechanics in heavy exercise. *J Appl Physiol* 66: 1824–1837, 1989.
16. **Goldman HI and Becklake MR.** Respiratory function tests. Normal values at median altitudes and the prediction of normal results. *Am Rev Tuberc* 79: 457–467, 1959.
17. **Greenberg HE, Rapoport DM, Gloeggler PJ, and Goldring RM.** Background ventilatory stimulus as a determinant of load compensation. *J Appl Physiol* 66: 1352–1358, 1989.
18. **Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickelle GA, Nelson WB, and Dempsey JA.** Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 82: 1573–1583, 1997.
19. **Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickelle GA, Nelson WB, Hanson P, and Dempsey JA.** Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol* 85: 609–618, 1998.
20. **Harms CA, Wetter TJ, St Croix CM, Pegelow DF, and Dempsey JA.** Effects of respiratory muscle work on exercise performance. *J Appl Physiol* 89: 131–138, 2000.
21. **Hussain SN, Pardy RL, and Dempsey JA.** Mechanical impedance as determinant of inspiratory neural drive during exercise in humans. *J Appl Physiol* 59: 365–375, 1985.
22. **Johnson BD, Beck KC, Olson LJ, O'Malley KA, Allison TG, Squires RW, and Gau GT.** Ventilatory constraints during exercise in patients with chronic heart failure. *Chest* 117: 321–332, 2000.
23. **Johnson BD and Dempsey JA.** Demand vs. capacity in the aging pulmonary system. *Exerc Sport Sci Rev* 19: 171–210, 1991.
24. **Johnson BD, Reddan WG, Pegelow DF, Seow KC, and Dempsey JA.** Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis* 143: 960–967, 1991.
25. **Johnson BD, Reddan WG, Seow KC, and Dempsey JA.** Mechanical constraints on exercise hyperpnea in a fit aging population. *Am Rev Respir Dis* 143: 968–977, 1991.
26. **Johnson BD, Saupé KW, and Dempsey JA.** Mechanical constraints on exercise hyperpnea in endurance athletes. *J Appl Physiol* 73: 874–886, 1992.
27. **Knudson RJ, Slatin RC, Lebowitz MD, and Burrows B.** The maximal expiratory flow-volume curve: normal standards, variability and effects of age. *Am Rev Respir Dis* 113: 587–600, 1976.
28. **Krishnan B, Zintel T, McParland C, and Gallagher CG.** Lack of importance of respiratory muscle load in ventilatory regulation during heavy exercise in humans. *J Physiol* 490: 537–550, 1996.
29. **McClaran SR, Babcock MA, Pegelow DF, Reddan WG, and Dempsey JA.** Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *J Appl Physiol* 78: 1957–1968, 1995.
30. **McClaran SR, Harms CA, Pegelow DF, and Dempsey JA.** Smaller lungs in women affect exercise hyperpnea. *J Appl Physiol* 84: 1872–1881, 1998.
31. **McClaran SR, Wetter TJ, Pegelow DF, and Dempsey JA.** Role of expiratory flow limitation in determining lung volumes and ventilation during exercise. *J Appl Physiol* 86: 1357–1366, 1999.
32. **McGregor M and Becklake MR.** The relationship of oxygen cost of breathing to respiratory mechanical work and respiratory force. *J Clin Invest* 40: 971–980, 1961.
33. **Milic-Emili J, Mead J, Turner JM, and Glauser EM.** Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol* 19: 207–211, 1964.
34. **Milic-Emili J and Tyler JM.** Relation between work output of respiratory muscles and end-tidal CO_2 tension. *J Appl Physiol* 18: 497–504, 1963.
35. **Oelberg DA, Kacmarek RM, Pappagianopoulos PP, Ginns LC, and Systrom DM.** Ventilatory and cardiovascular responses to inspired HeO_2 during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 158: 1876–1882, 1998.
36. **Officer TM, Pellegrino R, Brusasco V, and Rodarte JR.** Measurement of pulmonary resistance and dynamic compliance with airway obstruction. *J Appl Physiol* 85: 1982–1988, 1998.
37. **Olafsson S, Hyatt RE, and Potter WA.** Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *J Clin Invest* 48: 564–573, 1969.
38. **Poon CS.** Effects of inspiratory resistive load on respiratory control in hypercapnia and exercise. *J Appl Physiol* 66: 2391–2399, 1989.
39. **Poon CS.** Potentiation of exercise ventilatory response by airway CO_2 and dead space loading. *J Appl Physiol* 73: 591–595, 1992.
40. **Poon CS, Ward SA, and Whipp BJ.** Influence of inspiratory assistance on ventilatory control during moderate exercise. *J Appl Physiol* 62: 551–560, 1987.

41. **Raimondi AC, Edwards RH, Denison DM, Leaver DG, Spencer RG, and Siddorn JA.** Exercise tolerance breathing a low-density gas mixture, 35 per cent oxygen and air in patients with chronic obstructive bronchitis. *Clin Sci* 39: 675–685, 1970.
42. **Sheel AW, Derchak PA, Morgan BJ, Pegelow DF, Jacques AJ, and Dempsey JA.** Fatiguing inspiratory muscle work causes reflex reduction in resting leg blood flow in humans. *J Physiol* 537: 277–289, 2001.
43. **Spitler DL, Horvath SM, Kobayashi K, and Wagner JA.** Work performance breathing normoxic nitrogen or helium gas mixtures. *Eur J Appl Physiol* 43: 157–166, 1980.
44. **St. Croix CM, Morgan BJ, Wetter TJ, and Dempsey JA.** Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. *J Physiol* 529: 493–504, 2000.
45. **Sue DY, Wasserman K, Moricca RB, and Casaburi R.** Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 94: 931–938, 1988.
46. **Ward SA, Whipp BJ, and Poon CS.** Density-dependent airflow and ventilatory control during exercise. *Respir Physiol* 49: 267–277, 1982.
47. **Wasserman K, Hansen JE, Sue DY, and Whipp BJ.** *Principles of Exercise Testing and Interpretation*. Philadelphia, PA: Lea & Febiger, 1987, p. 261.
48. **Wilson GD and Welch HG.** Effects of varying concentrations of N_2/O_2 and He/O_2 on exercise tolerance in man. *Med Sci Sports Exerc* 12: 380–384, 1980.

