Progressive Mechanical Ventilatory Constraints with Aging

DARREN S. DELOREY and TONY G. BABB

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

To investigate the progressive nature of mechanical ventilatory constraints with aging, we studied 20 young (age 39 ± 3 yr), 14 senior (70 ± 2 yr), and 11 elderly (88 ± 2 yr) men and women during exercise. All subjects had normal pulmonary function and performed graded cycle ergometry to exhaustion. Minute ventilation ($\dot{V}_E$), lung volume, and expiratory airflow limitation (EAFL) were measured during each 1-min increment in work rate. Data were analyzed by two-way analysis of variance (ANOVA; age × gender) at rest, ventilatory threshold (VTh), and peak exercise. If an interaction was present, each gender was analyzed with a one-way ANOVA. Aging resulted in an increased $\dot{V}_E$ for a given submaximal work rate, although $\dot{V}_E$ during peak exercise was lowest in the elderly group ($p < 0.01$). End-expiratory lung volume (EELV, % of TLC) in men increased progressively with age and all groups were different at VTh ($p < 0.01$) and peak exercise ($p < 0.01$). In women, EELV (% of TLC) also increased with aging, the senior and elderly subjects had a greater EELV at VTh ($p < 0.01$) and peak exercise ($p < 0.01$) than the young group. Additionally, the normal decrease in EELV during the early stages of exercise was not observed in elderly subjects. End-inspiratory lung volume (EILV) also progressively increased with aging; senior and elderly subjects had a higher EILV at rest ($p < 0.05$), VTh ($p < 0.01$), and peak exercise ($p < 0.01$) than young subjects. EAFL (% of V_T) increased with aging; elderly subjects experienced greater EAFL at rest ($p < 0.05$), VTh ($p < 0.01$), and peak exercise ($p < 0.01$) than both young and senior subjects. We conclude that mechanical ventilatory constraints are progressive with aging, elderly subjects demonstrating marked mechanical ventilatory constraints during exercise. The impact of these constraints on exercise tolerance cannot be determined from this investigation and remains unclear.

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Aging is associated with a progressive decline in lung function, mainly because of a loss of elastic recoil (1, 2). The loss of elastic recoil of the lung with aging results in reduced maximal expiratory flow rates, and an increase in resting functional residual capacity (FRC). Recently, studies have reported that older subjects approach mechanical ventilatory limitations during exercise more so than younger subjects (3). Johnson and Dempsey (3) have shown that when relatively fit, healthy older subjects experience mechanical ventilatory constraints they alter their tidal volume (V_T) and breathing frequency (f_b) during exercise to achieve an appropriate ventilatory response for the metabolic demand. Additionally, previous work in our laboratory on 65- to 75-yr-old subjects (4) indicated that older sedentary subjects have little reserve for accommodating an increase in ventilatory demand. These studies (3, 4) suggest that the presence of mechanical constraints to minute ventilation ($\dot{V}_E$) during exercise affects not only the mechanical limits to ventilatory output, but also the regulation of ventilation during heavy-to-maximal exercise.

What remains unknown is the extent of ventilatory constraints beyond the age of 75 yr. To our knowledge a systematic study of mechanical ventilatory constraints during exercise in individuals in the ninth and tenth decades of life has never been conducted. McClaran and coworkers (5) who conducted a longitudinal study on aging and lung function only examined subjects with a mean age of 67 for a 6-yr period. Furthermore, it has been suggested that the decline in pulmonary function may be greater in older subjects, thus making them more susceptible to mechanical ventilatory constraints. For example, Ware and coworkers (6) recently reported that the rate of decline in pulmonary function is greater than would be predicted by cross-sectional studies and that there is a nonlinear decrease in pulmonary function beyond the age of 50. Additionally, McClaran and coworkers (5) demonstrated that the decline in pulmonary function with aging is not modified by habitual physical activity nor high aerobic capacity.

The findings of Ware and coworkers (6) and McClaran and coworkers (5) indicate that individuals in the ninth and tenth decades of life may be predisposed to marked mechanical ventilatory constraints during exercise simply as a result of living to that age. This is not to imply that these mechanical ventilatory constraints limit exercise (i.e., ventilatory limitation to exercise). However, if the decline in normal lung function ex-

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

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ceeded that of the cardiovascular system then ventilatory function could be a limiting factor to exercise. This, however, would require extensive cardiovascular and respiratory measurements to prove and is by no means within the scope of the present study. Nevertheless, we do agree with Ware and coworkers (6) and McClaran and coworkers (5) and would predict mechanical ventilatory constraints to be greater with advancing age, however, this has not been tested. In fact, there are limited studies on pulmonary function beyond the age of 65 to determine the extent of mechanical ventilatory constraints during exercise. Considering the possibility of an increased decline in pulmonary function beyond age 50, the extrapolation of available findings to subjects 85 to 95 yr of age is extremely difficult and questionable at best.

To investigate the progressive nature of mechanical ventilatory constraints with aging, we chose to study 20 young (age 35 to 45 yr), 14 senior (65 to 75 yr), and 11 elderly (85 to 95 yr) subjects with normal pulmonary function. It was hypothesized that lung function would progressively decrease with aging, and that senior and elderly subjects would experience greater mechanical ventilatory constraints during exercise evidenced by reduced $\dot{V}$max rates and increased lung volumes, which in combination with expiratory airflow limitation (EAFL) would reduce V_T reserve in the elderly and leave them with increases in f as their only avenue to increase $\dot{V}_E$.

METHODS

Subjects

Three groups of subjects were recruited through local advertisements. Twenty young (35 to 45 yr), 14 senior (65 to 75 yr), and 11 elderly (85 to 95 yr) subjects were included for study. 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, and caffeine for at least 2 h prior to exercise testing.

No subject 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. Subjects not meeting these guidelines were excluded as well as individuals with respiratory symptoms.

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 (7). Predicted values for flow rates were based on norms by Knudson and others (8). Normative data for FVC, and FEV_1/FVC in elderly subjects were from Enright and colleagues (9).

Maximal flow–volume loops were measured in a pressure-corrected volume-displacement body plethysmograph to eliminate the gas compression artifact (SensorMedics 6200). Exercise tidal flow–volume loops were compared with this maximal flow–volume loop.

Study Protocol

Pulmonary function tests and a resting electrocardiogram (ECG) were performed as an initial screening. If subjects met inclusion criteria for the study, they returned to the laboratory on a separate day for maximal exercise testing. Some of the subjects in the young and senior groups were part of smaller studies and completed additional exercise tests (4, 10, 11). The elderly subjects were only involved in this study, therefore, their data were collected after completion of data collection for the young and senior subjects.

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 computerized custom gas exchange system (NEC 486DX). Gas samples were drawn continuously at 60 ml/min from the mouthport and were analyzed with a mass spectrometer (model 1100; Marquette Electronics). Expired volume was measured at the mouth with a turbine flow device (Interface Associates, Aliso Veijo, CA). Subjects breathed through a mouthpiece attached to the flow device via a saliva trap (Interface Associates), which was attached to a two-way nonrebreathing valve (Model 2700; Hans Rudolph, Kansas City, MO). Elderly subjects had a Hans Rudolph four-way directional valve (model 2540) placed in line. Total system dead space was 175 ml for the breathing apparatus used by the elderly subjects and 120 ml for the breathing apparatus used by the young and senior groups. System resistance was < 2 cm H_2O per L/s through 6 L/s for expiration regardless of setup. A noseclip was worn during rest and exercise data collections.

Ventilatory threshold (VTh) was determined from a combination of gas exchange methods (12, 13). With these methods VTh was defined as the point at which $\dot{V}_E$ rises in proportion to $\dot{V}CO_2$ and disproportionally to $\dot{V}O_2$. We used VTh to differentiate between light-to-moderate and heavy-to-maximal exercise. VTh was designated as the work rate that was most congruent among the different threshold determination methods. However, the determination of VTh in elderly subjects was problematic because a break point in $\dot{V}_E$ was less apparent in that group, thus more emphasis was placed on the modified V-slope method of Sue and colleagues (14) to determine VTh in these subjects. This method has been shown to be effective in determining VTh in subjects who display a blunted ventilatory response to metabolic acidosis (14). Determinations of VTh were made independently by two investigators.

Expiratory and Inspiratory Flow Measurements

To measure both expiratory and inspiratory flow continuously during the maximal exercise test, the Hans Rudolph valve (model 2700) was connected to separate inspiratory and expiratory pneumotachographs via large-bore breathing tubes (model 4813, Hans Rudolph; Validyne pressure transducers, model MP45, ± 2 cm H_2O; and model CD19A amplifiers, Northridge, CA). The expired pneumotachograph was heated (Hans Rudolph, model 3850A). The separate expiratory and inspiratory flow signals were joined to give one bi directional flow signal (Validyne Buffer Amplifier, model BA112, Northridge, CA) and volume was determined from the digital integration of the single flow signal. The pneumotachographs were checked for linearity before the study using known flow rates. Calibration of volume was checked before each test using a calibrated syringe. Flow and volume were displayed on a strip chart recorder (model MT 95000; AstroMed, West Warwick, RI) and sampled realtime (100 Hz) on a computer (486Dx).

Breathing Mechanics

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. It was assumed that TLC does not change significantly during exercise (15, 16). 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 was calculated ($EILV = EELV + V_T$) and expressed as a percentage of TLC [(EILV/TLC)*100].

Exercise Protocol

Testing began with the subjects seated on the cycle ergometer while baseline measurements were made. After 3 min of baseline measurements, the subjects performed graded cycle ergometry on an electronically braked cycle ergometer (model CPE 2000; MedGraphics, St. Paul, MN). Initial workloads and increments in work were selected for each group and gender. Young men began exercising at 30 W and the work rate was increased by 30 W each minute, whereas young females began exercising at 20 W and the work rate was increased by 20 W each minute. The initial work rate for senior males was 20 W with 20-W increments every minute, and senior females had an initial work rate of 10 W which was incremented by 10 W each minute. Elderly males be-

TABLE 1

SUBJECTS' CHARACTERISTICS AND SMOKING HISTORY

Subjects	n	Age* (*yr*)	Height* (*cm*)	Weight* (*kg*)	Smoker (*n*)	Pack-years*	Years Quit*
Young	20	39 ± 4^{a†}	170 ± 11	70 ± 12	4	11 ± 4	12 ± 8
Senior	14	70 ± 3^{a†}	171 ± 10	71 ± 12	7	26 ± 17	15 ± 12
Elderly	11	88 ± 2^{a†}	165 ± 11	62 ± 11	6	20 ± 24	31 ± 12

* Values are mean ± SD.

† Values marked with like letters (a) are significantly different from each other, $p < 0.001$.

gan exercise at 10 W and the work rate was incremented by 10 W each minute, whereas elderly females began at 5 W and the work rate was incremented by 5 W every minute. Test termination criteria included volitional exhaustion, pedal rate not maintained at > 50 rpm, or observation of ECG changes. Gas exchange measurements were made during each increment in work rate. IC was measured during the last 20 s of each exercise increment and tidal flow–volume loops were measured continuously. At each work rate the ECG was monitored continuously through the use of a 12-lead ECG (Model CS 100; Schiller, Baar, Switzerland) and blood pressure was monitored with the use of an automated system (Suntech 4240; Raleigh, NC).

Maximal flow–volume loops were determined at rest, while the subjects were seated on the cycle ergometer just before the baseline measurements, and within 2 min after terminating exercise to determine if exercise had induced bronchodilation.

Data Analysis

VT, f, and $\dot{V}$E were calculated from the dual pneumotachograph volume signal by an interactive computer program developed in this laboratory. The interactive computer program was also used to generate exercise tidal flow–volume loops, which were then placed within the maximal flow–volume loop. A typical tidal flow–volume loop was chosen from the breaths preceding the maximal inspiration and were positioned within the maximal flow–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 EAFL, defined as the percentage of VT (%VT) where tidal expiratory flow impinged on maximal expiratory flow in the elderly subjects. Because most subjects in the young and senior groups were participants in separate concurrent studies (4, 10, 11), it was possible to confirm EAFL in these subjects with transpulmonary pressure (Ptp) measurements. In these subjects, EAFL was defined as the %VT where tidal expiratory flow impinged on maximal expiratory flow and where Ptp simultaneously exceeded the minimal critical pressure necessary to obtain maximal flow (Pcrit). Data were analyzed at rest, at VTh, and during peak exercise.

The ventilatory response to exercise was determined below and above VTh by least-squares regression. The slope of $\dot{V}$E versus work rate was calculated individually on all the points between rest and VTh (3.8 ± 0.7, 3.9 ± 0.6, 4.0 ± 1.6 points for young, senior, and elderly groups, respectively) and between VTh and peak exercise (4.9 ± 0.8, 5.7 ± 0.9, 5.7 ± 1.3 points for young, senior, and elderly groups, respectively). The fit of these data was considered good based upon the average coefficient of determination (R^2), which below VTh was 0.98 ± 0.02, 0.97 ± 0.03, and 0.98 ± 0.02, and above VTh, the average was 0.96 ± 0.03, 0.96 ± 0.02, and 0.95 ± 0.03 for young, senior, and elderly groups, respectively. The individual slopes were then averaged and used as indicators of ventilatory response below and above VTh. To compare the $\dot{V}O_2$ and work rate relationship across groups that used different increments in work rate, we utilized the above method to calculate the slope of $\dot{V}O_2$ versus work rate between the initial work rate and VTh. The average R^2 below VTh was 0.98 ± 0.03, 0.98 ± 0.02, 0.98 ± 0.03, and above VTh, the average was 0.98 ± 0.02, 0.98 ± 0.02, and 0.97 ± 0.02 for young, senior, and elderly groups, respectively.

Differences between groups were determined with a two way analysis of variance (ANOVA; age × gender). If an interaction was present, each gender was analyzed with a one-way ANOVA. Multiple contrasts were performed between groups when a significant F ratio was detected. Relationships among variables were determined by Pearson correlation coefficients. When the difference between only two means was to be tested (i.e., slopes below and above VTh), paired *t* tests were used. A p value < 0.05 was considered significant.

RESULTS

Subjects

Subject characteristics are shown in Table 1. In the young group there were 12 women (40 ± 1 yr, 164 ± 2 cm, 64 ± 3 kg, mean ± SD) and eight men (38 ± 1 yr, 178 ± 3 cm, 79 ± 4 kg). The senior group was made up of six women (70 ± 1 yr, 162 ± 3 cm, 61 ± 4 kg) and eight men (69 ± 1 yr, 178 ± 2 cm, 79 ± 2 kg). There were six women (88 ± 1 yr, 159 ± 3 cm, 59 ± 3 kg) and five men (87 ± 1 yr, 173 ± 5 cm, 67 ± 6 kg) in the elderly group. Four members of the young group had smoked 11 ± 4 pack-years and had quit 12 ± 8 yr ago. Seven senior subjects smoked for 26 ± 17 pack-years and had quit for 15 ± 2 yr. Six elderly subjects had a 20 ± 24 pack-year smoking history and had quit 31 ± 12 yr ago.

Pulmonary Function

Pulmonary function data are presented in Table 2. Based on predicted values (8, 9) all subjects had normal pulmonary function. However, in absolute terms, and in agreement with other studies (1, 2), aging resulted in a progressive decrease in expiratory flow rates and vital capacity (VC), as well as an increase in residual volume. Additionally, the FEV$_1$/FVC ratio and peak expiratory flow (PEF) as a percent of predicted appeared to be decreasing with aging. However, as Enright (9) points out the FEV$_1$/FVC ratio declines with aging and values below 70% do not necessarily indicate obstruction in older individuals. Furthermore, the apparent decrease in PEF

TABLE 2

PULMONARY FUNCTION*

Subjects	FVC (*% pred*)	FEV$_1$ (*% pred*)	FEV$_1$/FVC (*% pred*)	PEF (*% pred*)	TLC (*% pred*)	RV/TLC (*%*)	MVV (*% pred*)	DL$_{CO}$ (*% pred*)
Young	4.43 ± 0.94	3.50 ± 0.75	(79 ± 4)^{a‡}	8.84 ± 1.77	5.85 ± 1.15	(24 ± 4)^{a‡}	150.9 ± 36.9	25.7 ± 5.14
	(109 ± 9)	(104 ± 9)		(118 ± 1)^{a†}	(99 ± 11)^{ab†}		(115 ± 13)	(105 ± 14)
Senior	4.12 ± 1.08	2.92 ± 0.74	(72 ± 5)^{a‡}	7.85 ± 2.37	6.54 ± 1.31	(37 ± 6)^{a‡}	120.5 ± 30.6	21.6 ± 4.57
	(115 ± 17)	(104 ± 13)		(109 ± 14)	(114 ± 13)^{b†}		(110 ± 12)	(110 ± 16)
Elderly	3.08 ± 1.00	2.04 ± 0.67	(67 ± 7)^{a‡}	5.82 ± 1.33	5.55 ± 1.69	(45 ± 5)^{a‡}	86.0 ± 25.9	13.85 ± 2.75
	(109 ± 18)	(109 ± 16)		(100 ± 20)^{a†}	(110 ± 22)^{a†}		(97 ± 11)	(97 ± 11)

Definition of abbreviations: PEF = peak expiratory flow; MVV = maximal voluntary ventilation; RV = residual volume; DL$_{CO}$ = diffusing capacity.

* Values are mean ± SD.

Values marked with like letters (a, b) are significantly different from each other. Statistical tests were done on percent of predicted values.

† $p < 0.01$, ‡ $p < 0.001$.

TABLE 3

MAXIMAL EXERCISE VALUES*

Variable	Young Group	Senior Group	Elderly Group
Work rate, w	$166 \pm 59^{a\S}$	$119 \pm 41^{a\S}$	$53 \pm 14^{a\S}$
$\dot{V}_E$, L/min	$94 \pm 31^{a\S}$	$83 \pm 25^{b\S}$	$48 \pm 17^{a,b\S}$
$\dot{V}_{O_2}$, % pred	$91 \pm 18^{a,b\S}$	$120 \pm 25^{b\S}$	$133 \pm 30^{a\S}$
HR, % pred	$98 \pm 6^{b\ddagger}$	$99 \pm 7^{a\ddagger}$	$89 \pm 8^{a,b\ddagger}$
$\dot{V}_E$/MVV, %	$63 \pm 10^{a\ddagger}$	$69 \pm 9^{b\ddagger}$	$54 \pm 11^{a,b\ddagger}$
RPE, 6–20 scale	17 ± 3	$19 \pm 1^{a\dagger}$	$16 \pm 3^{a\dagger}$
RPB, 0–10 scale	9 ± 2	$9 \pm 2^{a\dagger}$	$7 \pm 3^{a\dagger}$
RER	$1.36 \pm 0.11^{a\S}$	$1.26 \pm 0.09^{a\S}$	$1.12 \pm 0.10^{a\S}$

Definition of abbreviations: W = watts; $\dot{V}_{O_2}$ = oxygen uptake; HR = heart rate; $\dot{V}_E$ = minute ventilation; MVV = maximal voluntary ventilation; RPE = rating of perceived exertion; RPB = rating of perceived breathlessness; RER = respiratory exchange ratio.

* Values are mean ± SD.

Values marked with like letters (a, b) are significantly different from each other. † $p < 0.05$, ‡ $p < 0.01$, § $p < 0.001$.

(%pred) was most likely related to the use of a prediction equation that was not generated for the elderly population. The American Thoracic Society (17) has recommended that "reference equations should, in general, not be extrapolated for ages or heights beyond those covered by the data that generated them." Although every attempt was made to avoid this situation, prediction equations developed for individuals in the ninth and tenth decades of life are not readily available, thus the interpretation of some pulmonary function variables must be made with caution. Despite a modest smoking history in the senior and elderly subjects, their pulmonary function did not appear to be reduced beyond what would be expected with normal aging.

Exercise Capacity

Table 3 lists the peak exercise values obtained during testing. Comparison with predicted values for $\dot{V}_{O_2}$ (18), heart rate (HR) (19), and the respiratory exchange ratio (RER) demonstrated maximal effort during testing and normal cardiorespiratory fitness for all three groups. However, the use of prediction equations and the determination of relative cardiorespiratory fitness with the elderly subjects was problematic because prediction equations for this age group are not available in the literature, and because elderly subjects may not be accustomed to maximal exercise, and the criteria for assessing a maximal effort during an exercise test in young subjects may not be applicable to this population. With these limitations in mind, we closely watched for subjective signs of a maximal effort (e.g., fatigue) and were satisfied that all subjects had given a maximal effort. Two elderly subjects had ECG abnormalities at peak exercise and testing was discontinued concurrent with volitional exhaustion. Although these ECG changes are not uncommon at peak exercise in individuals of this age, these findings were reported to the subject's primary care physicians for further evaluation; and because the changes occurred simultaneously with exhaustion, we accepted these tests as representative of maximal exercise capacity in these elderly subjects. These subjects were asymptomatic and had achieved $\geqslant 90\%$ of predicted maximal $\dot{V}_{O_2}$ and HR when the ECG abnormalities occurred, thus their data were included for analyses. Furthermore, we felt that exercise capacity was not limited by cardiac dysfunction in these subjects, although the potential exists to underestimate exercise capacity and the extent of mechanical constraints to $\dot{V}_E$ in these two subjects. The rating of perceived exertion (RPE) and rating of perceived breathlessness (RPB) values were lower in the elderly than in the senior subjects, although they were not significantly different from the young subjects, suggesting that the elderly subjects' effort was at least as great as that of the young subjects.

Ventilation and Ventilatory Response to Exercise

$\dot{V}_E$ is plotted against work rate in Figure 1, *panel A*. No significant differences were observed in $\dot{V}_E$ between groups at rest or VTh. At peak exercise, elderly subjects had a lower $\dot{V}_E$ ($p < 0.01$) than both young and senior subjects, whereas $\dot{V}_E$ was not different between young and senior subjects. Ratio of minute ventilation to maximal voluntary ventilation ($\dot{V}_E$/MVV [%]) (Table 3) was also significantly lower ($p < 0.01$) in the elderly subjects than in the young and senior groups at peak exercise. $\dot{V}_E$/MVV was not significantly different between young and senior subjects at peak exercise. To determine if the decrease in $\dot{V}_E$ at maximal exercise ($\dot{V}_E$max) was related to the decline

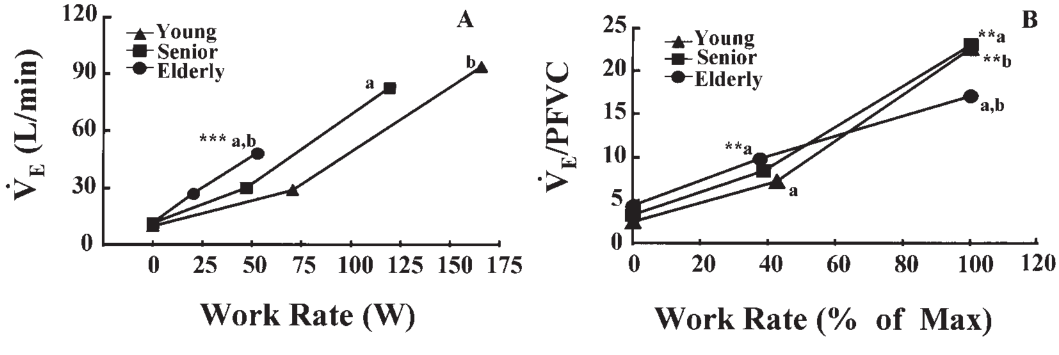

Figure 1. Ventilatory response to exercise. In *panel A*, $\dot{V}_E$ (L/min) is plotted against work rate (watts, W). In *panel B*, $\dot{V}_E$/predicted forced vital capacity ($\dot{V}_E$/PFVC) is plotted against work rate (percent of maximum work rate). Values marked with like letters (a, b) are significantly different from each other. **$p < 0.01$, ***$p < 0.001$. Comparisons are between groups at rest, ventilatory threshold (VTh), and maximal exercise (max). Values are in the following order, young, senior, and elderly groups, respectively (mean ± SD). (*Panel A*) Rest: $\dot{V}_E$ = 10 ± 2, 12 ± 4, 12 ± 3 L/min; VTh: $\dot{V}_E$ = 29 ± 7, 30 ± 10, 27 ± 7 L/min; Max: $\dot{V}_E$ = 94 ± 31, 83 ± 25, 48 ± 17 L/min. VTh: work rates = 71 ± 27, 47 ± 21, 21 ± 11 W; and Max: work rates = 166 ± 59, 119 ± 42, 53 ± 24 W. (*Panel B*) Rest $\dot{V}_E$/PFVC = 2.57 ± 0.50, 3.34 ± 1.51, 4.37 ± 1.14; VTh: $\dot{V}_E$/PFVC = 7.25 ± 1.45, 8.47 ± 2.40, 9.85 ± 2.61; Max $\dot{V}_E$/PFVC = 22.54 ± 4.25, 22.94 ± 4.06, 17.05 ± 3.77. Percent of maximum at VTh: = 42.68 ± 6.58, 38.82 ± 7.87, 37.62 ± 10.94.

observed in baseline pulmonary function, a correlation matrix was completed. Among all subjects a significant correlation ($r = 0.88$, $p < 0.001$) was observed between FEV_1 and peak $\dot{V}_E$. To account for the effect of body size on this correlation, the relationship between $\dot{V}_E$/predicted forced vital capacity (PFVC) and FEV_1 was examined. $\dot{V}_E$/PFVC was significantly correlated ($r = 0.47$, $p < 0.01$) with FEV_1.

As indicated in Figure 1, aging resulted in a progressive increase in $\dot{V}_E$ for a given submaximal work rate. To more appropriately examine this apparent increase in submaximal $\dot{V}_E$, we analyzed the ventilatory response to exercise (i.e., the slope of $\dot{V}_E$ versus work rate). The ventilatory response below VTh was significantly greater ($p < 0.01$) in elderly (0.82 ± 0.40 L/min/W) subjects than in young (0.28 ± 0.05 L/min/W) and senior (0.41 ± 0.12 L/min/W) subjects. The ventilatory response to exercise below VTh was not significantly different between the young and senior subjects. The ventilatory response to exercise above VTh (i.e., between VTh and maximal exercise [max]) was not significantly different between groups (slopes: 0.62 ± 0.13 L/min/W, 0.74 ± 0.22 L/min/W, 0.64 ± 0.22 L/min/W, for young, senior, and elderly groups, respectively).

To examine the ventilatory response relative to body size and exercise capacity, $\dot{V}_E$/PFVC was plotted against work rate as a percentage of maximum (Figure 1, *panel B*). $\dot{V}_E$/PFVC was also elevated in elderly subjects below VTh, indicating that the increase in submaximal $\dot{V}_E$ was not simply the result of body size or differences in incremental work rate. Above VTh, the ventilatory response was "flattened" in the elderly subjects suggesting that the elderly subjects had utilized a larger percentage (58 ± 9%) of their peak $\dot{V}_E$ relative to the young (33 ± 8%) and senior (37 ± 9%) subjects in response to exercise below the VTh. Thus, they were unable to further increase the rate of $\dot{V}_E$ above VTh in contrast to the young and senior subjects.

Because the increase in submaximal $\dot{V}_E$ could not be explained by differences in body size or exercise capacity, we wondered if the increase in $\dot{V}_E$ below VTh could be the result of an increased metabolic demand in the elderly. To examine the relationship between $\dot{V}O_2$ and work rate, we calculated the slope of $\dot{V}O_2$ versus work rate between the initial work rate and VTh. The slope of $\dot{V}O_2$ versus work rate below VTh was significantly higher in elderly subjects than young ($p < 0.01$) subjects (slopes: 10.8 ± 2.3 ml/min/W, 14.2 ± 3.7 ml/min/W, 17.2 ± 7.8 ml/min/W for young, senior, and elderly groups, respectively). The difference between the young and senior groups was not significantly different, suggesting that an increased metabolic demand was at least in part responsible for the increase in submaximal $\dot{V}_E$ observed in the elderly group.

To further investigate the increase in $\dot{V}_E$ during submaximal exercise relative to oxygen demand, we examined the ventilatory equivalents for O_2 and CO_2 (Table 4). We also examined end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$) (Table 4) for evidence of hyperventilation. $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ were significantly higher ($p < 0.001$) at rest in the elderly group than in the young and senior groups. At VTh, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ were significantly different ($p < 0.001$) across all three groups. At peak exercise, $\dot{V}_E/\dot{V}CO_2$ was significantly higher ($p < 0.01$) in the elderly subjects than the young and senior groups. Thus, it appears that the elderly subjects had an increased ventilatory demand for a given $\dot{V}O_2$ and $\dot{V}CO_2$ level. Before analysis of $P_{ET_{CO_2}}$, $P_{ET_{CO_2}}$ in the young subjects was corrected with the regression equation of Jones and coworkers (20) because $P_{ET_{CO_2}}$ tends to overestimate Pa_{CO_2} during exercise in young subjects (10, 20). In contrast, $P_{ET_{CO_2}}$ was not corrected in the senior and elderly subjects because $P_{ET_{CO_2}}$ appears to be a good estimate of Pa_{CO_2} in older subjects (10). $P_{ET_{CO_2}}$ was not significantly different between groups at rest, VTh, and peak exercise. These data suggest that $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ were elevated as a result of increased dead space $\dot{V}_E$, and not hyperventilation. In an attempt to confirm an increase in dead space ventilation with aging, ratio of dead space volume to tidal volume (V_D/V_T) was estimated using $P_{ET_{CO_2}}$ and mean expired P_{CO_2} (Table 4). At rest, there was a trend for V_D/V_T to increase with aging, although no statistical differences were observed between groups. V_D/V_T was significantly higher ($p < 0.01$) in the elderly subjects than in the young subjects at VTh. No differences in V_D/V_T were observed between groups at maximal exercise.

Breathing Mechanics

Analysis of EELV data revealed an interaction between gender and age. Thus, each gender was analyzed separately. EELV for men (Figure 2, *panel A*) and women (Figure 2, *panel B*) are plotted against $\dot{V}_E$ at rest, VTh, and peak exercise. At rest, senior and elderly men had a greater ($p < 0.01$) EELV than young men, whereas all groups were different at VTh ($p < 0.01$) and peak exercise ($p < 0.01$), indicating that EELV in men increased progressively with age. In women, EELV also increased with aging; the senior and elderly women had a greater EELV at VTh ($p < 0.01$) and peak exercise ($p < 0.01$) than the young women. Additionally, the normal decrease in EELV during the early stages of exercise was not observed in elderly men and women. EILV also progressively increased with aging (Figure 3). Resting EILV in the elderly subjects was greater ($p < 0.05$) than in the young subjects; both senior and elderly subjects had a higher EILV at VTh ($p < 0.01$) and peak exercise ($p < 0.01$) than young subjects.

In Figure 4, V_T and f are plotted against $\dot{V}_E$ at rest, VTh, and peak exercise. No differences in V_T were observed between groups at rest. Elderly subjects had a lower V_T than young and senior subjects at VTh ($p < 0.01$) and peak exercise ($p < 0.01$). Breathing frequency was significantly increased by aging. Elderly subjects had a greater f relative to

TABLE 4

SELECTED VENTILATORY VARIABLES*

	Young			Senior			Elderly		
	Rest	VTh	Max	Rest	VTh	Max	Rest	VTh	Max
$\dot{V}_E/\dot{V}O_2$	24.8 ± 6.3^{a‡}	20.75 ± 4.0^{a‡}	40.5 ± 10.1	28.9 ± 9.1^{b‡}	25.7 ± 6.6^{a‡}	42.6 ± 8.7	37.7 ± 8.0^{a,b‡}	32.9 ± 5.8^{a‡}	43.4 ± 10.0
$\dot{V}_E/\dot{V}CO_2$	31.1 ± 6.6‡	23.4 ± 4.0^{a‡}	29.5 ± 5.8^{b†}	34.8 ± 9.0^{b‡}	28.5 ± 5.5^{a‡}	33.1 ± 6.0^{b†}	46.6 ± 7.7^{a,b‡}	37.1 ± 7.0^{a‡}	38.7 ± 8.4^{a,b†}
$P_{ET_{CO_2}}$, mm Hg	37.4 ± 3.6	39.9 ± 3.1	32.4 ± 5.2	34.3 ± 4.7	37.2 ± 4.8	31.1 ± 4.5	36.1 ± 5.0	37.3 ± 5.8	35.8 ± 6.6
V_D/V_T	0.24 ± 0.09	0.19 ± 0.07^{a†}	0.21 ± 0.06	0.28 ± 0.16	0.23 ± 0.08	0.22 ± 0.09	0.31 ± 0.07	0.27 ± 0.05^{a†}	0.27 ± 0.04

Definition of abbreviations: $P_{ET_{CO_2}}$ = end-tidal CO_2; $\dot{V}CO_2$ = carbon dioxide production; V_D = estimated dead space volume.

* Values are mean ± SD. Comparisons are between groups at rest, VTh, and maximal exercise. Values marked with like letters (a, b) are significantly different from each other. † $p < 0.01$, ‡ $p < 0.001$.

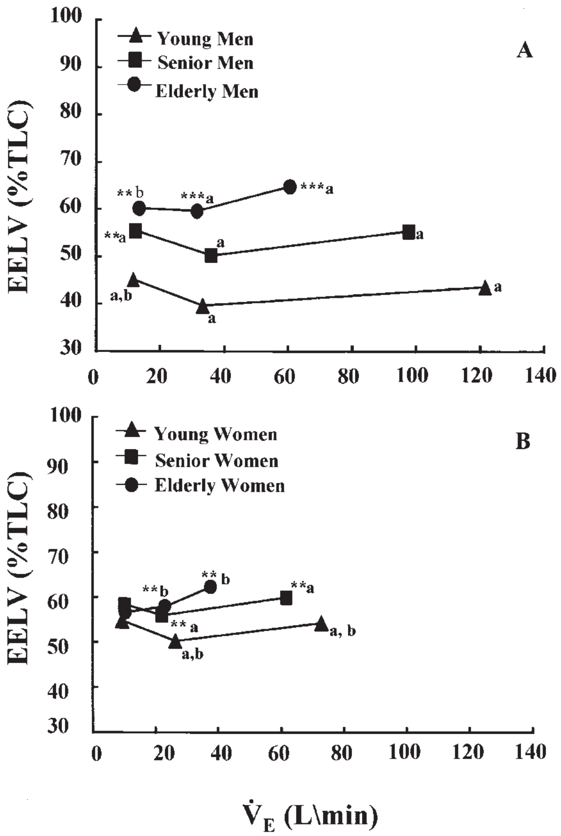

Figure 2. EELV (%TLC) plotted against $\dot{V}_E$ (L/min) at rest, VTh, and maximal exercise (max) for men (*panel A*) and women (*panel B*). Values marked with like letters (a, b) are significantly different from each other. **$p < 0.01$, ***$p < 0.001$. Comparisons are between groups at rest, VTh, and max. Values are in the following order, young, senior, and elderly groups, respectively (mean ± SD). Men: Rest EELV = 45 ± 4, 55 ± 8, 60 ± 8% TLC; VTh EELV = 40 ± 6, 50 ± 5, 60 ± 4% TLC; Max EELV = 44 ± 4, 55 ± 4, 65 ± 5% TLC. Rest $\dot{V}_E$ = 12 ± 2, 13 ± 2, 14 ± 3 L/min; VTh $\dot{V}_E$ = 33 ± 6, 36 ± 7, 32 ± 7 L/min; Max $\dot{V}_E$ = 122 ± 19, 98 ± 22, 61 ± 17 L/min. Women: Rest EELV = 55 ± 5, 58 ± 9, 57 ± 8% TLC; VTh EELV = 50 ± 5, 56 ± 6, 58 ± 3% TLC; Max EELV = 54 ± 6, 60 ± 4, 62 ± 2% TLC. Rest $\dot{V}_E$ = 9 ± 1, 10 ± 5, 11 ± 2 L/min; VTh $\dot{V}_E$ = 26 ± 6, 22 ± 6, 24 ± 6 L/min; Max $\dot{V}_E$ = 73 ± 20, 62 ± 9, 38 ± 7 L/min.

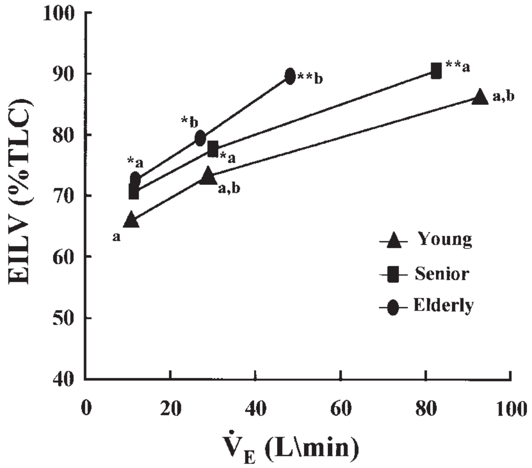

Figure 3. EILV (%TLC) plotted against $\dot{V}_E$ at rest, VTh, and maximal exercise (max). Values marked with like letters (a, b) are significantly different from each other. *$p < 0.05$, **$p < 0.01$. Comparisons are between groups at rest, VTh, and max. Values are in the following order, young, senior, and elderly groups, respectively (mean ± SD): Rest EILV = 66 ± 7, 71 ± 8, 73 ± 10% TLC; VTh EILV = 73 ± 6, 78 ± 7, 80 ± 3% TLC; Max EILV = 87 ± 4, 91 ± 3, 90 ± 3% TLC. $\dot{V}_E$ values are as in Figure 1.

young and senior subjects at rest ($p < 0.05$) and VTh ($p < 0.01$). At peak exercise, f was significantly lower ($p < 0.01$) in the elderly group than in the young group. Although not statistically significant, there was a tendency for V_T as a percentage of predicted FVC to be higher in the senior and elderly subjects relative to the young group at any given $\dot{V}_E$. It is likely that increases in EELV and EILV approaching the ceiling of TLC resulted in a decreased V_T reserve, which caused the elderly subjects to use a reduced V_T and increased f to generate the necessary $\dot{V}_E$.

EAFL progressively increased with aging. In Figure 5, tidal flow–volume loops measured at rest and during peak exercise are shown relative to the maximal flow–volume loop for a typical subject from each group. Elderly subjects (Figure 6) experienced greater EAFL at rest (9.9%V_T, $p < 0.05$), VTh (22.0%V_T, $p < 0.01$), and peak exercise (29.7%V_T, $p < 0.01$) than both young and senior subjects. In Figure 5, inspection of the exercise tidal flow–volume loops relative to the maximal flow–volume loops indicated that the elderly subjects had little ventilatory reserve in which to accommodate the increased ventilatory demand of heavy to maximal exercise and experienced marked airflow limitation. The greater levels of EAFL experienced by the elderly subjects also occurred at lower absolute ventilatory demands (Figure 6).

DISCUSSION

The findings of this study indicate that mechanical constraints to $\dot{V}_E$ during exercise are progressive with aging, elderly sub-

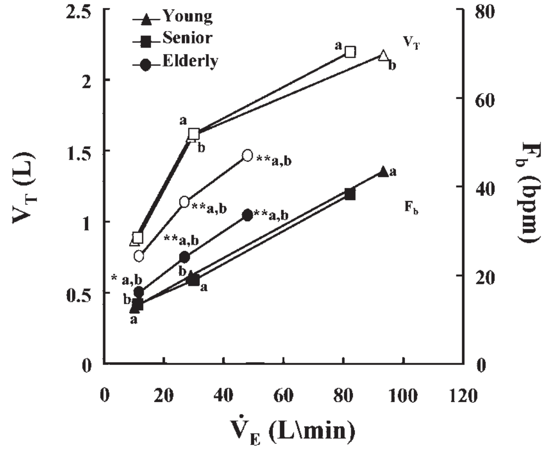

Figure 4. Breathing pattern (V_T and f) plotted against $\dot{V}_E$ (L/min) at rest, VTh, and maximal exercise (max). Values marked with like letters (a, b) are significantly different from each other. *$p < 0.05$, **$p < 0.01$. Comparisons are between groups at rest, VTh, and max. Values are in the following order, young, senior, and elderly groups, respectively (mean ± SD): Rest V_T = 0.87 ± 0.4, 0.89 ± 0.3, 0.76 ± 0.2 L; VTh V_T = 1.60 ± 0.6, 1.62 ± 0.4, 1.14 ± 0.4 L; Max V_T = 2.18 ± 0.7, 2.20 ± 0.6, 1.47 ± 0.6 L. Rest f = 13 ± 3, 14 ± 4, 16 ± 4 breaths/min; VTh f = 20 ± 6, 19 ± 4, 24 ± 4 breaths/min; Max f = 44 ± 8, 38 ± 9, 34 ± 7 breaths/min. $\dot{V}_E$ values are as in Figure 1.

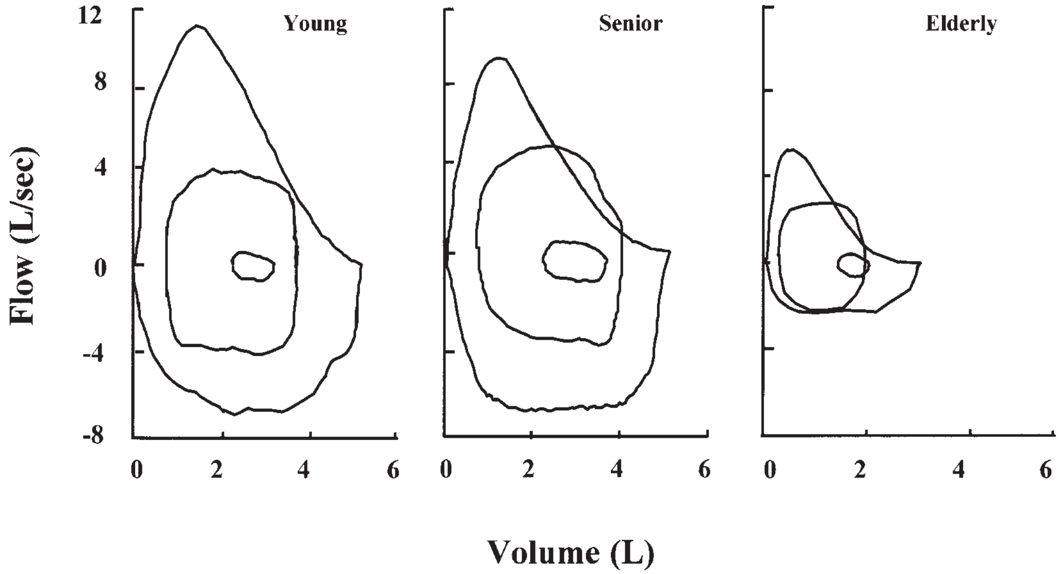

Figure 5. Maximal and tidal flow–volume loops for a typical subject from each group. Maximal flow–volume loops measured in a pressure-corrected volume displacement body plethysmograph and tidal flow–volume loops measured during rest and maximal exercise are shown for each subject. EAFL was defined as %V_T that was equal to or greater than maximal flow and was 0, 15, and 27% for the young, senior, and elderly subjects, respectively.

jects demonstrating marked mechanical ventilatory constraints and an increased ventilatory requirement during exercise. These ventilatory constraints were evidenced by increases in EELV and EILV, which limited V_T reserve, and by increases in EAFL. To our knowledge this is the first study to examine the extent of ventilatory constraints in the ninth and tenth decades of life, and to determine how these constraints affect the ventilatory response to exercise. Elderly subjects also exhibited an increased ventilatory demand during light-to-moderate exercise and experienced mechanical ventilatory constraints at higher ventilatory demands, which resulted in a relatively "flattened" ventilatory response to exercise above VTh.

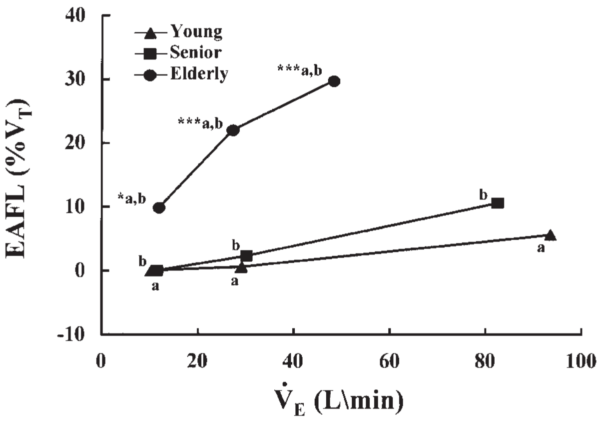

Figure 6. EAFL plotted against ventilation at rest, VTh, and maximal exercise (max). Values marked with like letters (a, b) are significantly different from each other. $*p < 0.05$, $*** p < 0.001$. Comparisons are between groups at rest, VTh, and max. Values are in the following order, young, senior, and elderly groups, respectively (mean ± SD): Rest EAFL = 0, 0, 10 ± 17% V_T; VTh EAFL = 1 ± 2, 2 ± 4, 22 ± 19% V_T; Max EAFL = 6 ± 6, 11 ± 11, 30 ± 21% V_T.

Ventilatory Response to Exercise

Elderly subjects in this study had an elevated $\dot{V}_E$ for a given submaximal work rate below VTh. Others (21, 22) have attributed this to increased dead space ventilation in the elderly and suggested that the increase in $\dot{V}_E$ actually gives the older subject an alveolar ventilation similar to that of a younger person. The increased $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ at rest and VTh in the elderly supports an increase in dead space ventilation. Estimates of V_D/V_T also revealed a tendency for dead space to increase with aging. However, if mechanical constraints limit an increase in V_T in the elderly, V_D/V_T would be higher in these subjects relative to the other two groups even without an increase in V_D. The larger valve dead space utilized by the elderly subjects would also contribute to a higher V_D/V_T. However, based on the work of Barlett and colleagues (23), we do not believe that a difference in valve dead space of 55 ml would significantly affect $\dot{V}_E$.

Additionally, the increase in $\dot{V}_E$ during submaximal exercise could be the result of an increased metabolic demand in the elderly. Several investigators (24, 25) have reported an increased $\dot{V}O_2$ and $\dot{V}_E$ in elderly subjects during submaximal exercise. The observed increase in the slope of $\dot{V}O_2$ versus work rate below VTh in our elderly subjects suggests that they had an increased metabolic demand. According to Hansen and coworkers (26) the slope for 1-min incremental cycle ergometer work is 10.2 ± 1.0 ml O_2/min/W for normal subjects. Our elderly subjects had a mean slope of 17.2 ml O_2/min/W, almost twice the value reported by Hansen and coworkers (26). This suggests that mechanical inefficiency, increased dead space, and the possibility of an increased work of breathing (WOB) are potential factors which could contribute to this increased metabolic demand. We believe the increased mechanical constraints of EAFL and elevations in EELV and EILV at rest and during submaximal exercise in elderly subjects could increase the WOB, which is reflected in an increased metabolic demand. This in combination with a decrease in efficiency, which has been reported in older subjects (25, 27) may help explain the increased $\dot{V}O_2$ per watt, and consequently, the increase in $\dot{V}_E$ below VTh.

Normally, for a given increment in work rate, $\dot{V}_E$ increases at a greater rate above VTh than below VTh. Elderly subjects in this study did not increase $\dot{V}_E$ at a greater rate above Vth than below VTh, which relative to the young and senior groups is not a normal response to progressive exercise. Regardless, the ventilatory response to exercise above VTh appears adequate in the elderly subjects because the slope of $\dot{V}_E$ versus work rate above VTh is not different among groups. However, if you consider that the ventilatory response to exercise below VTh was elevated in the elderly subjects because of either increased dead space ventilation and or mechanical inefficiency, these factors should also be encountered above VTh. Thus, the ventilatory response of the elderly subjects should be proportionally increased above VTh. We propose that as a result of an increased ventilatory demand during submaximal exercise the elderly subjects approached mechanical ventilatory constraints relatively early during exercise. Thus, it appears that these elderly subjects had used a large portion of their ventilatory capacity by VTh and could not further increase $\dot{V}_E$ because they were mechanically constrained. Previously, Babb (4) demonstrated that some of these same senior subjects, unlike younger subjects, have little reserve for accommodating an increase in ventilatory demand while breathing 3% CO_2. Based on the progressive nature of mechanical ventilatory constraints with aging, we would predict that the elderly subjects would have an even smaller ventilatory reserve in which to accommodate an increased ventilatory demand. Were we to give these elderly subjects inspired CO_2, they could potentially have an even lower ventilatory response to inspired CO_2.

In agreement with several other investigations (28–30) we observed a decline in $\dot{V}_E$ and $\dot{V}_E$/MVV at peak exercise with aging (Table 3). Although $\dot{V}_E$/MVV is commonly used as an indicator of ventilatory constraint, it has been shown to be a poor indicator of mechanical ventilatory constraints (31) and is misleading in mild chronic obstructive pulmonary disease (COPD) (32), which is probably true for the elderly as well. In 1991, Blackie and coworkers (28) in a cross-sectional study of 231 men and women established normal values and ranges for $\dot{V}_E$ at maximal exercise and demonstrated a progressive decrease in maximal ventilatory variables with aging. Our data for $\dot{V}_E$ and $\dot{V}_E$/MVV at maximal exercise show a similar rate of decline, and mean data at comparable ages are almost identical to that reported by Blackie and coworkers (28). Some would suggest that the observed decreases in $\dot{V}_E$ and $\dot{V}_E$/MVV are simply the result of a decrease in maximal oxygen consumption ($\dot{V}O_2$max). Yerg and associates (29) and others (28, 30) have reported that the decline in maximal $\dot{V}_E$ is closely linked to the decline in $\dot{V}O_2$max with aging. Furthermore, studies (29, 30) have shown that $\dot{V}_E$/MVV is also closely related to $\dot{V}O_2$max and that $\dot{V}_E$/MVV can be increased by physical training which increases $\dot{V}O_2$max, whereas MVV is unchanged. These investigators (29, 30) have suggested that ventilatory capacity is not a determinant of $\dot{V}O_2$max in normal individuals. However, these investigations examined individuals in the sixth and seventh decades of life, and we believe that given the limited ventilatory reserve in subjects 85 to 95 yr of age, ventilatory constraints could potentially have an influence on $\dot{V}O_2$max in the elderly subject who may have mechanical ventilatory constraints. However, a similar rate of decline for $\dot{V}_E$ and $\dot{V}O_2$ does not indicate cause and effect, only association. Nevertheless, it is our belief that physical training of elderly subjects may increase $\dot{V}O_2$max by lessening their ventilatory demand during submaximal exercise. By decreasing $\dot{V}_E$ during submaximal exercise elderly subjects could accomplish more work before they encounter mechanical ventilatory constraints, resulting in an increased maximal work rate and $\dot{V}O_2$max. Thus, for the same peak $\dot{V}_E$ these subjects could accomplish more work and have a higher $\dot{V}O_2$max.

Additionally, Ware and coworkers (6) have reported that the loss of FEV_1 with aging proceeds in a nonlinear fashion beyond age 50. Thus, it is conceivable that with advancing age, the nonlinear decreases in pulmonary function could eventually produce a respiratory system that could constrain exercise capacity. In this study, there was a nonlinear decrease in $\dot{V}_E$ at peak exercise with aging (Figure 7). The nonlinear decrease in peak $\dot{V}_E$ observed in this study would suggest that ventilatory capacity mimics the nonlinear decrease in FEV_1 reported by Ware and coworkers (6). The significant correlation between FEV_1 and maximal $\dot{V}_E$ observed in this study would further support this conclusion. However, this study cannot refute or establish $\dot{V}_E$ as a limiting factor to exercise at the age of 85 to 95 yr, only that ventilatory capacity is limited in these subjects and that the potential for $\dot{V}_E$ to play a role in limiting exercise capacity is much greater in the elderly than the young subject.

Breathing Mechanics

The most distinguishing mechanical effect of aging is the increase in EELV at rest and the subsequent increase with exercise. The increase in EELV at rest with aging is reportedly from a loss of elastic recoil of the lung (33, 34) and a stiffening of the chest wall (35). When increases in EELV are coupled with EILV approaching the ceiling of TLC, V_T reserve is reduced, thus limiting V_T. EILV averaged 90% of TLC in the senior and elderly groups and reached 95 to 97% of TLC in some senior and elderly subjects. Johnson and colleagues (36) in a study of men and women with a mean age of 70 yr reported that at an EILV $>$ 90% of TLC subjects will keep a constant V_T and endure further EAFL rather than increase lung volume at the expense of more elastic work. A reduced V_T reserve in combination with decreased maximal expiratory flow can result in limitations to f. Furthermore, many elderly subjects experience EAFL, which can result in further increases in EELV (37, 38). Elderly subjects in this study experienced EAFL at rest and throughout exercise. Consequently, EELV did not decrease during exercise in these subjects (16, 39) and EELV exceeded resting FRC during peak exercise. Thus, we believe the strategy used to accomplish an increase in $\dot{V}_E$ is mechanically constrained with aging, elderly subjects showing marked limitations. Young healthy subjects encroach

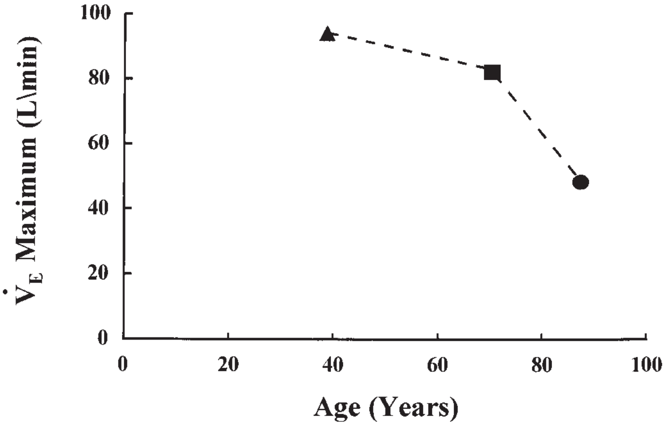

Figure 7. Maximal ventilation plotted against age.

on both the expiratory and inspiratory reserve volume to increase V_T over most of the exercise range. Relative to young subjects, elderly subjects' smaller VC, reduced maximal flow rates, and inability to decrease EELV impose substantial limits on their ability to increase V_T. This leaves the elderly subject with increases in f as their only strategy to increase $\dot{V}_E$. Elderly subjects in this study had a reduced V_T reserve and used increases in f early in exercise to increase $\dot{V}_E$. This strategy was effective until they began to experience marked EAFL. It is also possible that f was mechanically constrained in the elderly. The expiratory flow rates available to the elderly subjects may increase the time in which these subjects can expire a given volume, thus placing constraints on f. In conclusion, the results of this investigation suggest that mechanical ventilatory constraints are progressive with aging. Furthermore, while we believe that exercise is not ventilatory limited during peak exercise, individuals in the ninth and tenth decades of life demonstrate marked ventilatory constraints which limit their ventilatory reserve and potentially increase the respiratory work necessary to further augment $\dot{V}_E$. The impact of these constraints on exercise tolerance cannot be determined from this investigation and remains unclear. This situation is similar to that observed in younger patients with mild COPD.

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