5
Demand vs. Capacity in the Aging Pulmonary System

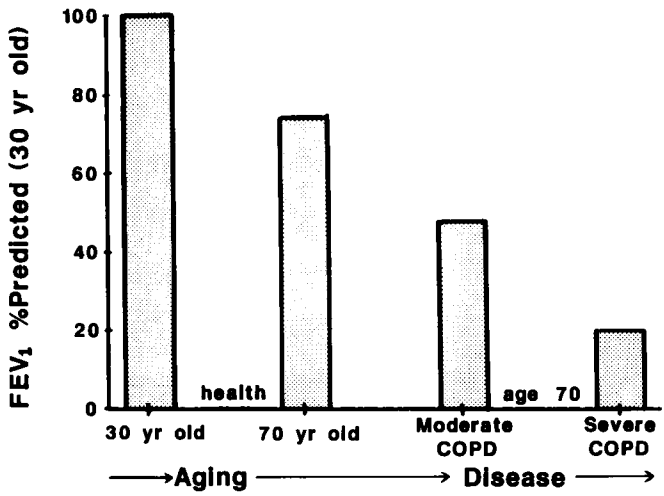
BRUCE D. JOHNSON, Ph.D.
JEROME A. DEMPSEY, Ph.D.

The primary focus of this review is on the remarkable capacity of the healthy pulmonary system, even the significantly compromised system, for gas transport during exercise in the older adult (60–80 yrs of age). Numerous structural and functional changes in the lung, chest wall, respiratory muscles, and vasculature occur with age [9, 27, 38, 82, 74, 139]. These changes encroach significantly on the reserve of the healthy pulmonary system to produce expiratory airflow and inspiratory muscle pleural pressure, to ensure diffusion equilibrium of alveolar and end-capillary partial pressure of oxygen (P_{O_2}), to uniformly distribute inspired gas, and to maintain a low pulmonary vascular resistance in the face of high pulmonary blood flow. Nonetheless, the healthy pulmonary system, even in the later years of life (>70 years of age) continues to meet the extraordinary demands placed on it by heavy exercise to maintain arterial blood gas and pH homeostasis. Even in the highly trained and fit older athlete capable of achieving very high maximal metabolic requirements, these reserves are further reduced, but only in extremely rare instances are they surpassed [61, 62]. The only major, consistent consequence of the aging process may be the degree of efficiency and, therefore, metabolic cost with which exercise hyperpnea is achieved [61].

In the first decade of life the respiratory system undergoes extensive growth and development [106, 129, 117]. By the second decade cellular proliferation ceases and only hypertrophy of existing structures occurs, reaching maturity between the 20th and 25th years of life [70, 71, 106]. Following these developmental years the aging process begins, apparently affecting the majority if not all the tissues of the respiratory system. Although the process is extremely gradual during most of adulthood, the process may accelerate in the later years, beyond the age of 60 to 65 [71, 95, 117].

Because the aging process mimics so closely changes in lung tissue that are associated with a disease process (i.e., emphysema) [108, 142] it often is difficult to factor out changes associated with aging alone versus accelerated changes caused by a history of exposure to environ-

FIGURE 5.1
Representative FEV_1 for healthy 30- and 70-year-old adults and for 70-year-old adults with moderate and severe chronic obstructive pulmonary disease expressed as a percent of predicted for 30-year-old adults. The loss of lung recoil with aging causes FEV_1 to move towards the disease state; however, the aging affect alone is substantially less than that resulting from the disease process.

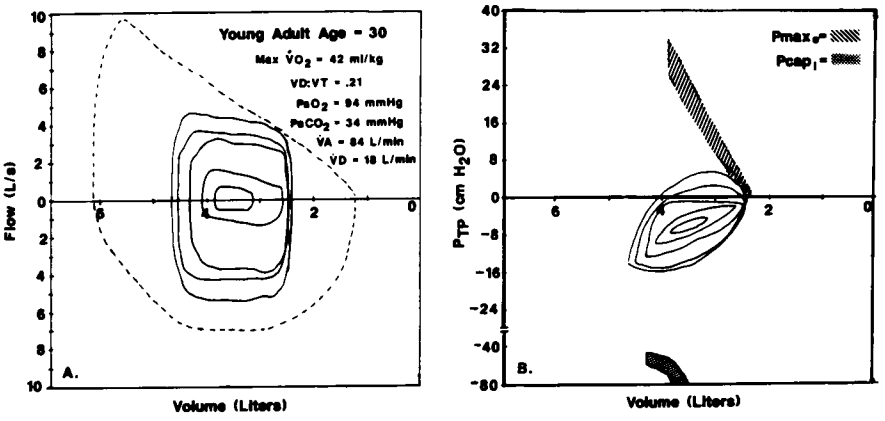


mental pollutants, pulmonary infections, and differences in lifestyle, such as smoking habits [134]. Although the aged lung appears to fit on a continuum leading to the disease state as shown in Figure 5.1, the nonsmoking, aging lung (in this case showing the forced expiratory volume in one second, FEV_1) falls much closer to the healthy state than the diseased state. The majority of studies dealing with aging also are cross-sectional, which, when compared to longitudinal studies, may tend to overestimate declines in respiratory function with age [71, 134, 44, 28]. The aim of this review is to examine the changes in pulmonary function and airway mechanics that are associated with aging, discuss morphological correlates for these changes and how they might alter the normal ventilatory response to exercise, and review what actually is known about the response of the respiratory system to exercise in an aging population. We frequently will refer to data from our own studies [61, 62] of 30 healthy, physically active older persons.

MAJOR RESPONSES OF THE PULMONARY SYSTEM TO EXERCISE IN THE HEALTHY, UNTRAINED YOUNG ADULT

The pulmonary system in the young adult (20 to 30 yrs of age) responds to exercise by a precise neuromechanical regulation of alveolar venti-

FIGURE 5.2
Typical ventilatory response to progressive exercise in an untrained young adult. The solid lines represent the flow:volume (on the left) and pressure:volume (on the right) response at rest and during mild-, moderate-, heavy-, and maximum-intensity work loads. Loops were placed on the volume axis according to a measured end expiratory lung volume (EELV). The flow:volume loops are placed within the maximum volitional postexercise (dashed line) flow:volume loop, and the tidal pressure:volume loops are placed within the shaded area, representing the maximal effective pressures on expiration ($Pmax_e$) and the capacity for inspiratory muscle pressure generation ($Pcap_i$) at the volume and flow rate at which peak pressure occurred during tidal inspiration.



lation matched to metabolic demand [24], as well as through myriad changes that occur to optimize the transfer of oxygen from alveolar gas to arterial blood [21]. Figure 5.2 summarizes the normal flow:volume (f:v) and pleural pressure:volume (p:v) response to exercise in the young adult and lists the normal gas exchange parameters obtained at maximal exercise in this group of subjects.

Four key mechanical responses occur as exercise progresses from mild to maximal. First, the lung volume at the end of expiration (EELV) decreases with progressive exercise because of recruitment of expiratory muscles [56, 64]. The energy stored in the abdominal wall because of the active expiration provides some passive recoil at the initiation of the ensuing inspiration [49]. A more optimal (longer) length also is achieved for tension development by the diaphragm [29, 113]. Second, tidal volume (V_T) is increased by encroaching equally on inspiratory and expiratory reserve volume, avoiding the less compliant areas of the lung and chest wall [56, 145]. Third, maximum flow rates achieved during tidal breathing are well within the maximum available flow rates

[100]. Pleural pressure development during expiration only approaches flow-limiting pressures ($Pmax_e$) near EELV [100, 57]. That is, for a given lung volume, pleural pressure development does not reach a pressure that causes airways to narrow and therefore limit expiratory airflow. Fourth, on inspiration, peak pleural pressure reaches only 50% of the estimated capacity for pressure generation ($Pcap_i$) as determined at the lung volume and flow rate at which peak pressure was obtained [2, 79]. The result of these major mechanical responses to exercise is a highly efficient increase in alveolar ventilation with substantial reserve available to increase ventilation ($\dot{V}E$) even at maximal levels of exercise.

Several major adjustments in the pulmonary system occur to optimize gas transfer. The distribution of ventilation (VA) to perfusion (Qc) remains uniform during exercise [43] and overall VA/Qc rises substantially, both of which minimize the chances of arterial hypoxemia. Pulmonary capillary blood volume increases threefold with exercise, assuring an adequately long red blood cell transit time and diffusion surface area for alveolar to end-capillary O_2 equilibrium as cardiac output increases [21, 112]. Any rise in pulmonary arterial pressures that cause an increased turnover of lung water during exercise is matched by an increase in lung lymph flow, which assures that the lung stays dry [14]. Despite these significant adjustments to optimize gas transfer during exercise in the young adult, the alveolar-to-arterial-oxygen difference widens two- to threefold during exercise. This has been attributed to slight intraregional VA/Qc inhomogeneities, a 1% anatomical shunt with mixed venous blood composition [42], and a potential diffusion disequilibrium for oxygen in end-capillary blood even at work loads requiring only 3 L/min $\dot{V}O_2$ [135, 136].

AGE-DEPENDENT STRUCTURAL CHANGES IN THE RESPIRATORY SYSTEM

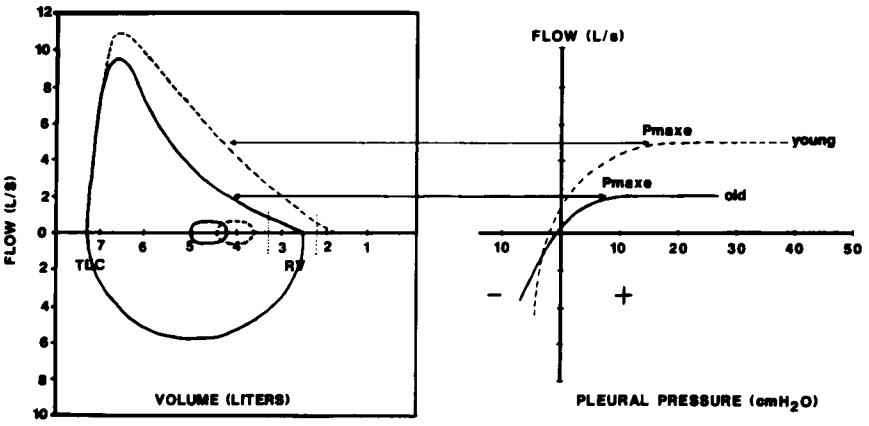
Pulmonary Mechanics

Four major changes appear to affect lung function, pulmonary mechanics, and expiratory flow rates as aging occurs. The primary change is a decrease in elastic recoil of the lung tissue [40, 39, 60, 104, 105, 133] and to a lesser extent a stiffening of the chest wall [115, 94, 96], a decrease in intervertebral spaces [32, 90], and an apparent loss of respiratory muscle strength [7].

These changes result in the age-related declines in lung volumes and flow rates as shown in Figure 5.3, which describes the mean volitional maximal flow:volume loop (MFVL) for 30 older subjects (age = 70, range 61 to 79) tested in our laboratory [62] compared to that predicted for height- and weight-matched 30-year-old adults. The smaller loop within the MFVL represents the resting tidal breaths for each age

FIGURE 5.3

Expiratory Reserve. *Changes in lung mechanics with age. The figure on the left shows the MFVL for 30 older subjects (average age = 70 ± 2 yrs, solid line) versus the MFVL for height- and weight-matched 30-year-olds (predicted, Knudson et al. [71] dashed line). The smaller loops represent the resting tidal loops for the older and younger subjects placed at their respective functional residual capacity (FRC). The dotted vertical lines represent the closing capacity in each age group, with the line at the highest lung volume representing the older subjects. The figure on the right shows the flow and pleural pressure relationship at a single lung volume of 60% total lung capacity (TLC) in the older (solid) and younger (dashed) subjects (Iso-volume, pressure flow curves). Maximal effective pressure ($Pmax_e$) occurred at 12 cm H_2O vs 21 cm H_2O in the older and younger subjects, respectively. Values were obtained from the following regression equations: Young: $Pmax_e$ = 0.93 * (Lung Volume, %TLC) − 34.4, r = .84), Old: $Pmax_e$ = 1.02 * (Lung Volume, %TLC) − 48.6, r = .83). Note the evidence for reduced lung elastic recoil in the older fit subject: elevated FRC and closing capacity, reduced maximal expiratory flow (MEF) 50%, and lower expiratory pressure (and higher lung volume) at which airways are dynamically compressed and flow rate becomes effort-independent.*



group. As shown, vital capacity (VC) and maximal expiratory flow rates (MEF) decreased, and functional residual capacity (FRC), residual volume (RV), and closing capacity (CC, dotted lines) increased. Total lung capacity (TLC) showed little change with aging.

Although a dominant mechanical change in the intact lung, which leads to the changes in pulmonary function, appears to be the loss of elastic recoil (increased compliance), biochemical correlates with elastin and collagen content (the predominant structural proteins in the lung)

and structural changes within the matrix of these components are still not conclusive [74, 4, 36, 76, 77]. Because of the lack of evidence showing specific changes in the content of these proteins, there may be simply a disorganization of the normal crosslink patterns with age [102, 107, 111, 118]. More recent work using immune histochemical techniques shows a decrease in elastic fibers along the alveolar walls, together with an increase in type III collagen with age [25]. No variations of these components were noted in the alveolar ducts or in the respiratory bronchioles. Of the elderly subjects studied [25] (mean age = 76 yrs) who died of nonrespiratory causes, some also showed an increase in the thickness of the alveolar basement membrane. Modifications of the surfactant in the aging lung appear to be minimal [121, 143].

The loss of elastic recoil of the lungs has classically been shown by a shift to the left of the static p:v relationship of the lung [15, 40, 133]. At a given percentage of the TLC, therefore, the recoil pressure is less in the aged lung. Conversely, the compliance characteristics of the chest wall reveal that with aging the chest wall is compliant at any given lung volume, which yields a higher recoil pressure. The increased recoil of the chest wall has been attributed primarily to calcification of the costal cartilages [32, 94]. During ventilatory maneuvers over the range of the VC, it appears that older persons expand the rib cage less than do younger persons, resulting in a greater reliance on the diaphragm for ventilation [115]. This skeletal alteration of the costal cartilages apparently reduces the mobility of the rib cage more during expiration below FRC than during inspiration above FRC [115]. The balance of these two forces (i.e., the recoil of the lung tending towards collapse and the outward pull of the cest wall) yields the resting FRC, which (when measured by means of body plethysmography) usually increases with aging [82].

Changes in the intervertebral spaces, along with decalcification of the vertebrae, lead to decreased height in the elderly and an increase in anterior-posterior diameter. This could account for some decreases in TLC reported in the literature in older subjects [32]. Changes in TLC with age are variable (usually decrease or no change) and are the balance of the ability of the respiratory muscles to inspire versus the recoil of the lung and chest wall.

Some controversy persists over the major reason why RV rises with age and VC declines. A loss of lung recoil and air trapping, as well as a decreased chest wall compliance or decreased expiratory muscle strength [80], would account for this rise [5]. Chest wall strapping studies performed on aging and young adults tend to favor the loss of elastic recoil as the major mechanism [60].

The fall in VC and FEV_1 averages from 27 to 41 mL/yr and 21 to 51 mL/yr, respectively, in cross-sectional studies and significantly lower, 6 to 12 mL/yr, for both variables in longitudinal studies [134, 44, 71].

The apparent discrepancies between cross-sectional and longitudinal studies, however, have not been resolved but may be related to younger adults today being generally taller than their counterparts 50 years ago, or to statistical methodology or equipment changes [134].

Maximal expiratory airflow rates between RV and approximately 75% of TLC (effort independent region of the MFVL) also are reduced with age primarily because of the loss of elastic recoil. As one exhales forcefully, the pressure created outside the lung in the thoracic cavity causes large increases in airflow. The recoil pressure within the airways maintains airway pressure above the thoracic pressures and keeps the airway open; the recoil pressure is reduced as long volume falls during expiration. The radius of the airways and turbulent flow cause a resistance to airflow, which also causes airway pressure to fall below thoracic pressure as air is exhaled. At the "equal pressure point", expiratory air flow becomes effort-independent and any additional pressure generated by expiratory muscles is ineffective. The older adult reaches this "equal pressure point" at a higher lung volume than a younger adult because the recoil pressure within the airway is reduced from the start of an exhalation, therefore reducing the maximal flow rate at a given lung volume.

We demonstrated [61] this principle in a group of 12 older subjects representative of the 30 tested in our laboratory. We determined the largest pleural pressure generated ($Pmax_e$) to obtain maximal expiratory airflow at various lung volumes (50–75% of TLC) according to the methods of Olafsson and Hyatt [100]. We compared their response to young adults (age = 26) also tested in our laboratory. As shown in Figure 5.3, at a given lung volume, in this case 60% of TLC, the maximum pleural pressure generation achieved at the point expiratory air flow levels off is lower in the older adults than in the younger adults. The amount, therefore, of maximal expiratory air flow achieved at any lung volume within the effort-independent region is reduced. These measurements of maximal effective pressure generation in each of the older subjects were later used to determine how close tidal breaths during exercise came to flow limiting pressures.

The loss of elastic recoil also is manifested in the lung volume at which airways "close", or at least markedly narrow (closing volume, CV). In the young adult the closing capacity (RV + CV) occurs at 30% of TLC; at age 70 it occurs at 45% of TLC, a rise of approximately 250 ml/decade [17, 13, 5, 78].

In summary, the major changes in resting lung function associated with aging appear to be due to the loss of elastic recoil of the lung. This leads to the dynamic narrowing or closure of airways during expiration at elevated lung volumes relative to younger adults. In turn, this limits the maximum available expiratory flow rates, causes a mild hyperinflation, and increases the volume of trapped alveolar gas in

dependent regions of the aging lung, especially at the lower lung volumes.

Respiratory Muscles

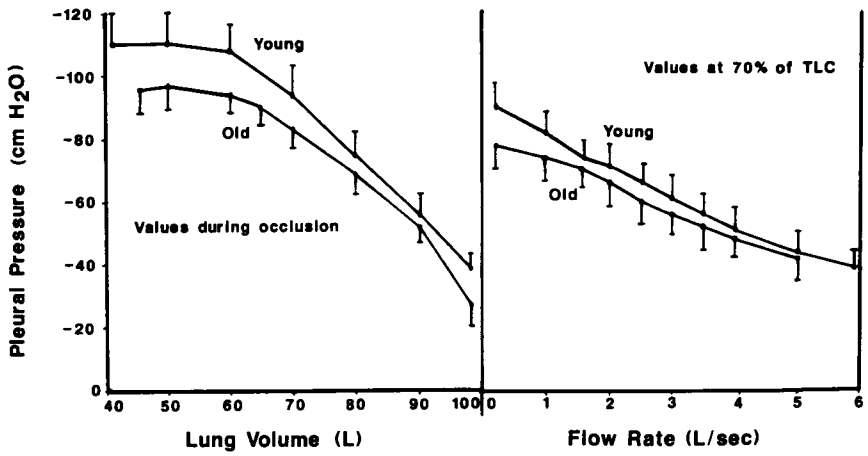
Age-related changes noted in some rodent locomotor skeletal muscles (i.e., decreased isometric and dynamic strength) [11, 30, 33, 132] appear to be attenuated in the diaphragm muscle [123]. Type II muscle fiber size or distribution does not appear to change with age [30, 46]. Capillary density also appears to remain constant in the diaphragm muscle from rats 4 to 27 months old [46]. There appears to be no apparent age-related differences in myosin heavy chain and light chain between old and young rats [123, 124]. Diaphragmatic neuromuscular coupling also is not significantly altered by the normal aging process [123, 124].

Indicators of respiratory muscle strength in humans, such as the maximal amount of mouth pressure that can be developed on inspiration against an occlusion, either do not show any significant changes [91], or show a moderate decline with increasing age [7]. Maneuvers such as this are volitional and highly variable and recruit muscles that probably do not normally play a major role in ventilation. It is difficult, therefore, to assess what is happening in the major respiratory muscles with age.

We attempted to better define inspiratory muscle strength in the twelve older subjects referred to previously that were tested in our laboratory [61]. Maximal pleural pressure development (measured with an esophageal balloon) was determined in duplicate over six different lung volumes from RV up to TLC to determine the effect of lung volume (length-tension relationship) on maximal pleural pressure [79]. In addition, the effect of flow rate (velocity of shortening) on pleural pressure development was determined at rest by having subjects perform maximal inspiratory efforts with different resistances so that the flow rate varied [79]. These measurements were later compared with the inspiratory pleural pressure development during tidal breathing in exercise to determine its proximity to the available capacity for pressure development ($Pcap_i$). Maximal inspiratory pressure development against an occlusion was greatest (-97 cmH_2O) from approximately 40–60% of TLC in the older subjects, which compared to 35–59% of TLC (-110 cmH_2O) in the younger adults tested in our laboratory using an identical protocol. The effects of lung volume and flow rate on inspiratory pressure development are shown in Figure 5.4 together with regression equations showing the combined effect of flow rate and lung volume on the inspiratory pleural pressure development. As shown, neither the effect of increasing lung volume nor the effect of increasing flow rate on pressure generation by inspiratory muscles was significantly different between the younger and older subjects.

Considering the animal studies and the limited amount of human work, it appears that age-related changes in the respiratory muscles are

FIGURE 5.4
Inspiratory Reserve. *The effect of lung volume and flow rate on pleural pressure development by inspiratory muscles in older (n = 12, age = 70 ± 2) and younger (n = 8, age = 26 ± 2) subjects. The effect of lung volume is shown from values obtained during occlusion (zero flow) and the effect of flow rate is shown from values obtained at 70% of TLC. The combined effect of lung volume and flow rate are summarized in the following regression equations: Young: $Pcap_i$ (% of max occlusion pressure) = 113 − 0.65 * (Lung Volume, %TLC) − 5.21 * (Flow rate L/s), r = .83. Old: $Pcap_i$ = 140 − .97 * (Lung Volume, %TLC) − 6.0 * (Flow rate L/s), r = .80.*



minimal. In older sedentary subjects, the potential for atrophy of accessory muscles and motivation level may play a factor in age-related changes associated with common volitional tests.

Alveolar to Arterial Gas Exchange

Five major changes potentially could affect gas exchange as aging occurs: (1) a loss of elastic recoil of the lung [58, 5, 133], (2) decreased surface area of the lung [130], (3) decreased pulmonary capillary blood volume [18, 34], (4) increased dead space ventilation [10, 109, 114, 89], and (5) decreased distensibility of the pulmonary arterial vasculature [110].

The loss of recoil in the lung not only effects the static lung volumes and MEF rates but also effects how ventilation is distributed. As the lung ages, the decline in recoil throughout the lung is most likely not a uniform process. This results in regions of the lung that may be more or less compliant than other regions, which causes areas of unequal mechanical time constants so that distribution of a breath is most likely

not as uniform as in youth [53, 31, 58, 98, 72, 137]. Topographically, at rest, in the normal tidal breathing range ventilation in an older person may not be preferential to the lower regions of the lung as in the young adult [31]. This is presumably due to airway narrowing or closure in these dependent areas of the lung. These topographical differences with age were made worse with a forced expiration preceding the measurement of VA distribution and abolished with augmented inspiratory flow rates [31]. Blood flow to the apex of the lung is higher in the older adult relative to the younger one; however, like the younger adult, the majority of blood flow in the older adult is still directed to the lung base [58, 73].

The inert gas technique quantifies intraregional distribution of V_A/Q_c. To date, a small number of measurements in a few older, healthy adults showed a greater nonuniformity of V_A/Q_c relative to the young [137]. In no cases, however, was the V_A/Q_c distribution abnormal (i.e., markedly skewed to extremely low or high V_A/Q_c) such as occurs with a diseased state [137].

Structural changes in the aging lung lead to a decrease in alveolar capillary surface area (75 m^2 age 20 to 60 m^2 age 70) [130, 128]. The alveolar septa decrease and the alveolar duct diameter increases [99, 131], resulting in a decreased surface area for diffusion of gases into the pulmonary capillaries. In fact, the lung weight at autopsy is approximately 20% lighter in the aged adult [74]. The decreased surface area results in a decrease in the diffusion capacity for carbon monoxide of the lung, DLCO (approximately 4–8% per decade) [59, 18, 37], a measure of alveolar-capillary interface.

The reduction of pulmonary capillary interface as well as a stiffening of the pulmonary arteries and capillaries result in an age-related decrease in pulmonary capillary blood volume. The decline, however, appears to be small, resulting in a fall in this volume of approximately 2 to 5 ml per decade [18, 45]. In the normal young adult (20–30 yrs) this volume averages 75 ml and in the 70-year-old adult 50–65 ml.

The increased stiffness of the pulmonary vasculature with age has little or only a mild effect (increased slightly) on pulmonary arterial pressure (Ppa) with age at rest [47, 48, 34] which, although small, could account for the increased perfusion to the apex of the lung in the elderly as previously noted.

There appears to be a slight but significant age-dependent rise in dead space ventilation at rest in the aged adult, which has been attributed to the increased diameter of the large airways (anatomical) as well as to increases in areas of the lung that are over ventilated, i.e., high VA/Qc regions (physiological dead space) [109, 127].

Numerous regression equations have been published which describe an age-related decrease in arterial oxygen tension and the resulting widening of the alveolar to arterial oxygen difference (A-a D_{O_2}) [125,

109, 93, 6, 67, 98, 86, 87, 140]. The change in partial pressure of oxygen in the arterial blood (PaO_2) with age appears to be variable, however, ranging from very little change (<1 mmHg per decade) to substantial decline (>5 mmHg per decade). Reasons for the discrepancies are undetermined but may be because many studies were not controlled for body position, smokers and nonsmokers, and general health status of the subjects.

SUMMARY

Figure 5.5 summarizes the potential effects that the structural and functional changes in the respiratory system with age may have on the response to exercise. Clearly, the available reserve for increasing V_T and expiratory air flow and inspiratory muscle pressure during exercise in the elderly person is reduced. In addition, the established rise in closing volume and decreased surface area of the lung (i.e., DLCO) may limit the available strategies of the aging respiratory system for meeting the demands imposed by heavy exercise. Of course, the effect of these changes with age on the exercise response will depend greatly on the demand imposed by the severity of the exercise. These responses are now discussed in detail throughout the remainder of the review.

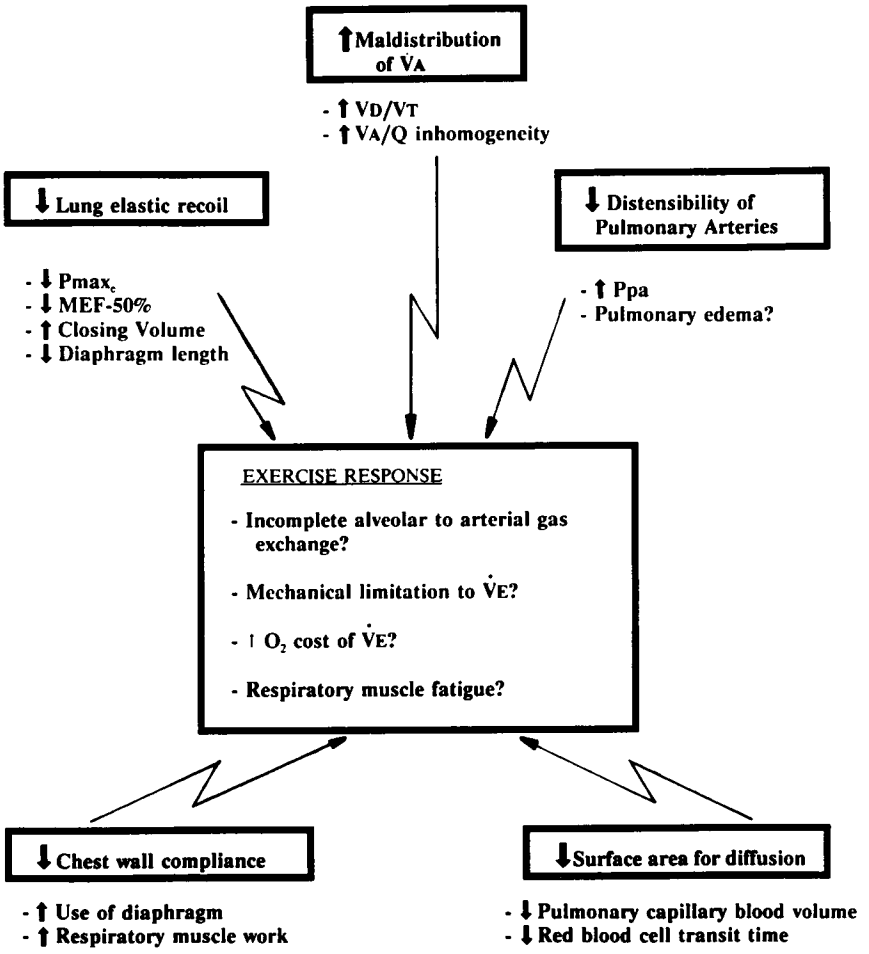
RESPONSE OF THE RESPIRATORY SYSTEM TO EXERCISE IN THE ELDERLY

Although a good deal of literature describes ventilatory responses in the elderly during exercise [20, 55, 54, 26, 3, 41, 50, 84], few data address pulmonary mechanics and gas exchange. We now discuss these topics based on our recently completed comprehensive study [61, 62] in an older population of 30 relatively fit, healthy older subjects (see Table 5.1). Data have already been presented from this group of subjects on resting lung and chest wall function (see Table 5.2 and Fig. 5.3).

Mechanics, Breathing Pattern, Ventilatory Work, and Cost

The flow, pleural pressure, and volume response to progressive exercise in 12 of the older subjects (representative of the group tested in our laboratory, age = 70, $\dot{V}O_2max$ = 44 ml/kg/mn, max HR = 165 bpm, max $\dot{V}E$ = 110 L/mn) is shown in Figure 5.6 and Table 5.3. These are contrasted with those in the 30-year-old untrained subject who reaches about the same mean $\dot{V}O_2max$ and $\dot{V}Emax$ (see Fig. 5.1). The habitually active and relatively fit older subjects showed the usual age-related changes in pulmonary function and mechanics. Like the young adult, the older subjects tended to increase $\dot{V}E$ primarily through increases in

FIGURE 5.5
Summary of potential aging effects on the response of the respiratory system to exercise. The numerous structural changes that occur in the pulmonary system with aging potentially reduce the capacity of the pulmonary system for responding to the increased need for gas transport.



VT during the lighter exercise loads, with a leveling off of VT at 58% of VC (75% of $\dot{V}O_2$max), which is slightly greater than that normally reported in younger adults (although the range is substantial, see Table 5.3). After 75% of $\dot{V}O_2$max, primarily a frequency of breathing (fb) response to exercise is noted. These findings are similar to those reported by DeVries and Adams [26]. Ventilatory timing variables (i.e.,

TABLE 5.1
Subject Characteristics and Maximal Exercise Performance In Older, Physically Active Adults (N = 30)

	Age (yrs)	*Ht (cm)*	*Wt (kg)*	*Max $\dot{V}O_2$ (ml/kg/mm)*	*Pred* (%)*	*Max HR (bpm)*	*Pred† (%)*	*Wlk/Rn (mi/wk)*
Mean	70	173.0	66.8	43.7	199	165	100	28
SEM	1	1.3	1.8	1.7	9	2	2	3
Range	61–79	162–194	54–86	25–62	116–306	148–184	89–112	12–60

* Normal predicted values for $\dot{V}O_2$max based on age, from Jones et al. [66].
† Normal predicted values for maximal heart rate (HR) based on age, from Lange-Anderson et al. [75].

expiratory and inspiratory time) were similar to those in younger subjects at rest and throughout exercise.

The older person appears to have a higher ventilatory response at a given submaximal metabolic demand, so that in our subjects and in other studies [41, 55] the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ relationship is elevated, although in some studies the reported differences are small [144, 52]. This higher $\dot{V}E/\dot{V}CO_2$ relationship, combined with a higher dead space ventilation, gives the older subjects a near identical $\dot{V}A/\dot{V}CO_2$ and $PaCO_2$ to the younger subjects at any given $\dot{V}CO_2$. The fitness level of the older subject, like the younger subject, also will determine the magnitude of the ventilatory response to heavier exercise, because the onset of metabolic acidosis (and the coincidental compensatory hyperventilation) occurs at a higher work load in the trained person [65]. Accordingly, physical training causes a decrease in the $\dot{V}E/\dot{V}O_2$ relationship in older persons [144, 119, 120].

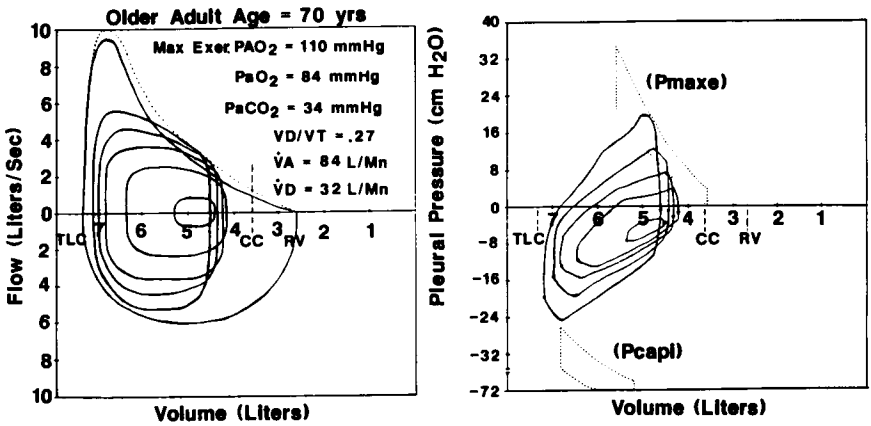
End expiratory lung volume decreased significantly from rest with mild (50% $\dot{V}O_2$max) and moderate exercise (75% $\dot{V}O_2$max) in a similar manner to that described in the young adult. Unlike the young adult,

TABLE 5.2
Preexercise Lung Volumes and Flow Rates in Older Subjects (Age = 70 yrs)

Preexercise (N = 29)	*Actual ($\bar{x}$ ± SEM)*	*% PRED (70 yr olds)*	*% PRED (30 yr olds)*
TLC (L)	6.98 ± .17	105*	99*
VC (L)	4.28 ± .13	109*	84*
FRC (L)‡	4.07 ± .11	100*	118*
RV (L)	2.68 ± .08	90*	123*
CC (L)	3.33 ± .10	99†	150†
$FEV_{1.0}$ (L)	3.07 ± .09	101**	74**
MEF-50% (L/s)	3.26 ± .20	90**	65**

‡ Values obtained in a body plethysmograph.
** Normal predicted values for maximal expiratory air flow rates and $FEV_{1.0}$ based on age and height, from Knudson et al. [71].
* Normal predicted values for lung volumes based on age, height, and weight, from Needham et al. [97].
† Normal predicted values for CC based on age and height, from Cherniack [13].

FIGURE 5.6
Group mean ventilatory response to exercise in older adults (n = 12, age = 70 ± 2 yrs). The solid lines represent tidal breathing, flow: and pleural pressure: volume loops plotted according to a measured EELV at rest through maximal exercise. The flow: volume loops are plotted within the pre- (solid) and post- (dotted) maximal volitional flow: volume loops. The dashed vertical line represents the closing capacity for the group as measured at rest. On the right, the tidal pressure: volume loops are plotted with respect to the dotted areas representing the maximal effective pressures on expiration and the capacity for pressure development on inspiration. Also shown are relevant arterial blood gas and ventilatory parameters obtained at max exercise (see Figs. 5.3 and 5.4 for explanation of mechanical parameters).



however, flow limitation and maximal effective pressure generation are approached at these lower submaximal exercise levels. To achieve greater expiratory flow with increased metabolic demand, EELV is increased, thus moving a portion of the tidal pressure and flow: volume breath away from flow limitation. During maximal exercise, this results in an EELV that is significantly elevated (60% of TLC) relative to the young adult (40% TLC). This results in a less optimal operating length of the diaphragm in the older person when the demand for inspiratory air flow is near maximal. These changes in lung volumes and capacities for rest, moderate, and maximal exercise are shown in Figure 5.7 for the 30 older subjects tested and compared to the volume changes in $\dot{V}O_2$ matched younger subjects. The rising EELV and constant V_T over the highest work intensities cause mean end inspiratory lung volume (EILV) to rise to 93% of TLC and the capacity for pressure generation by inspiratory muscles to fall. As shown in Figure 5.6, peak inspiratory pressure comes within 80% of the capacity of the inspiratory muscles

TABLE 5.3
Metabolic, Ventilatory, and Timing Variables During Exercise in Older Subjects (Age = 70 yrs)

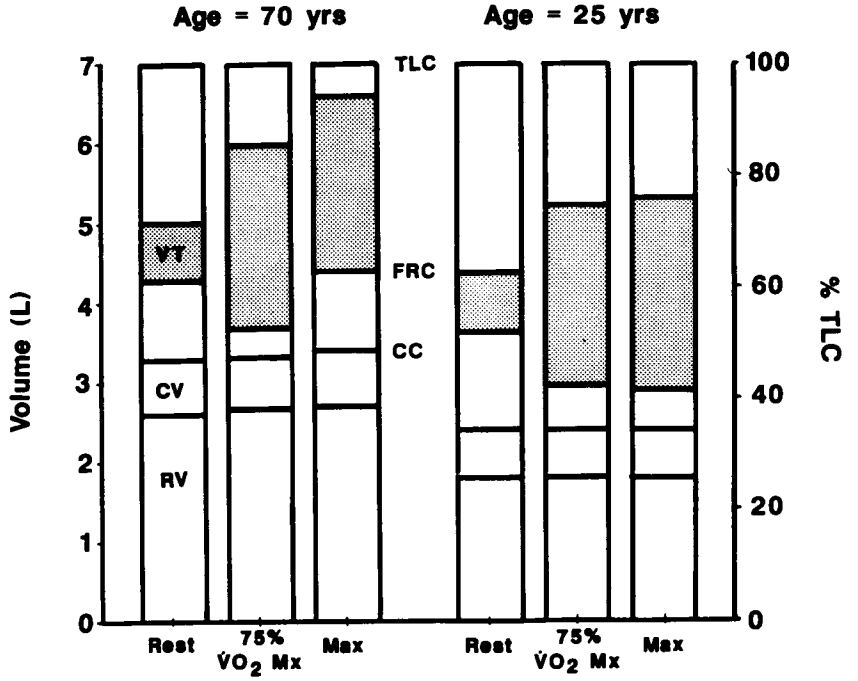
n = 30	*Rest* ($\bar{x}$ ± *SEM*)	*Moderate* (75%)*	*Max* (100%)*	*Range* (at max)
$\dot{V}O_2$ (ml/kg/m)	4.2 ± .2	31.3 ± 1.1	42.8 ± 1.6	25.6–62.0
$\dot{V}_E$ (L/mm)	11.3 ± .84	71.5 ± 3.4	113.6 ± 4.8	64.5–158
$\dot{V}_E/\dot{V}O_2$	40.3 ± .9	34.2 ± 1.1	38.1 ± 1.6	24.7–50.5
$\dot{V}_E/\dot{V}CO_2$	47.5 ± .9	32.4 ± .6	35.5 ± 1.4	22.5–53.1
f (bpm)	14 ± 1	29 ± 1	46 ± 1.2	32–58
VT (L)	.82 ± .05	2.43 ± .11	2.45 ± .08	1.41–3.4
Ti/Ttot	.47 ± .02	.48 ± .01	.48 ± .01	.43–.61
VT/Ti (l/sec)	.42 ± .04	2.47 ± .12	3.75 ± .15	2.16–5.88
VT/VC	.20 ± .02	.57 ± .02	.58 ± .03	.43–.86
EELV (L)	4.07 ± .11	3.69 ± .13	4.04 ± .15	2.84–5.44
$\frac{n = 12}{Cdyn}$ (l/cm H_2O)	.24 ± .02	.25 ± .03	.17 ± .01	.08–.24
RLe (cmH_2O/l/sec)	3.17 ± .18	3.61 ± .40	5.20 ± .38	3.6–7.6
RLi (cmH_2O/l/sec)	2.86 ± .20	2.46 ± .20	3.17 ± .21	2.4–5.1

* Represents approximate percent of $\dot{V}O_2$max.
Cdyn = dynamic compliance, RLe = expiratory pulmonary resistance, RLi = inspiratory pulmonary resistance. Resistance calculated at peak flow [92].

for pressure generation and is actually reached in 4 of the 12 subjects tested. This is in contrast to younger, untrained subjects who reach <50% of this pressure generation capacity (as shown in Figure 5.1) at this level of ventilation [79]. Without the rise in EELV in the older subjects, peak inspiratory pressure would have reached only 65% of the capacity for pressure generation. In summary, owing to decreased reserve for expiratory flow rate, EELV is elevated, reducing the length:tension relationship of the inspiratory muscles, and causing the capacity for inspiratory pressure generation to fall.

Despite the rising EELV, flow limitation still occurred over >40% of the V_T at maximal exercise, and expiratory pressure generation reached maximal effective pressures over 25% of the V_T. The large, positive expiratory pressures indicate a significant recruitment of expiratory muscles, greatly adding to the ventilatory work. Like the younger adult, however, the older adult generally does not develop excessive expiratory pleural pressure (i.e., pressure without increased flow); as a result, highly inefficient breathing is avoided. Expiratory resistance rises as a result of the disproportionate rise in pleural pressure for the given flow rate because of dynamic airway narrowing. This is unlike the younger adult who shows no significant rise in resistance at this level of ventilation (see Fig. 5.2) [145, 56]. Dynamic compliance of the lung (Cdyn) falls in the elderly subjects, especially over the top two work loads, most likely because the EILV reached such a high percentage of the TLC and an alinear portion of the pressure:volume relationship of the lung and chest wall. The younger adult also shows a progressive

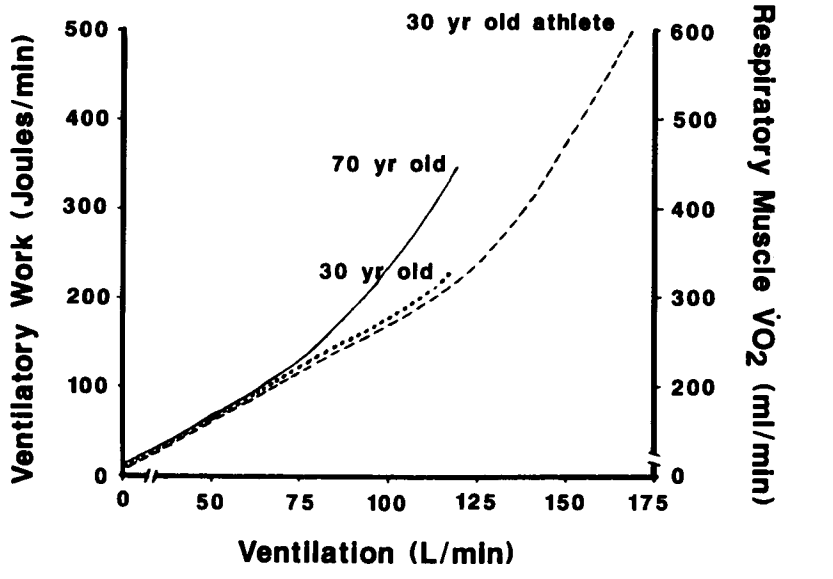
FIGURE 5.7
Changes in lung volumes during exercise in older (n = 30, age 70 ± 2 yrs) and $\dot{V}O_2$ max matched younger (age = 30) subjects. $\dot{V}E$max is also similar for young (100 L/min) and older (115L/min) subjects. Shaded areas represent the tidal volume. Starting from the bottom of each bar graph the first line represents RV, the second line, CC, third line EELV, fourth line EILV, and the top line TLC. Note in the older subjects the increased EELV and end-inspiratory lung volumes at rest and exercise.



decrease in the Cdyn during exercise, although EILV achieves only 75 to 85% of the TLC [56]. This decrease in Cdyn is attributable to the tidal breath reaching the less compliant portion of the elderly person's lung and chest wall owing to a high inspiratory volume as well as a reduced EELV [56].

The expiratory flow limitation and concomitant increase in expiratory resistance (flow resistive work) and decreased Cdyn (elastic work) in the older subject cause the ventilatory work ($\dot{W}_v$) to increase curvilinearly with exercise. This curvilinear increase is out of proportion to the increase in work determined in younger adults at similar levels of ventilation [1, 101]. Because the measurement of work (i.e., integrated p:v loops) does not take into account several components of ventilatory

FIGURE 5.8
*Ventilatory work ($\dot{W}_v$) and the estimated respiratory muscle $\dot{V}O_2$ (ml/min) in fit older subjects (n = 12, age = 70 ± 2) and $\dot{V}O_2$ matched younger subjects [1] and in younger athletes at a much higher $\dot{V}O_2$max. The work and cost of ventilation increases disproportionately at a lower ventilation in the older subjects versus the younger adults who require a greater percent of the total body $\dot{V}O_2$ at any given $\dot{V}E$ to support the muscles of respiration. At maximal exercise the $\dot{V}O_2$max devoted to ventilation was 13% (range 7 to 23%) in the older subjects, 6% (range 5–8%) in the younger untrained subjects, and 13% (range 10–16%) in the younger athletes. Ventilatory work was measured in all cases from the pressure:volume loops. $\dot{V}O_2$ of maximal exercise ventilation was estimated from ventilatory work according to the relationship defined by Aaron et al. [1]: $\dot{V}O_2$ of the respiratory muscles during exercise − the resting $\dot{V}O_2$ = .081 + .001 * (exercise $\dot{W}_v$ − rest $\dot{W}_v$).*



work (such as chest wall distortion, etc.), which are exaggerated in the elderly, our calculated $\dot{W}_v$ values are low. Figure 5.8 shows the differences in $\dot{W}_v$ between young and older adults tested in our laboratory.

We estimated the O_2 cost of breathing based on a regression equation derived on young adults from the increase in $\dot{V}O_2$ required when the mechanical characteristics and respiratory muscle recruitment patterns achieved during exercise were mimicked at rest [1]. The oxygen cost of breathing in our older subjects averaged 13% of the total body $\dot{V}O_2$ at maximal exercise, with values as high as 15–23% in the fittest subjects

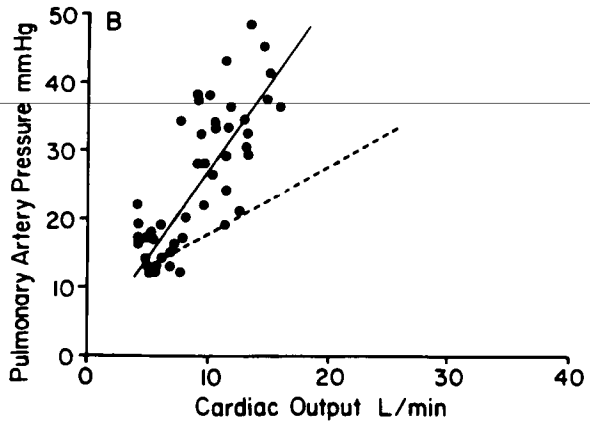
with the greatest ventilatory responses. This compares with approximately 5–7% for the same $\dot{V}_E$ in the younger adult [1]. The relationship of the change in respiratory muscle oxygen consumption to the change in ventilation appears to increase dramatically as mechanical limits for flow and pressure development are approached [16]. This represents a significant increase in the need for blood flow to the respiratory muscles and would theoretically compromise blood flow to the working locomotor muscles.

The postexercise MFVL of the elderly subjects shown in Figure 5.6 shows a significant rise in the MEF rates relative to preexercise. The apparent bronchodilation which occurs during exercise allows an additional 10 to 15 L/min of ventilation during maximal exercise. This significant effect on airway diameter helps to counteract some of the rise in the flow resistive work of breathing in these subjects [141]. The exercise-induced bronchodilation occurs in both young and old, but was greater in the older subjects tested in our laboratory.

Pulmonary Vasculature

Minimal literature exists on the hemodynamic changes in the pulmonary vasculature in the healthy aged subject [47, 48, 51, 110]. The data available describe changes in pulmonary arterial pressure (Ppa), pulmonary wedge pressure (Ppw), and the resultant pulmonary vascular resistance (PVR) (Ppa-Ppw/Q) with exercise. There is some debate over the accuracy of Ppw as an indicator of left atrial pressure, mainly because of intrathoracic pressure changes associated with hyperpneic states such as exercise, which yield erroneously high results. Figure 5.9 shows the changes in Ppa in response to supine exercise in a group of older subjects (61–83 years) relative to that determined on younger adults [47, 110]. At rest in the supine position, Ppas are only slightly elevated in the older adults as are Ppws and the estimated PVR. To increase blood flow through the lung, one must increase vascular driving pressure from the pulmonary artery to the left atrium. During heavy exercise in the older subjects, the Ppa increases (i.e., 100% from rest) out of proportion to those determined at a similar $\dot{V}_{O_2}$ and Q in younger adults (50%). Similarly, Ppw increases 120% in the older subjects versus only 25% in the younger adults. The pressure difference Ppa-Ppw was similar in both age groups and, therefore, PVR was similar in both groups. Although the older adults were more hypertensive than the younger ones at a given $\dot{V}_{O_2}$ and Q, the younger adults were able to achieve much higher metabolic work rates and therefore reach Ppas and Ppws similar to those achieved in the older adults at lower workloads. Measurements obtained in the sitting position at rest and during exercise reveal similar trends between the old and young, although differences are not as striking as while supine [47]. We emphasize that despite the relative pulmonary hypertension, we have no evidence for accumulation

FIGURE 5.9
Pulmonary hemodynamics with age. Shown are the pulmonary arterial pressures with increased cardiac output from rest to exercise in the supine position in 14 healthy older men aged 61 to 83 years (solid regression line) and in young men and women (dashed regression line). From Reeves et al. [110] and Granath et al. [47].

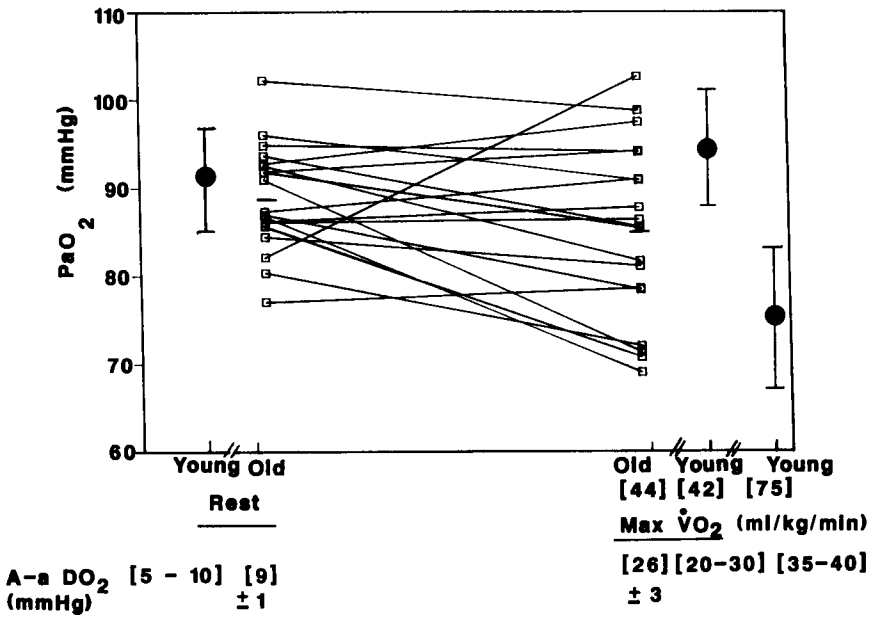


of extra vascular lung water in the older subjects, even during very heavy exercise, at least as judged indirectly by means of the A-a D_{O_2} during exercise (see below). Furthermore, we were unable to detect any change in lung volume subdivisions, closing volume, or diffusion capacity immediately following maximal exercise in our older subjects.

Pulmonary Gas Exchange
We investigated the adequacy of pulmonary gas exchange in 19 of our sample of 30 elderly subjects, as described earlier. Tonometered blood was used to ensure accurate calibration of blood gas electrodes. Three to six arterial blood samples were obtained in the steady-state at rest and at each workload in each subject and averaged to best represent each condition; all exercise samples were corrected for changes in core temperature. Individual subject values for PaO_2 at rest and at maximal exercise are shown in Figure 5.10, together with a comparison with average values for untrained 30 year olds at rest and at their max $\dot{V}O_2$ and with highly trained younger athletes.

In general, at rest and during all exercise loads through maximum, alveolar to arterial gas exchange and arterial blood gas homeostasis showed very little effect of aging in our group of healthy, fit subjects. Note the following evidence. At rest in the sitting posture, PaO_2 averaged in the high 80s, with a mean $PaCO_2$ of 38–40 mmHg. Only 3 of the 19

FIGURE 5.10
Arterial P_{O_2} and A-a D_{O_2} values in 19 older subjects (age = 70 ± 2) at rest and during maximal exercise. These values are shown relative to the resting and maximal exercise values in $\dot{V}_{O_2}$ matched young adults and in young endurance athletes at higher max $\dot{V}_{O_2}$max (n = 24) [21, 23]. The mean values for the older subjects are shown by the horizontal dashes.



subjects showed a PaO_2 of less than 85 mmHg, and this was due to mild hypoventilation ($PaCO_2$ 43–44 mmHg). Thus, in almost all cases, our older subjects fit well within the 95% confidence limits of resting arterial blood gases for younger adults. The alveolar to arterial O_2 difference (A-a DO_2) was more variable but remained only slightly wider (2–5 mmHg) than the usual mean values for younger subjects; only 3 of the 19 older subjects exceeded 15 mmHg. The dead space to tidal volume ratio (V_D/V_T) was consistently higher by 15–20% in the older subjects, but extreme values, i.e., greater than 0.5 V_D/V_T, did not occur. During exercise the group mean A-a DO_2 gradually widened to about three times rest at $\dot{V}_{O_2}$max; PaO_2 remained within 5 mmHg of resting values. The mean A-a DO_2 was within the upper range of the average values achieved by younger untrained adults at a similar max $\dot{V}_{O_2}$. The A-a DO_2 exceeded 30 Torr in 8 of the 19 subjects tested, but the accompanying hyperventilatory response was usually sufficient to raise alveolar PO_2 high enough so that arterial hypoxemia was pre-

vented. As described earlier, V_D/V_T was elevated (relative to younger subjects) at any given $\dot{V}O_2$, but fell progressively with exercise; when combined with a vigorous ventilatory response, this ensured that alveolar hyperventilation was usually sufficient at all work loads for adequate CO_2 elimination (see Fig. 5.6). In only 4 of 19 subjects was there evidence of exercise-induced hypoxemia as PaO_2 fell to less than 75 mmHg and SaO_2 to less than 92% at max exercise. These subjects were characterized by wider A-a DO_2 in the 35 to 45 mmHg range, and only one of the four had an alveolar PO_2 less than the average value (see subject RA, Fig. 5.14). During submaximal exercise, PaO_2 was reduced to less than 75 mmHg in four subjects; this usually coincided with a hypoventilatory response, with $PaCO_2$ in the 42–46 mmHg range.

These data support the conclusion that alveolar to arterial gas exchange and blood gas homeostasis during even markedly intense exercise is, for the most part, almost independent of the aging process. Theoretically, one might predict otherwise, given the propensity for maldistribution of ventilation secondary to the older subjects' high closing capacity and the age dependent decline in pulmonary diffusion surface area. Under conditions of controlled, inspiratory flow rate and tidal volume, initiating inspiration from within the closing volume does cause a clear maldistribution of ventilation [35, 19]. Accordingly, some studies do report markedly widened A-a DO_2 (greater than 20 mmHg) and PaO_2 only 70–75 mmHg range at rest in some groups of otherwise healthy adults greater than 60 years of age; however, others support the findings in our group of a barely measurable aging effect or no change from the young [69, 93, 98, 109]. Perhaps more surprising is our finding that alveolar to arterial PO_2 differences only rarely widened markedly in the older subject, even at extremely high workloads. During moderate to heavy exercise, 11 of our subjects did reduce their EELV so that inspiration was initiated below their closing capacity, an average of 0.26L (0.07–0.6L); thus, about 15–20% of their V_T occurred within their closing capacity. The A-a DO_2 or V_D/V_T in 9 of these 11 subjects was not abnormally increased. To study this further, we examined the effects of posture in 10 subjects and found that closing capacity fell an average of 169 ml and end expiratory lung volume fell 435 ml from upright to supine position at rest, so that all subjects, even at rest, were breathing very close to or slightly within their closing capacity. Again, the A-a DO_2 at rest or during heavy exercise in the supine position remain very similar to that shown in these same subjects while upright; V_D/V_T was actually reduced slightly in the supine position both at rest and during exercise.

Given these findings on A-a DO_2, we speculate that distribution of ventilation during exercise must have been relatively unaffected by the aging effect of elastic recoil on airway closure—at least to the extent that would be manifested in overall pulmonary gas exchange. On the

one hand, breathing at these low lung volumes must certainly bring into play a maldistribution of mechanical time constants among peripheral airways [35, 19]. Perhaps, during exercise, these effects are overridden by the homogeneity in ventilation distribution promoted by inspiratory flow rates that are 8 to 10 times the resting level, and the fact that the greater majority of the augmented tidal inspiration still occurs above closing volume, and probably on the linear portion of the pressure:volume relationships of most of these open airways. Furthermore, as exercise intensity increased, expiratory flow limitation caused most of these subjects to raise their EELV, thereby moving their tidal breath not only away from flow limitation (see Fig. 5.6) but also well above their closing capacity. Furthermore, although the aging effect on alveolar-capillary diffusion surface area is significant (shown by the 30% decrease in single breath DLCO from age 30 to 70 years at rest), the available reserve for diffusion and pulmonary-capillary blood volume in the healthy elderly subject is apparently sufficient to meet the demands for pulmonary oxygen transport imposed by their max $\dot{V}O_2$, as well as to ensure sufficiently long red cell transit time in the pulmonary-capillary bed to provide alveolar to end pulmonary-capillary O_2 equilibrium at their maximum pulmonary blood flow. In most elderly, healthy, fit adults, therefore, the widened A-a DO_2 with heavy exercise is, as in the young, probably explained by a small but significant exercise-induced increase in the nonuniformity of VA:Qc distribution and by the contributions from a normal anatomical shunt of about 1% of total cardiac output containing reduced O_2 content similar to that in mixed venous blood [42, 43].

Finally, we note a significant portion of the group did show some significant problems with gas exchange at maximal exercise; 8 of the 19 subjects had an A-a $DO_2 > 30$ mmHg, and four of the eight had significant hypoxemia with $PaO_2 < 75$ mmHg and A-a DO_2 in the 35 to 45 mmHg range. These subjects were not necessarily those with the highest $\dot{V}O_2$max values; 6 of the 8 subjects had a $\dot{V}O_2$max > than the group mean, but an *equal number* of subjects with a $\dot{V}O_2$max in this 45–55 ml/kg/min range had A-a $DO_2 < 25$ mmHg. A significant but weak correlation existed between lung closing capacity and max A-a DO_2 ($r = 0.48$, $p < .05$) and seven of eight subjects with A-a $DO_2 > 30$ mmHg were among those with the highest closing capacities. These relationships may be an indirect indication of propensity toward nonuniformity in ventilation distribution. Resting DLCO was not abnormally low in any of these subjects. We believe these cases in the young or old are examples of the demand for oxygen transport and more rarely, CO_2 transport, exceeding capacity [21]. More specifically, in the case of the older athlete, these subjects have reached an appropriate position on the demand versus capacity continuum, in which either the negative aging effects on diffusion surface or the mechanical characteristics of

the small airways, or both, have surpassed the negative aging effects on the more primary determinants of $\dot{V}O_2max$, such as the dimensions of the cardiovascular system and the aerobic capacity of locomotor skeletal muscle. This disparity in the relative capacities of the organ systems may, of course, occur with continued physical training in the elderly, if the training stimulus had a greater effect on the cardiovascular-skeletal muscular dimensions than it did on the lung. These concepts are developed further in the remaining sections of this review.

EXERCISE DEMAND VERSUS RESPIRATORY SYSTEM CAPACITY

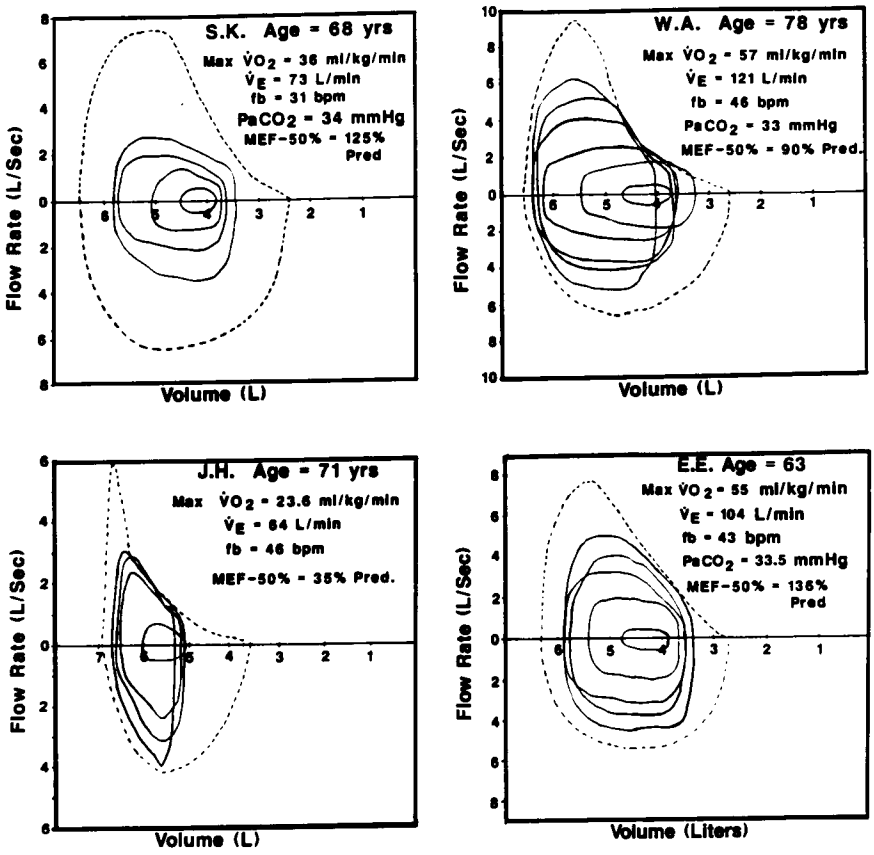
We have viewed the aging process as a reduction in the capacity or available reserve of the respiratory system to adjust to the increased demands imposed on it through exercise. As the degree of fitness increases because of either a training effect on the cardiovascular and skeleto-muscular systems or a genetic endowment, the reduced capacity of the aging respiratory system may present a greater relative influence on $\dot{V}O_2max$ or exercise performance. We now address this balance between the demands placed on the respiratory system and the ability or capacity of the system to respond. This concept applies either to the ability and cost to the lung and chest wall to generate airflow or to the capability of the system to exchange alveolar gas.

Four representative examples showing variations in the aging effect on the lung and chest wall versus the level of fitness as defined by the $\dot{V}O_2max$ are shown in Figure 5-11 and exemplifies the responses observed in the 30 older subjects tested.

LESS FIT ($\dot{V}O_2max$ 23–43 ml/kg/min): Compare subject SK to subject JH. JH experienced a much larger effect of aging on elastic recoil. Subject SK had a relatively low ventilatory demand during maximal exercise compared to the normal amount of airflow reserve available (MEF–50% = 125% predicted); subject JH also had a very low absolute ventilatory demand but a significant demand relative to his more limited reserve (i.e., MEF–50% = 35% of predicted). The major difference between these two subjects is related to the apparent aging effect on the lung, specifically affecting the available maximal expiratory flow rates.

HIGHLY FIT ($\dot{V}O_2max$ = 44–62 ml/kg/min): Subject WA represents someone with normal lung function for his age (78 yrs), but with an extraordinarily high $\dot{V}O_2max$ and thus substantial demand for ventilation and flow rate. Subject WA had to increase his EELV over the last three workloads to continue increasing flow rates; as a result his EILV reached 95% of his TLC at end inspiration. Subject EE also is highly fit and has a tremendous ventilatory demand; however, he has

FIGURE 5.11
Ventilatory demand versus capacity in the aged lung. Tidal flow:volume loops (solid loops) from progressive exercise tests (demand) *in four older subjects plotted according to measured EELV within the maximal volitional flow:volume loops* (capacity). *Note the variability in* $\dot{V}O_2max$ *(and therefore airflow and volume demand) relative to the available reserve for flow and volume in these four subjects.*



much better than normal lung function for his age, so that his ventilatory response to exercise and his flow and volume reserve at maximal exercise look similar to that noted in a younger adult (i.e., decreased EELV, little flow limitation) (see Fig. 5.2).

Contrast the large differences in $\dot{V}O_2max$ between subjects EE and JH. Despite his low ventilatory demand, subject JH is very close to reaching the limits for generating airflow because of a substantial aging effect on the MEF–50%. Subject EE, however, still has significant room

to increase V_E at maximal work because, even though his ventilation and flow requirements are much higher than JH, his aging effect on elastic recoil is virtually nonexistent. This substantial reserve at maximal work is even greater in a few additional subjects with lower levels of fitness who also showed (like subject EE) little effect of aging on lung mechanics.

Subject EE also represents an older subject with extreme metabolic demands, yet who demonstrates an adequate hyperventilatory response at maximal exercise sufficient to decrease $PaCO_2$ to 33.5 mmHg. He also demonstrates very effective gas exchange because he has a small A-a DO_2 (14 mmHg) during maximal exercise. This is in contrast to subject RA (Fig. 5.14), who not only shows an inadequate hyperventilatory response to exercise ($PaCO_2$ = 38.5 mmHg) but an extremely widened A-a DO_2 at a similar $\dot{V}O_2$max and $\dot{V}E$max. Although subject RA had a MEF–50% that was normal for his age, it is significantly reduced relative to subject EE; in view of his widened A-a DO_2, his lung must have greater inhomogeneity in VA/Qc or approach a diffusion limitation for O_2 transfer owing to his extreme level of metabolic demand.

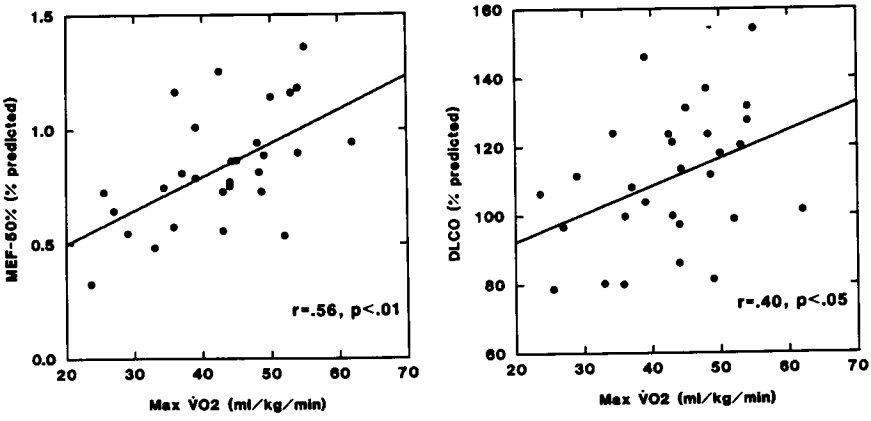
The balance struck, therefore, between ventilatory demand versus the capacity of the respiratory system to respond in the healthy elderly subject shows a great deal of variability among subjects. It depends critically on the contrast of aging effects on the morphological dimension of the pulmonary system *versus* exercise capacity.

What Role does Training or Fitness Have in Modulating the Aging Effects on the Pulmonary System?

There is limited evidence from cross-sectional studies that training or fitness may somehow influence lung volumes and airway mechanics both in older and in younger subjects [52]. Although our data represent cross-sectional information, we can make some inferences from our data to this question. Our subjects as a group represent a high level of fitness relative to their age predicted maximum (i.e., $\dot{V}O_2$max = 199 ± 10% of predicted). Despite this relatively fit population, the lung volumes (i.e., VC, FRC, CC, RV), MEF rates at 50% and 75% of VC, and gas exchange surface area as indicated by the DLCO still show the usual age-related changes. As a result, our group mean values average 100% of predicted values for their age. The data clearly show, therefore, that our highly fit group as a whole has undergone a significant aging effect on lung function. However, it is more difficult to determine any significant effect of "fitness" on this process because the normative predicted equations are based on broad ranges in the normative population.

A more definitive approach to this question takes advantage of the substantial variation in fitness in our group. Even though most of our

FIGURE 5.12
Relationship between lung function (i.e., MEF–50% and DLCO) expressed as a percent of age-predicted normal values and fitness level (i.e., $\dot{V}O_2$max) in 30 older adults (age = 70 ± 2 yrs).



subjects exceed 150% of their predicted $\dot{V}O_2$max, the range extended from 110–306% or 23 mL/kg per minute to 62 mL/kg per minute (Fig. 5.12). Within our group there were significant correlations (Fig. 5.12) between either % predicted MEF–50% or $FEV_{1.0}$ and $\dot{V}O_2$max (mL/kg per min) ($r = .56$, $p < .01$) as well as with % predicted DLCO and $\dot{V}O_2$max (mL/kg/per min) ($r = .40$, $p < .05$). Although these correlations are rather low, they tend to support the concept that either training or the level of fitness somehow does modulate or coincide with exceptional lung function. This impression is further demonstrated by taking the highest fit subjects (n = 15) and the lowest fit subjects (n = 15) in our group of older subjects and comparing mean values as shown in Table 5.4.

MEF–50% is 10% higher in the most fit group, as was the DLCO. The A-a DO_2 was similar at rest and had a tendency to be higher during submaximal exercise at 50–60% of $\dot{V}O_2$max in the less fit group. At $\dot{V}O_2$max the A-a DO_2 was similar in the two groups, but the fitter group achieved this at a substantially higher $\dot{V}O_2$max.

The mechanical differences in lung function between the two groups (i.e., reduced MEF – 50%) were further manifested at a given $\dot{V}E$ during submaximal exercise by a greater degree of expiratory flow limitation and hyperinflation in the least fit subjects. However, owing to the reduced maximal $\dot{V}O_2$ and therefore ventilatory demand in the least fit group, the degree of expiratory flow limitation during maximal exercise was similar regardless of the fitness level. If the less fit subjects had the

TABLE 5.4
The Effect of Fitness Level on Lung Function in Older Adults (Mean ± SEM) (N = 30)

	$\dot{V}O_2max$ >43 ml/kg/min (n = 15)		$\dot{V}O_2max$ <44 ml/kg/min (n = 15)	
	Absolute Value	*% Pred*	*Absolute Value*	*% Pred*
Max $\dot{V}O_2$ (ml/kg/min)	50 ± 1	229 ± 10	35 ± 2	160 ± 9*
(L/min)	3.28 ± .12		2.44 ± .14	
MEF-50% (L/s)	3.41 ± .18	98 ± 5	2.75 ± .25	78 ± 6*
CC (L)	3.32 ± .10	100 ± 4	3.33 ± .17	98 ± 4
FRC (L)	3.92 ± .13	95 ± 3	4.24 ± .17	105 ± 3*
VC (L)	4.20 ± .15	111 ± 3	4.25 ± .21	110 ± 4
DLCO (ml/min/mmHg)	28.9 ± .6	116 ± 5	26.5 ± 1.2	106 ± 4
A-a DO_2 (mmHg):				
rest	8.4 ± 1.3		9.1 ± 1.2	
50% $\dot{V}O_2$	9.8 ± 1.6		14.9 ± 2.6	
Max	25.0 ± 2.9		25.8 ± 2.6	

* Significant difference between the two groups ($p < .05$).

maximum ventilatory demands of the higher fit group, this would had to have been achieved through greater hyperinflation, a reduced VT and greater tachypnea, and much more severe expiratory flow limitation. Undoubtedly, within our group, there are those less fit subjects with the extremes of reduced MEF–50% who could not have achieved the level of maximum $\dot{V}E$ that some of the more fit subjects achieved no matter what the strategy they attempted.

There was a consistent tendency among our group for those subjects with the highest level of fitness to have better lung function and more efficient pulmonary gas transport. At the same time, the effect of aging on lung elastic recoil was still very evident in the lungs of the highly trained person. The aging process occurred across all fitness ranges. There is no consistent evidence of training-induced changes in lung function as studied in younger subjects or animals [22, 112, 8], nor do many groups of young adult athletes show superior pulmonary function relative to their untrained contemporaries. We propose, then, that the most likely explanation for this tendency in our older healthy sample is that $\dot{V}O_2max$ and lung elastic recoil are both good indicators of the physiological aging process. The fitter subjects may therefore be thought of as having a certain genetically based resistance to aging.

Is Maximal Exercise Ventilation Mechanically Limited in the Active Older Adult (Demand > Capacity)?

All but four subjects reached a significant degree of flow limitation during maximal exercise (40–90% of VT occurred along the expiratory boundary of the MFVL). Of the 30 subjects, 22 also reached a significant degree of flow limitation during submaximal exercise (>25% of VT at

75% of $\dot{V}O_2max$), causing EELV to increase with further increases in ventilatory demand. Despite this degree of mechanical limitation, the submaximal and maximal ventilation and CO_2 elimination for the metabolic demand was adequate, because on the average the group showed a significant hyperventilation and compensatory arterial hypocapnia.

In a subgroup of six subjects representative of the group of subjects tested in fitness levels and degree of mechanical limitation during maximal exercise, we increased the fractional percent of the inspired CO_2 concentration ($FICO_2$) in an attempt to stimulate ventilation further during maximal exercise to determine if $\dot{V}E$ was truly at a "physiological" limit. In subjects who had achieved flow limitation over >40% of their maximal air breathing VT and had reached the capacity for pressure generation at peak inspiratory pressure, we found that $\dot{V}E$ did not increase further. Generally only the fittest older subjects ($\dot{V}O_2max$ > 45 mL/kg/per min) tended to show this level of mechanical limitation to ventilation, which was compatible with an inability to increase ventilation with further chemical stimulation at maximal levels of exercise. As previously noted in Figure 5.11, however, some subjects showed much greater age-dependent declines in resting lung function and achieved significant mechanical limitation at very low maximal oxygen uptakes (25 to 35 mL/kg/per min). It appears, therefore, that in the majority of older, especially highly fit subjects, maximal oxygen uptake is achieved *just prior to* or more usually, *commensurate with* attainment of the mechanical limits to ventilation. This is reflected by the significant alveolar hyperventilation in most subjects, so that as a group the capacity of the respiratory system for airflow and pulmonary gas transport is adequate to meet the maximal metabolic demand.

We investigated whether mechanical flow limitation or respiratory muscle pressure development in our older subjects was manifested in perceptions of dyspnea or shortness of breath. Our older subjects rated their perceived level of breathlessness as well as total body effort according to a 10-point scale [68] which asked how "heavy" the work was. During maximal exercise, dyspnea ratings averaged 7.1 ("very heavy" work to breathe), which was similar to that reported for total body effort (7.0). In all 30 subjects for $\dot{V}O_2max$ maximal ventilatory output, peak inspiratory or expiratory pleural pressure development, degree of expiratory flow limitation, and tidal volume limitation (EILV as a % TLC), we found no significant correlations with the perceived level of dyspnea or the ratio of dyspnea to total body effort. The subjects who used the greatest percentage of their reserve, however, for inspiratory muscle pressure development during tidal breathing at maximal exercise (peak inspiratory pressure/$Pcap_i$, see Fig. 5.6) did show a significant tendency to have the highest rates of dyspnea to total effort ($r = 0.66$, $p < .05$). (This was determined in a smaller subset of

12 subjects in which $Pcap_i$ was measured.) Our limited data in the older, fit subjects do show, therefore, that a relatively high level of dyspnea is manifested at maximal exercise and that the degree of dyspnea is positively correlated with the percent of maximal inspiratory muscle pressure used, but not with the magnitude of expiratory flow limitation or ventilatory output. We cannot determine if these dyspneic sensations contributed significantly to exercise limitation in our subjects.

Respiratory Muscle Fatigue

Any decline in respiratory muscle power output would decrease the capacity of the inspiratory muscles for pressure development. In younger subjects, the issue of respiratory muscle fatigue during exercise is unclear. Some studies claim reductions in maximal inspiratory pressure following exhaustive exercise or fatigue-like changes in diaphragmatic electromyographic (EMG) frequency spectra during exercise [81, 12, 83, 85], but the validity of these indices of fatigue is questionable either because of the volitional nature of the tests, the interpretation of the EMG changes [122], or the problem of EMG analysis of an electrocardiogram-contaminated EMG signal. Because of the stiffened rib cage which causes an increased reliance on the diaphragm, as well as shortened inspiratory muscles due to flow limitation and a rising EELV, and the use of >80% of the capacity of the inspiratory muscles for pressure generation (increased work), one would consider the aged diaphragm as a prime candidate for fatigue. At least in short-term heavy work (3 minutes), however, it is apparent that pressure generation by inspiratory muscles is maintained and even rises over this time in the older subjects we tested. Furthermore, the peak inspiratory pleural pressure generated during tidal breathing at maximal exercise during air breathing or with increased levels of $FICO_2$ often equalled the capacity for pressure generation by the "fresh" inspiratory muscles (as determined at rest) (for example, see Fig. 5.14). Moreover, there was no indication from the arterial blood gases that there was a failure in achieving the appropriate alveolar hyperventilation for the metabolic demand. In the subjects we tested whose respiratory muscles required an estimated 13% and perhaps as high as 23% of the total body $\dot{V}O_2$, it is evident that these muscles were very capable of responding to the demands for pressure development placed on them. The situation might be quite different during endurance, high-intensity exercise in the older athlete, who must sustain these high-ventilatory responses and pressure generation in the face of shortened inspiratory muscle length and a high metabolic cost of breathing.

What Portion of the Pulmonary System Appears to be the Most Vulnerable to the Aging Process in the Exercise Response?

From the results of our mechanics and gas exchange data, there may be a disparity within the pulmonary system concerning the effect of

aging on the exercise response. The decline in the mechanics of lung function (i.e., reduced flow and vital capacity) has significant effects on the available strategies an older subject can choose from to increase minute ventilation, and it forces an increased metabolic cost for a given level of ventilation. Potential factors that could affect gas exchange, the high closing volume, maldistribution of mechanical time constants, the decline in DLCO, loss of diffusion surface area with age, and the rise in V_D/V_T, do not exert profound effects, however, even at maximal levels of exercise. The healthy pulmonary system is vigilant in its protection against hypoxemia and CO_2 retention. Accordingly as the lung ages either through the failure of sufficient age-related change or because of the large reserve present in youth, gas exchange is maintained and hypoxemia is prevented, even at extraordinary demands for gas transport (with few exceptions, see below). Although V_D/V_T increases, therefore, a relatively high overall V_A/Q relationship throughout the aged lung must be maintained and the number of regions with low V_A/Q ratios could not have been any greater than in a healthy young adult. That DLCO falls with age and yet A-a DO_2 at rest or maximal exercise does not widen abnormally exemplifies the substantial reserve of the pulmonary capillary blood volume and the limited minimum time required for complete end-capillary equilibration of alveolar and end-capillary blood [126]. Although there were a significant number of cases in which A-a DO_2 at maximal exercise widened greater than the upper range of normal in the young (at the same $\dot{V}O_2max$), most of these persons even compensated with sufficient alveolar hyperventilation to avoid hypoxemia.

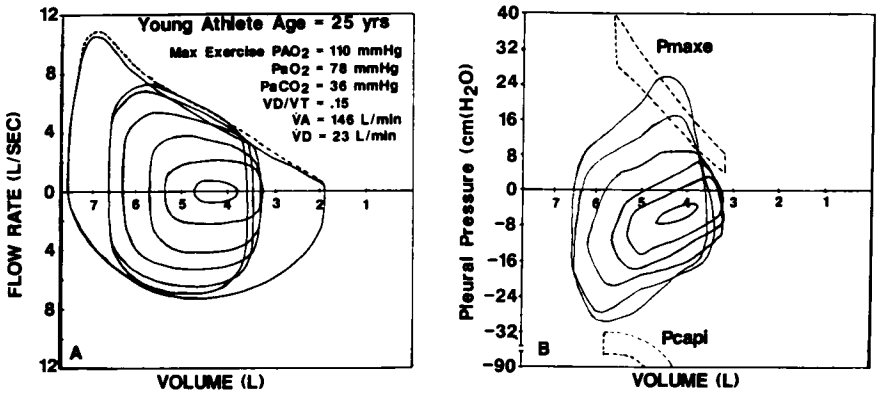
A disparity is therefore apparent between the influence that aging has on pulmonary gas exchange versus the mechanical cost and efficiency of breathing. That is, the loss of lung recoil, increased work of breathing, and increased V_D/V_T greatly influence the metabolic cost of V_E; however, overall alveolar ventilation and alveolar to arterial O_2 exchange remain sufficient to maintain an adequate arterial HbO_2 saturation and CO_2 elimination.

How Does the Fit Older Athlete Compare to the Young Athlete?

Our comparisons to this point have contrasted the older, physically active person and the untrained younger adult with a comparable $\dot{V}O_2max$ and $\dot{V}_E$; major differences in flow limitation, FRC regulation, and the work of breathing were noted. When comparing the degree of mechanical limitation, however, in the older fit subjects we tested to that in younger athletes, the latter, operating at a $\dot{V}O_2max$ and $\dot{V}_E$ which were 70% and 45% higher, respectively, had a remarkably similar degree of mechanical limitation (see Figure 5.13). Because the young athletes approach flow limitation at a much greater metabolic demand than in the older adults, they also increase EELV, and ventilatory work

FIGURE 5.13

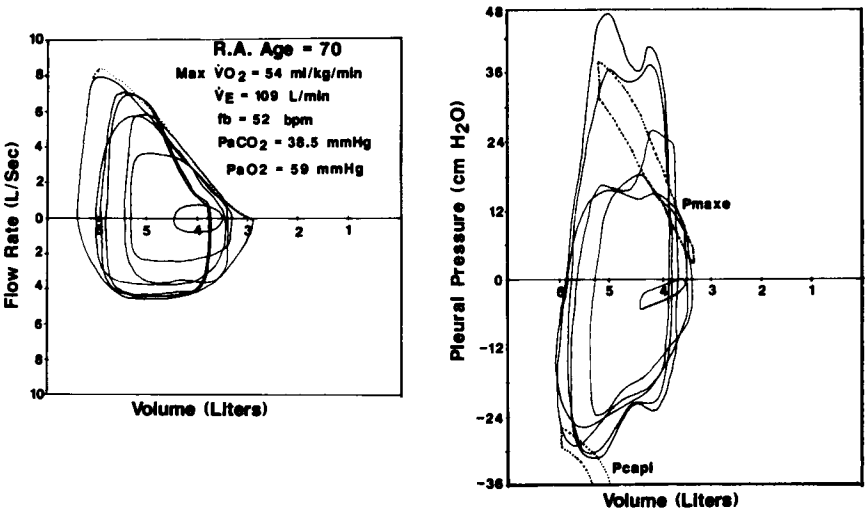
Mean ventilatory response to progressive exercise in young endurance athletes (n = 8). Tidal flow (on the left) and pressure (on the right) volume loops (solid lines) are plotted from rest through maximal exercise. The flow: volume loops are plotted within the pre- (solid) and postexercise (dashed) maximal volitional flow: volume loops relative to a measured EELV. The tidal pressure: volume loops are plotted relative to the maximal effective pressures on expiration and the capacity for pressure generation on inspiration $\dot{V}O_2max$ = 74 ± 1 ml/kg/min (range 66 to 80). Also shown are relevant maximal exercise blood gas and ventilatory parameters. Because of the much greater $\dot{V}_E$ demand in the young athletes, they approach a level of mechanical limitation similar to that noted in the older, relatively fit adult during maximal exercise at a much lower $\dot{V}O_2max$ (Fig. 5.6).



rises disproportionately. The work of breathing and the oxygen cost of ventilation approach those of the elderly at maximal exercise; but, of course, a much greater ventilatory response is required. Both groups therefore use virtually all their mechanical capacity for the generation of flow rate and inspiratory muscle pressure. In both groups it also is a rare occurrence that alveolar hyperventilation or CO_2 elimination at max work is inadequate. The widening A-a D_{O_2} at maximal exercise becomes even more extreme in the young athletes than in the older subjects. The additional drop in PaO_2 in the young and their higher incidence of exercise-induced hypoxemia is attributed to a diffusion disequilibrium due to shortened red cell transit times secondary to a combination of normal maximal pulmonary capillary blood volume with an extraordinarily high cardiac output [21, 136]. It appears that although the capacity of the lung for diffusion and flow rate are much greater in the young athlete, in a significant number of these athletes the demand for gas transport is increased disproportionately.

In summary, there are some key similarities but also important

FIGURE 5.14
Demand exceeds capacity. Subject RA showed the usual age-related declines in lung function (i.e., MEF–50% = 100% predicted, DLCO = 109% of predicted). With progressive exercise, the mechanical limits to $\dot{V}_E$ are reached at a submaximal exercise load. During both heavy (but submaximal) and maximal exercise, the maximal effective expiratory pressures were significantly exceeded, the capacity for inspiratory pressure development was reached at peak pressure, the cost of breathing approached an estimated 23% of the total body $\dot{V}O_2$, and PaO_2 fell to 59 mmHg, and $PaCO_2$ rose throughout the final work load.



differences in where the young versus the older athlete reside on their respective continuums of maximal demand versus capacity. In the younger and older subjects alike the mechanical constraints and metabolic cost of ventilation during heavy and maximal exercise are excessive relative to the less fit subject. The incidence of inadequate pulmonary O_2 transport, however, is probably significantly greater in the younger athlete, suggesting that demand for pulmonary gas transport more often exceeds capacity in the young. With aging, lung function (i.e., MEF–50%, CV, VC, DLCO) declines at a rate similar to the rate of decline in $\dot{V}O_2$max (20–40% from age 25 to age 70) [116].

Failure: Does Demand Ever Exceed Capacity in the Healthy Aging Respiratory System?
Figure 5.14 shows one of the fittest older athletes we studied. This older athlete failed to increase $\dot{V}_E$ over the highest two work intensities he performed. With the addition of CO_2 to the inspired air, the $\dot{V}_E$ did

not increase further during maximal exercise. He reached the capacity of his inspiratory muscles for developing pressure during tidal breathing and reached expiratory flow limitation over 80% of the VT. This subject used virtually all of his maximal flow:volume loop available to him at a very heavy but submaximal work load. Nonetheless, he was capable of completing yet another workload with little further increase in total body $\dot{V}O_2$. In addition, during maximal exercise the partial pressure of alveolar O_2 (P_{AO_2}) failed to increase above 100 mmHg and arterial P_{CO_2} even started to rise throughout the highest work load. The extremely widened A-a DO_2 also showed a failure for complete gas exchange, and probably contained a significant component of diffusion disequilibrium. This subject represents a rare point of intersection on the continuum of demand versus capacity, in which the cardiovascular and musculoskeletal systems response capabilities are able to push the aging, healthy respiratory system to the point of failure. Our studies with added inspired CO_2 at maximal exercise do show the coincidence of mechanical limitation to flow and pressure generation and ventilation at maximal exercise, which occurs in many highly fit older and especially younger athletes. It is the rarity with which this point of intersection between capacity and demand is exceeded that is so remarkable. Perhaps the incidence of this "failure" in the slightly younger 55 to 65-year-old "master athlete" competing at an international level with $\dot{V}O_2$max values commonly in excess of 60–65 mL/kg/per minute might be significantly different [3].

SUMMARY—AGING, FITNESS AND LIMITATIONS TO $\dot{V}O_2$ MAX

Do the significant aging effects on lung mechanics and on gas exchange mean that the pulmonary system may "become" a significant limitation to max O_2 transport, as it does in some younger athletes. Theoretically, in a very limited sense this does occur; the 30-year old, highly trained athlete clearly could not achieve his max $\dot{V}O_2$ with the lungs of most fit, healthy 70-year olds. In reality, however, because aging also affects all links in the chain of O_2 transport and utilization, the pertinent question becomes, To what extent is the capacity of the pulmonary system curtailed by the aging process *relative to* that of the capacity of the cardiac pump, the total blood volume and its distribution, capillary-to-muscle mitochondria diffusion capacity, and metabolic capacity of locomotor muscle? As we have seen, the margin between demand and capacity in the pulmonary system does indeed narrow with age, especially in the highly fit adult in whom the selective effect of the training "stimulus" on the pulmonary system seems relatively small or negligible. This narrowing of the demand *versus* capacity margin does require

some degree of compensatory response, as well as a mechanically inefficient and higher cost of exercise hyperpnea in the older athlete. Nonetheless, in all but the rarest cases, the pulmonary system capacity continues to exceed (or at least precisely meet) demand throughout the aging process.

ACKNOWLEDGEMENTS

Research supported by NHLBI, USARDC and the WI Heart Association. We are indebted to our subjects who gave extraordinary amounts of their time and effort and who never lost their spirit of cooperation nor their sense of humor. The aging process clearly builds character.

REFERENCES

1. Aaron, E., B. Johnson, D. Pegelow, and J. Dempsey. The oxygen cost of exercise hyperpnea: a limiting factor? *Am. Rev. Resp. Dis.* 141:4, A122, 1990.
2. Agostoni, E., and W.O. Fenn. Velocity of muscle shortening as a limiting factor in respiratory air flow. *J. Appl. Physiol.* 15:349–353, 1960.
3. Allen, W.K., D.R. Seals, B.F. Hurley, A.A. Ehsani, and J.M. Hagberg. Lactate threshold and distance-running performance in young and older endurance athletes. *J. Appl. Physiol.* 58:1281–1284, 1985.
4. Andreotti, L., A. Bussotti, D. Cammelli, et al. Connective tissue in aging lung. *Gerontology* 29:377–387, 1983.
5. Anthonisen, N.R., J. Danson, P.C. Roberton, et al. Airway closure as a function of age. *Respir. Physiol.* 8:58–65, 1970.
6. Bachofen, H., H.J. Hobi, and M. Scherrer. Alveolar-arterial N_2 gradients at rest and during exercise in healthy men of different ages. *J. Appl. Physiol.* 34:137–142, 1973.
7. Black, L.E., and R.E. Hyatt. Maximal respiratory pressures: normal values and relationship to age and sex. *Am. Rev. Resp. Dis.* 99:696–702, 1969.
8. Blomquist, G., R.L. Johnson, and B. Saltin. Pulmonary diffusion capacity limiting human performance at altitude. *Acta Physiol. Scand.* 76:284–287, 1969.
9. Brandsetter, R.D., and H. Kazemi. Aging and the respiratory system. *Med. Clin. North Am.* 67:419–431, 1983.
10. Brischetto, M.S., R.P. Millmen, D.D. Peterson, D.A. Silage, and A.I. Pack. Effect of aging on ventilatory response to exercise and CO_2. *J. Appl. Physiol.* 56:1143–1150, 1984.
11. Brooks, S.V., and J.A. Faulkner. Contractile properties of skeletal muscles from young, adult, and aged mice. *J. Physiol.* (London) 404:71–82, 1988.
12. Bye, P.T., G.A. Farkas, and C. Roussos. Respiratory factors limiting exercise. *Ann. Rev. Physiol.* 45:439–51, 1983.
13. Cherniak, R.M. *Pulmonary Function Testing.* Philadelphia:WB Saunders 1977, p. 249.
14. Coates, G.H., H. O'Bradovich, A.L. Jerreries, and G.W. Gray. Effects of exercise on lung lymph flow in sheep and goats during normoxia and hypoxia. *J. Clin. Invest.* 74:133–141, 1984.
15. Colebatch, H.J.H., I.A. Greaves, and C.K.Y. Ng. Exponential analysis of elastic recoil and aging in healthy males and females. *J. Appl. Physiol.* 47:683–691, 1979.
16. Collett, P.W., and C.A. Engel. Influence of lung volume on oxygen cost of resistive breathing. *J. Appl. Physiol.* 61:16–24, 1986.

17. Craig, D.B., W.M. Wahba, H.F. Don, J.G. Couture, and M.R. Becklake. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J. Appl. Physiol.* 31:717–721, 1971.
18. Crapo, R.O., A.H. Morris, and R.M. Gardner. Reference values for pulmonary tissue volume, membrane diffusing capacity, and pulmonary capillary blood volume. *Bull. Europ. Physiopath. Resp.* 18:893–899, 1982.
19. Crawford, A.B.H., D.J. Cotton, M. Paiva, and L.A. Engel. Effect of lung volume on ventilation distribution. *J. Appl. Physiol.* 66:2502–2510, 1989.
20. Cunningham, D.A., E.A. Nancekievill, D.H. Paterson, A.P. Donner, and P.A. Rechnitzer. Ventilation threshold and aging. *J. Gerontol.* 40:703–707, 1985.
21. Dempsey, J.A. Is the lung built for exercise? *Med. Sci. Sports Exerc.* 18:143–155, 1986.
22. Dempsey, J.A., and R. Fregosi. Adaptability of the pulmonary system to changing metabolic requirements. *Am. J. Cardiol.* 55:59D–67D, 1985.
23. Dempsey, J.A., B.D. Johnson, and W.M. Bayly. Constraints on the ventilatory response to maximum exercise in health. *Hypoxia: The Adaptations.* J.R. Sutton, G. Coates, and J.E. Remmers (eds.). Canada: B.C. Decker, Inc., 1990, pp. 178–181.
24. Dempsey, J.A., E.H. Vidruk, and G.H. Mitchell. Pulmonary control systems in exercise: update. *Fed. Proc.* 44:2260–70, 1985.
25. D'Errico, A., P. Scarani, E. Colosimo, M. Spina, W.F. Grigioni, and A.M. Mancini. Changes in the alveolar connective tissue of the ageing lung. *Virchows Archiv. A Pathol. Anat.* 415:137–144, 1989.
26. DeVries, H.A., and G.M. Adams. Comparison of exercise responses in old and young men. II. Ventilatory Mechanics. *J. Geronotol.* 27:349–352, 1972.
27. Dhar, S., S. Shastri, and R. Lenora. Aging and the respiratory system. *Med. Clin. North Am.* 60:1121–1136, 1976.
28. Dockery, D.W., F.E. Speizer, B.G. Ferris, J.H. Ware, T.A. Louis, A. Spiro III. Cumulative and reversible effects of lifetime smoking on simple tests of lung function in adults. *Am. Rev. Resp. Dis.* 137:286–292, 1988.
29. Druz, W.S., J.T. Sharp. Activity of respiratory muscles in upright and recumbent humans. *J. Appl. Physiol.* 51:1522–1561, 1981.
30. Eddinger, T.J., R.G. Cassens, and R.L. Moss. Mechanical and histochemical characterization of skeletal muscles from senescent rats. *Am. J. Physiol.* (Cell Physiol.) 152:C421–C430, 1986.
31. Edelman, N.H., C. Mittman, A.H. Norris, and N.W. Shock. Effects of respiratory pattern on age differences in ventilation uniformity. *J. Appl. Physiol.* 24:49–53, 1968.
32. Edge, J.R., F.J. Millard, L. Reid, et al. The radiographic appearance of the chest in persons of advanced age. *Br. J. Radiol.*, 37:769, 1964.
33. Edstrom, L., and L. Larsson. Effects of age on contractile and enzyme-histochemical properties of fast- and slow-twitch single motor units in the rat. *J. Physiol.* 392:129–145, 1986.
34. Emirgil, C., B.J. Sobol, S. Campodonico, W.M. Herbert, and R. Mechkati. Pulmonary circulation in the aged. *J. Appl. Physiol.* 23:631–640, 1967.
35. Engel, L. Gas mixing within the acinus of the lung. *J. Appl. Physiol.* 54:609–618, 1983.
36. Eyre, D.R., M.A. Paz, and P.M. Gallop. Crosslinks in elastin and collagen. *Annu. Rev. Biochem.* 53:717–748, 1984.
37. Farney, R.J., A.H. Morris, R.M. Gardner, and J.D. Armstrong Jr. Rebreathing pulmonary capillary and tissue volume in normals after saline infusion. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* 43:246–253, 1977.
38. Fowler, W.S., E.R. Cornish, Jr., and S.S. Kety. Lung function studies. VIII. Analysis of alveolar ventilation by pulmonary N_2 clearance curves. *J. Clin. Invest.* 31:40–50, 1952.

39. Frank, N.R., J. Mead, and B.G. Ferris Jr. The mechanical behaviour of the lungs in healthy elderly persons. *J. Clin. Invest.* 36:1680–1687, 1957.
40. Gibson, G.J., N.B. Pride, C. O'Cain, et al. Sex and age differences in pulmonary mechanics in normal nonsmoking subjects. *J. Appl. Physiol.* 41:20–25, 1976.
41. Gladden, L.B., J.W. Yates, W. Stremel, and B.A. Stanford. Gas exchange and lactate anaerobic thresholds: inter and intra evaluater agreement. *J. Appl. Physiol.* 58:2082–2089, 1985.
42. Gledhill, N., A.B. Forese, F.J. Buick, and A.C. Bryan. Va:Qc inhomogeneity and $AaDO_2$ in man during exercise: effect of SF_6 breathing. *J. Appl. Physiol.* 45:512–515, 1978.
43. Gledhill, N., A. Froese, and J. Dempsey. Ventilation to perfusion distribution during exercise in health. *Muscular Exercise and the Lung.* J. Dempsey and C. Reed (eds.). Madison: University of Wisconsin Press, 1977, pp. 325–344.
44. Glindmeyer, H.W., J.E. Diem, R.N. Jones, et al. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. *Am. Rev. Resp. Dis.* 125:544–548, 1982.
45. Georges, R., G. Saumon, and A. Loiseau. The relationship of age to pulmonary membrane conductance and capillary blood volume. *Am. Rev. Resp. Dis.* 117:1069–1078, 1978.
46. Gosselin, L.E., T. Bohlmann, and D.P. Thomas. Effects of age and endurance training on capillary density and fiber type distribution in rat diaphragm muscle. *Med. Sci. Sports Exerc.* 20:59, 1988.
47. Granath, A., B. Jonsson, and T. Strandell. Circulation in healthy old men, studied by right heart catheterization at rest and during exercise in supine and sitting position. *Acta Med. Scand.* 176:425–446, 1964.
48. Granath, A., and T. Strandell. Relationships between cardiac output, stroke volume, and intracardiac pressures at rest and during exercise in supine position and some antropometric data in healthy old men. *Acta Med. Scand.* 176:447–466, 1964.
49. Grassino, A.E., J.P. Derenne, J. Almirall, J. Milic-Emili, and W. Whitelaw. Configuration of the chest wall and occlusion pressures in awake humans. *J. Appl. Physiol.* 50:134–142, 1981.
50. Grimby, G., and B. Saltin. Physiological analysis of physically well-trained middle-aged and old athletes. *Acta Med. Scand.* 179:513–526, 1966.
51. Gurtner, H.P., P. Walser, and B. Fassler. Normal values for pulmonary hemodynamics at rest and during exercise in man. *Prog. Resp. Res.* 9:295–315, 1975.
52. Hagberg, J.M., J.E. Yerg II, and D.R. Seals. Pulmonary function in young and older athletes and untrained men. *J. Appl. Physiol.* 65:101–105, 1988.
53. Harf, A., and J.M.B. Hughes. Topographical distribution of V_A/Q in elderly subjects using krypton-81 m. *Respir. Physiol.* 34:319–327, 1978.
54. Hartley, R.H., Grimby, G., Kilbom, A., et al. Physical training in sedentary middle aged and older men. *Scand. J. Clin. Lab. Invest.* 24:335–344, 1969.
55. Heath, G.W., J.M. Hagberg, A.A. Ehsani, and J.O. Holloszy. A physiological comparison of young and older endurance athletes. *J. Appl. Physiol.* 51:634–640, 1981.
56. Henke, K.G., M. Sharratt, D. Pegelow, and J.A. Dempsey. Regulation of end-expiratory lung volume during exercise. *J. Appl. Physiol.* 64:135–146, 1988.
57. Hesser, C.M., D. Linnarsson, and L. Fagraeus. Pulmonary mechanics and work of breathing at maximal ventilation and raised air pressure. *J. Appl. Physiol.* 50:747–53, 1981.
58. Holland, J., J. Milic-Emili, P.T. Macklem, et al. Regional distribution of pulmonary ventilation and perfusion in elderly subjects. *J. Clin. Invest.* 47:81–92, 1968.
59. Horvath, S.M., and J.F. Borgia. Cardiopulmonary gas transport and aging. *Am. Rev. Resp. Dis.* 129:568–571, 1984.

60. Islam, M.S. Mechanism of controlling residual volume and emptying rate of the lung in young and elderly healthy subjects. *Respiration* 40:1–8, 1980.
61. Johnson, B.D., W.G. Reddan, K.C. Seow, and J.A. Dempsey. Mechanical constraints on exercise hyperpnea in a fit aging population. *Am. Rev. Resp. Dis.* 1990 (accepted for publication).
62. Johnson, B.D., W.G. Reddan, D.F. Pegelow, K.C. Seow, and J.A. Dempsey. Flow limitation and regulation of FRC during exercise in a physically active aging population. *Am. Rev. Resp. Dis.* (accepted for publication).
63. Johnson, B.D., W.G. Reddan, D.F. Pegelow, and J.A. Dempsey. Aging effects on expiratory flow limitation during exercise. *FASEB J.* 3:4, 6248, 1989.
64. Johnson, B.D., K.C. Seow, D.F. Pegelow, and J.A. Dempsey. Adaptation of the inert gas FRC technique for use in heavy exercise. *J. Appl. Physiol.* 68:802–809, 1990.
65. Jones, N.L. Normal values for pulmonary gas exchange during exercise. *Am. Rev. Resp. Dis.* 129:Suppl. 544–546, 1984.
66. Jones, N.L., and E.J.M. Cambell. *Clinical Exercise Testing, 2nd Edition.* Philadelphia: WB Saunders, 1982, p. 249.
67. Kanber, G.J., F.W. King, Y.R. Eshchar, and J.T. Sharp. The alveolar-arterial oxygen gradient in young and elderly men during air and oxygen breathing. *Am. Rev. Resp. Dis.* 97:376–381, 1968.
68. Killian, K.J. Breathlessness: the sense of respiratory muscle effort. *The Perception of Exertion in Physical Work.* G. Borg, D. Ottasan (eds.). London: Macmillan Press Ltd., 1985, pp. 71–82.
69. Kitamura, H., Sawa, T., and E. Ikezono. Postoperative hypoxemia: The contribution of age to the maldistribution of ventilation. *Anesthesiology* 36:244–252, 1972.
70. Knudson, R.J., D.F. Clark, T.C. Kennedy, et al. Effect of aging alone on mechanical properties of the normal adult human lung. *J. Appl. Physiol.* 43:1054–1062, 1977.
71. Knudson, R.J., M.D. Lebowitz, C.J. Holberg, and B. Burrows. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am. Rev. Resp. Dis.* 127:725–734, 1983.
72. Kronenberg, R.S., C.W. Drage, R.A. Ponto, and L.E. Williams. The effect of age on the distribution of ventilation and perfusion in the lung. *Am. Rev. Resp. Dis.* 108:576–586, 1973.
73. Kronenberg, R.S., P.O. L'Heurex, and R.A. Ponto. The effect of aging on lung-perfusion. *Ann. Intern. Med.* 76:413–421, 1972.
74. Krumpe, P.E., R.J. Knudson, G. Parsons, and K. Reiser. The aging respiratory system. *Clin. Ger. Med.* 1:143–175, 1985.
75. Lange-Anderson, K., R.J. Shepherd, and H. Denolin. *Fundamentals of Exercise Testing.* Geneva: World Health Organization, 1971.
76. Last, J.A., T.E. King, Jr., A.G. Nerlich, and K.M. Reiser. Collagen cross-linking in adult patients with acute and chronic fibrotic lung disease. *Am. Rev. Resp. Dis.* 141:307–313, 1990.
77. Last, J.A., P. Summers, K.M. Reiser. Biosynthesis of collagen crosslinks. II. In vivo labelling, stability and turnover of collagen in the developing rat lung. *Biochim. Biophys. Acta* 990:182–189, 1989.
78. Leblanc, P., F. Ruff, and J. Milic-Emili. Effects of age and body position of "airway closure" in man. *J. Appl. Physiol.* 28:448–481, 1970.
79. Leblanc, P., E. Summers, M.D. Inman, N.L. Jones, E.J.M. Campbell, and K.J. Killian. Inspiratory muscles during exercise: a problem of supply and demand. *J. Appl. Physiol.* 64:2482–2489, 1988.
80. Leith, D.E., and J. Mead. Mechanisms determining residual volume of the lungs in normal subjects. *J. Appl. Physiol.* 23:221–227, 1967.
81. Levine, S., and D. Henson. Low frequency diaphragmatic fatigue in spontaneously breathing humans. *J. Appl. Physiol.* 64:672–680, 1988.

82. Levitzky, M.G. Effects of aging on the respiratory system. *The Physiologist* 27:102–106, 1984.
83. Loke, J., D. Mahler, and A. Virgulto. Respiratory muscle fatigue after marathon running. *J. Appl. Physiol.* 52:821–824, 1982.
84. Makrides, L., G.F. Heigenhuser, N. McCartney, and N.L. Jones. Physical training in young and older healthy subjects. *Sports Medicine for the Master Athlete.* J.R. Sutton and R.M. Brock (eds.). Indianapolis: Benchmark Press, 1986, pp. 363–373.
85. Maron, M.B., L.H. Hamilton, and M.B. Maksud. Alterations in pulmonary function consequent to competitive marathon running. *Med. Sci. Sports* 2:244–249, 1979.
86. Marshall, B.E., P.J. Cohen, C.H. Klingenmaier, and S. Aukberg. Pulmonary venous admixture before, during and after halothane-oxygen anesthesia in man. *J. Appl. Physiol.* 27:653–657, 1969.
87. Marshall, B.E., and R.A. Millar. Some factors influencing post-operative hypoxemia. *Anesthesiology* 20:408, 1965.
88. Masoro, E.J. (ed.). *CRC Handbook of Physiology in Aging.* Boca Raton, Florida: CRC Press, 1984.
89. Martin, C.J., S. Das, and A.C. Young. Measurement of the dead space volume. *J. Appl. Physiol.* 47:319–324, 1979.
90. Mauderly, J.L., and F.F. Hahn. The effects of age on lung function and structure of adult animals. *Adv. Vet. Sci. Comp. Med.* 26:35–77, 1982.
91. McElvaney, G., S. Blackie, J. Morrison, P.G. Wilcox, M.S. Fairbarn, and R.L. Pardy. Maximal static respiratory pressures in the normal elderly. *Am. Rev. Resp. Dis.* 39:277–281, 1989.
92. Mead, J., and J.L. Whittenberger. Physical properties of human lungs measured during spontaneous respiration. *J. Appl. Physiol.* 12:779–796, 1953.
93. Mellemgaard, K. The alveolar-arterial oxygen difference: its size and components in normal man. *Acta Physiol. Scan.* 67:10–20, 1966.
94. Mittman, C., N.H. Edelman, A.H. Norris, et al. Relationship between chest wall and pulmonary compliance and age. *J. Appl. Physiol.* 20:1211–1216, 1965.
95. Morris, J.G., A. Koski, and L.C. Johnson. Spirometric standards for healthy nonsmoking adults. *Am. Rev. Resp. Dis.* 103:57–67, 1971.
96. Muiesan, B., C.A. Sorbini, and V. Grassi. Respiratory function in the aged. *Bull. Physio-Pathol. Respir.* 7:973–1003, 1971.
97. Needham, C.D., M.C. Hogan, and F. McDonald. Normal standards for lung volumes, pulmonary gas mixing and maximum breathing capacity. *Thorac* 9:313–325, 1954.
98. Neufeld, O., J.R. Smith, and S.L. Goldman. Arterial oxygen tension in relation to age in hospital subjects. *J. Am. Ger. Soc.* 21:4–9, 1973.
99. Niewoehner, D.E., and J. Kleinerman. Morphologic basis of pulmonary resistance in the human lung and effects of aging. *J. Appl. Physiol.* 36:412–418, 1974.
100. Olafsson, S., R.E. Hyatt. Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *J. Clin. Invest.* 48:564–573, 1969.
101. Otis, A.B. The work of breathing. *The Handbook of Physiology* Section 3: *Respiration*, Volume I. W.O. Fenn, and H. Rahn (eds.). Philadelphia: Waverly Press Inc, 1964, pp.463–476.
102. Palecek, F., and E. Jezova. Elastic properties of the rat respiratory system related to age. *Physiologia Bohemoslovaca* 37:39–48, 1988.
103. Peterson, D.D., A.I. Pack, D.A. Silage, and A.P. Fishman. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. *Am. Rev. Resp. Dis.* 124:387–391, 1981.
104. Pierce, J.A. Tensile strength of the human lung. *J. Clin. Invest.* 66:652–658, 1965.
105. Pierce, J.A., and R.V. Ebert. Fibrous network of the lung and its change with age. *Thorax* 20:469–476, 1965.
106. Polgar, G., and T.R. Weng. The functional development of the respiratory system. From the period of gestation to adulthood. *Am. Rev. Resp. Dis.* 120:625–695, 1979.

107. Prockop, D.J., K.I. Kivirikko, and L. Tuderman. The biosynthesis of collagen and its disorders. *N. Engl. J. Med.* 302:13–23, 77–95, 1979.
108. Pump, K.K. Emphysema and its relation to age. *Am. Rev. Resp. Dis.* 114:5–13, 1976.
109. Raine, J.M., and J.M. Bishop. A-a difference in O_2 tension and physiological dead space in normal man. *J. Appl. Physiol.* 18:284–288, 1963.
110. Reeves, J.T., J.A. Dempsey, and R.F. Grover. Pulmonary circulation during exercise. *Pulmonary Vascular Physiology and Pathophysiology.* E.K. Weir and J.T. Reeves, eds. New York: Marcel Dekker, Inc., 1989, pp. 107–133.
111. Reiser, K.M., S.M. Hennessy, and J.A. Last. Analysis of age-associated changes in collagen crosslinking in the skin and lung in monkeys and rats. *Biochim. Biophys. Acta* 926:339–348, 1987.
112. Reuschlein, P.L., W.G. Reddan, J.F. Burpee, J.B.L. Gee, and J. Rankin. The effect of physical training on the pulmonary diffusing capacity during submaximal work. *J. Appl. Physiol.* 24:152–158, 1968.
113. Road, J.D., S. Newman, J.P. Derenne, and A. Grassino. The in vivo length-force relationship of the canine diaphragm. *J. Appl. Physiol.* 60:63–70, 1986.
114. Rubin, S., M. Tack, and N.S. Cherniack. Effect of aging on respiratory responses to CO_2 and inspiratory resistive loads. *J. of Gerontol.* 37:306–312, 1982.
115. Rizzato, G., and L. Marazzini. Thoracoabdominal mechanics in elderly men. *J. Appl. Physiol.* 28:457–460, 1970.
116. Saltin, B. The aging endurance athlete. *Sports Medicine for the Mature Athlete.* J.R. Sutton and R.M. Brock (eds.). Indianapolis: Benchmark Press, 1986, pp. 59–80.
117. Schoenberg, J.B., G.T. Beck, and A. Bouhuys. Growth and decay of pulmonary function in healthy blacks and whites. *Respir. Physiol.* 33:367–393, 1978.
118. Schofield, J.D. Connective tissue aging: differences between mouse tissues in age-related changes in collagen extractability. *Exp. Gerontol.* 15:113–119, 1979.
119. Seals, D.R., J.M. Hagberg, B.F. Hurley, A.A. Ehsand, and J.O. Holloszy. Endurance training in older men and women. I. Cardiovascular responses to exercise. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 57:1024–1029, 1984.
120. Seals, D.R., B.F. Hurley, J. Schultz, and J.M. Hagberg. Endurance training in older men and women II. Blood lactate response to submaximal exercise. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 57:1030–1033, 1984.
121. Shimura, S., E.S. Boatman, and C.J. Martin. Effects of aging on the alveolar pores of Kohn and on the cytoplasmic components of alveolar type II cells in monkey lungs. *J. Pathol.* 148:1–11, 1986.
122. Sieck, G.C., and M. Fournier. Changes in diaphragm motor unit EMG during fatigue. *J. Appl. Physiol.* 68:1917–1926, 1990.
123. Smith, D.O. Physiological and structural changes at the neuromuscular junction during aging. *The Aging Brain: Cellular and Molecular Mechanisms in the Nervous System.* E. Giacobini, G. Filogamo, G. Giacobini, A. Vernadakis (eds.). New York: Raven Press, 1982, pp. 123–137.
124. Smith, D.O., and J.L. Rosenheimer. Aging at the neuromuscular junction. *Aging and Cell Structure* J.E. Johnson, Jr. (ed.). New York: Plenum Press, 1984, pp. 111–137.
125. Sorbini, C.A., V. Grassi, E. Solinas, and G. Muiesan. Arterial oxygen tension in relation to age in healthy subjects. *Respiration* 25:3–13, 1968.
126. Sue, D.Y., Oren, A., Hansen, J.E., and K. Wasserman. Diffusing capacity for carbon monoxide as a predictor of gas exchange during exercise. *New Engl. J. Med.* 316:1301–1306, 1987.
127. Tenney, S.M., and R.M. Miller. Dead space ventilation in old age. *J. Appl. Physiol.* 9:321–327, 1956.
128. Terry, P.B., R.J. Traystman, H.H. Newball, G. Batra, and H.A. Menkes. Collateral ventilation in man. *N. Engl. J. Med.* 298:10–15, 1978.

129. Terry, P.B., H.A. Menkes, and R.J. Traystman. Effects of maturation and aging on collateral ventilation in sheep. *J. Appl. Physiol.* 62:1028–1032, 1987.
130. Thurlbeck, W.M. The internal surface area of non-emphysematous lungs. *Am. Rev. Resp. Dis.* 95:765–773, 1967.
131. Thurlbeck, W.M. The effect of age on the lung. *Aging—Its Chemistry.* A.A. Dietz (ed.). Washington: Association for Clinical Chemistry, 1980, pp. 88–109.
132. Trounce, I., E. Byrne, and S. Marzuki. Decline in skeletal muscle mitochondrial respiratory chain function: possible factor in ageing. *Lancet* 1:637–639, 1989.
133. Turner, J.M., J. Mead, and M.E. Wohl. Elasticity of human lungs in relation to age. *J. Appl. Physiol.* 25:664–671, 1968.
134. Vollmer, W.M., L.R. Johnson, L.E. McCamant, and A.S. Buist. Longitudinal versus cross-sectional estimation of lung function decline-further insights. *Statistics in Medicine*, 7:685–696, 1988.
135. Wagner, P.D. Influence of mixed venous PO_2 on diffusion of O_2 across the pulmonary blood:gas barrier. *Clin. Physiol.* 2:105–115, 1982.
136. Wagner, P.D., G.E. Gale, R.E. Moon, J. Torre-Bueno, B.W. Stolpe, and H.A. Saltzman. Pulmonary gas exchange in humans at sea-level and simulated altitude. *J. Appl. Physiol.* 61:260–270, 1986.
137. Wagner, P., R. Laravuso, R. Uhl, and J.B. West. Continuous contributions of ventilation-perfusion ratios in normal subjects breathing air at 100% O_2. *J. Clin. Invest.* 54:54–68, 1974.
138. Wahba, W.M. Body build and preoperative arterial oxygen tension. *Can. Anaesth. Soc. J.* 22:653–658, 1975.
139. Wahba, W.M. Influence of aging on lung function—clinical significance of changes from age twenty. *Anesth. Analg.* 62:764–76, 1983.
140. Ward, R.J., A.G. Tolas, R.J. Benveniste, J.M. Hansen, and J.J. Bonica. Effect of posture on normal arterial blood gas tensions in the aged. *Geriatrics*:139–143, 1966.
141. Warren, J.B., S.T. Jennings, and T.J.H. Clark. Effect of adrenergic and vagal blockade on the normal human airway response to exercise. *Clin. Sci.* 66:79–85, 1984.
142. Wilson, R.M., R.S. Meadow, B.E. Jay, and E. Higgins. The pulmonary pathologic physiology of persons who smoke cigarettes. *N. Engl. J. Med.* 262:956–961, 1960.
143. Yasuoka, S., H. Manabe, T. Oaki, and E. Tsubura. Effect of age on the saturated lecithin contents of human and rat lung tissues. *J. Gerontol.* 32:387–391, 1977.
144. Yerg, J.E. II, D.R. Seals, J.M. Hagberg, and J.O. Holloszy. Effect of endurance exercise training on ventilatory function in older individuals. *J. Appl. Physiol.* 58:2082–89, 1985.
145. Younes, M., and G. Kivinen. Respiratory mechanics and breathing pattern during and following maximal exercise. *J. Appl. Physiol.* 57:1773–1782, 1984.