Aging of the Respiratory System: Impact on Pulmonary Function Tests and Adaptation to Exertion

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Life expectancy has risen sharply during the past century and is expected to continue to rise in virtually all populations throughout the world. In the United States population, life expectancy has risen from 47 years in 1900 to 77 in 2001 (74.4 for the male and 79.8 for the female population) [1]. The proportion of the population over 65 years of age currently is more than 15% in most developed countries and is expected to reach 20% by the year 2020. Healthy life expectancy, at the age of 60, is at present 15.3 years for the male population and 17.9 years for the female population [2]. These demographic changes have a major impact on health care, financially and clinically. Awareness of the basic changes in respiratory physiology associated with aging and their clinical implication is important for clinicians. Indeed, age-associated alterations of the respiratory system tend to diminish subjects’ reserve in cases of common clinical diseases, such as lower respiratory tract infection or heart failure [3,4].

This review explores age-related physiologic changes in the respiratory system and their consequences in respiratory mechanics, gas exchange, and respiratory adaptation to exertion.

Structural changes in the respiratory system related to aging

Most of the age-related functional changes in the respiratory system result from three physiologic events: progressive decrease in compliance of the chest wall, in static elastic recoil of the lung (Fig. 1), and in strength of respiratory muscles.

Age-associated changes in the chest wall

Estenne and colleagues measured age-related changes in chest wall compliance in 50 healthy subjects ages 24 to 75: aging was associated with a significant decrease (~31%) in chest wall compliance, involving rib cage (upper thorax) compliance and compliance of the diaphragm-abdomen compartment (lower thorax) [5]. Calcifications of the costal cartilages and chondrosternal junctions and degenerative joint disease of the dorsal spine are common radiologic observations in older subjects and contribute to chest wall stiffening [6]. Changes in the shape of the thorax modify chest wall mechanics; age-related osteoporosis results in partial (wedge) or complete (crush) vertebral fractures, leading to increased dorsal kyphosis and anteroposterior diameter (barrel chest). Indeed, prevalence of vertebral fractures in the elderly population is high and increases with age; in Europe, in female subjects over 60, the prevalence of vertebral fractures is 16.8% in the 60 to 64 age group, increasing to 34.8% in the 75 to 79 age group [7]. Men also show an increase in vertebral fractures with age, but rates are approximately half those of the female population [8]. A study of 100 chest radiographs of subjects ages 75 to 93 years, without cardiac or pulmonary disorders, illustrates the frequency of dorsal kyphosis in this age group: 25% had severe kyphosis as a consequence of vertebral wedge or crush fractures (>50°), 43% had moderate kyphosis (35°–50°), and only 23% had a normal curvature of the spine [6].
Respiratory muscle function

Respiratory muscle performance is impaired concomitantly by the age-related geometric modifications of the rib cage, decreased chest-wall compliance, and increase in functional residual capacity (FRC) resulting from decreased elastic recoil of the lung (Fig. 2) [9]. The kyphotic curvature of the spine and the anteroposterior diameter of the chest increase with aging, thereby decreasing the curvature of the diaphragm and thus its force-generating capacity [6]. Changes in chest wall compliance lead to a greater contribution to breathing from the diaphragm and abdominal muscles and a lesser contribution from thoracic muscles. The age-related reduction in chest-wall compliance is somewhat greater than the increase in lung compliance; thus, compliance of the respiratory system is 20% less in a 60-year-old subject compared with a 20-year-old (see Fig. 1) [9]. As such, during normal resting tidal breathing, the increase in breathing-related energy expenditure (elastic work) in a 60-year-old man is estimated at 20% compared with that of a 20-year-old, placing an additional burden on the respiratory muscles [8].

Respiratory muscle strength decreases with age (Table 1). Polkey and colleagues report a significant, although modest, decrease in the strength of the diaphragm in elderly subjects (n = 15; mean age 73, range 67–81 years) compared with a younger control group (n = 15; mean age 29, range 21–40 years): −13% for transdiaphragmatic pressure during a maximal sniff (sniff Pdi: 119 versus 136 cm H2O) and −23% during cervical magnetic stimulation (twitch Pdi: 26.8 versus 35.2 cm H2O) [10]. There was, however, a considerable overlap between groups, and the magnitude of the difference in this study was relatively small.
Similarly, Tolep and coworkers report maximal $P_{di}$ values in healthy elderly subjects ($n = 10$; ages $65–75, 128 \pm 9 \text{ cm H}_2\text{O}$), which were $25\%$ lower than values obtained in young adults ($n = 9$; ages $19–28, 171 \pm 8 \text{ cm H}_2\text{O}$) [11]. Although one cross-sectional study fails to demonstrate any relationship between age and maximal static respiratory pressures in 104 subjects over 55 [12], larger studies—also based on noninvasive measurements (maximal inspiratory and expiratory pressures [MIP and MEP] at the mouth and sniff nasal inspiratory pressure [SNIP])—document an age-related decrease in respiratory muscle performance [13–16]

Respiratory muscle strength is related to nutritional status, often deficient in the elderly. Enright and colleagues demonstrate significant correlations between MIP or MEP pressures and lean body mass (measured by bioelectric impedance), body weight, or body mass index [14]. Arora and Rochester show the deleterious impact of undernourishment on respiratory muscle strength or maximal voluntary ventilation: the decrease in respiratory muscle strength and maximal voluntary ventilation was highly significant in undernourished subjects ($71 \pm 6\%$ of ideal body weight) compared with control subjects ($104 \pm 10\%$ of ideal body weight) [17]. Necropsy studies confirm the correlation between body weight and diaphragm muscle mass further [18].

Age-associated alterations in skeletal muscles also affect respiratory muscle function [19]. MIP and MEP in elderly subjects are correlated strongly and independently with peripheral muscle strength (hand-grip) [13]. Peripheral muscle strength declines with aging. Bassey and Harries report a $2\%$ annual decrease in handgrip strength in 620 healthy subjects over age 65 [20]. Decrease in muscle strength results from a decrease in cross-sectional muscle fiber area (process referred to as sarcopenia), a decrease in the number of muscle fibers (especially type II fast-twitch fibers and motor units), alterations in neuromuscular junctions, and loss of peripheral motor neurons with selective denervation of type II muscle fibers [21–26]. Other proposed mechanisms of age-related muscular dysfunction include impairment of the sarcoplasmic reticulum $Ca^{++}$ pump resulting from uncoupling of ATP hydrolysis from $Ca^{++}$ transport (which may reduce maximal shortening velocity and relaxation), loss of muscle proteins resulting from decreased synthesis (ie, decreased “repair” ability and protein turnover), and a decline in mitochondrial oxidative capacity [27–31].

Respiratory muscle function also is dependent on energy availability (ie, blood flow, oxygen content, and carbohydrate or lipid levels) [32]. Decreased respiratory muscle strength is described in patients who have chronic heart failure (CHF). Mancini and colleagues show that CHF has a highly significant impact on respiratory muscle strength and on the tension-time index [33]. The tension-time index describes the relationship between force of contraction ($P_{di}/P_{dimax}$) and duration of contraction (ratio of inspiratory time to total respiratory cycle duration [$TI/TTOT$]) and is related inversely to respiratory muscle endurance. In elderly subjects who have heart

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failure, the tension-time index increases, primarily because of an increase in Pdi/Pdi\text{max} and, during exercise, approaches values shown to generate fatigue [34]. Evans and coworkers show a significant correlation between cardiac index and sniff Pdi [35]. Nishimura and coworkers make a similar observation in subjects who have CHF, showing significant correlations between MIP and cardiac index or maximal oxygen consumption (VO₂\text{max}) per body weight, as an index of cardiovascular performance [36].

Other frequent clinical situations that produce diminished respiratory muscle function in the elderly include Parkinson’s disease and sequelae of cerebral vascular disease [37,38]. Myasthenia gravis is another cause of respiratory muscle weakness, although encountered less commonly.

**Changes in the lung parenchyma and peripheral airways**

The human respiratory system is exposed continuously to air and a variety of inhaled pollutants. This creates a challenge for physiologists and clinicians, namely to differentiate—the true impact of normal aging (ie, physiologic aging) from that of environmental exposure. Environmental tobacco smoke and particulate air pollution have measurable and well-documented effects on respiratory symptoms and disease in the elderly [39–41]. Appropriate animal models, therefore, are needed to study pathologic changes that occur with aging per se. Senescence-accelerated mice (SAM; a murine model of accelerated senescence) is proposed as such a model, permitting investigation of the differences between the aging lung and cigarette smoke–related airspace enlargement [42,43]. Morphometric studies of SAM show a notable homogeneous enlargement of alveolar duct size with aging. Cellular infiltrates in the alveoli rarely are seen, suggesting that the airspace enlargement does not result from inflammation, as opposed to what is seen in emphysema. The ratio of lung weight to body weight does not decrease with aging, suggesting little or no lung destruction [42]. Elastic fibers of the lung in SAM have a reduced recoil pressure, causing distention of the alveolar spaces and increased lung volume [43]. Age-related changes in the pressure-volume curves show a shift leftwards and upwards (ie, loss of elastic recoil of the lung) (see Fig. 1). These changes are similar to those described in senile emphysema of the lung in humans [9,44].

As noted in SAM during the course of aging, alveolar ducts in humans increase in diameter and alveoli become wider and shallower [45]. This enlargement is remarkably homogeneous as opposed to the irregular distribution of airspace enlargement in emphysema. Morphometric studies consistently find an increase in the average distance between airspace walls (mean linear intercept) and a decrease in the surface area of airspace wall per unit of lung volume beginning in the third decade of life. The decrease in surface area of airspace wall per unit of lung volume approximately is linear and continues throughout life, resulting in a 25% to 30% decrease in nonagenarians [46,47]. Although these changes are histologically different from emphysema (no destruction of alveolar walls), they result in similar changes in lung compliance. Thus, as described by Turner coworkers in subjects ages 20 to 60, static elastic recoil pressure of the lung decreases as a part of normal aging (0.1 – 0.2 cm H₂O · year⁻¹), and the static pressure-volume curve for the lung is shifted to the left and has a steeper slope [9,48]. Verbeken and coworkers propose that the changes in structural and functional characteristics caused by isolated airspace enlargement that are seen in the elderly be differentiated from emphysema by the absence of alveolar wall destruction and inflammation and designated as senile lung [45].

In a postmortem study, mean bronchiolar diameter also decreased significantly after age 40 [49]. Bronchiolar narrowing and increased resistance were independent of any emphysematous changes or of previous bronchiolar injury. This decline in small airway diameter may contribute to the decrement in expiratory flow noted with aging [49]. Reduction in supporting tissues around the airways further increases the tendency for the small airways (<2 mm) to collapse.

**Pulmonary function tests**

*Specifics of pulmonary function testing in an older population*

The application of conventional quality control standards to objective assessment of pulmonary function in older subjects may prove difficult because of mood alterations, fatigability, lack of cooperation, or cognitive impairment. Indeed, prevalence of dementia increases with aging, reaching 5.6% after age 75, 22% after age 80, and 30% as of age 90 [50]. The relationship between ability to perform spirometry and cognitive function in the elderly is reported by several investigators [51–54]. The feasibility of high-quality spirometry in elderly subjects who do not have cognitive impairment is confirmed in a large
Italian study of 1612 ambulatory subjects ages 65 and older who did nor did not have chronic airflow limitation: tests with at least three acceptable curves were obtained in 82% of normal subjects and in 84% of patients who have chronic airflow limitation [55]. Cognitive impairment, however, lower educational level, and shorter 6-minute walking distance levels were found to be independent predictors of a poor acceptability rate [55]. Pezzoli and colleagues performed spirometric testing in 715 subjects who had respiratory symptoms and reported a feasibility rate (according to ATS criteria) of 82%; low Mini–Mental State Examination and activities of daily living scores were associated with poor spirometric performance [56]. Lower feasibility rates for spirometry are reported in elderly patients who were institutionalized (41%) and hospitalized (50%), with a clear relationship between the degree of cognitive impairment and feasibility of testing [53,54]. The prevalence of delirium in older people on hospital admission ranges from 10% to 24%, whereas delirium develops in 5% to 32% of older patients after admission [57]. Underdiagnosis, therefore undertreatment, of chronic obstructive pulmonary disease (COPD) in older subjects may be related to difficulties encountered in performing spirometry adequately in this population.

Alternative tests for the measurement of COPD in the elderly have been explored to find methods that may be less cooperation dependent for test subjects. Measurement of airway resistance using the forced oscillation technique (FOT) is applied more easily than spirometry in older patients who have cognitive disorders [53,54]. In elderly patients who are hospitalized or institutionalized, measurement of airway resistance by FOT was successful in 74% to 76% of patients tested. The reported sensitivity and specificity for the detection of COPD in older subjects were 76% and 78%, respectively; thus, FOT is useful in this population [54]. Conversely, assessment of airway resistance using the interrupter technique, widely used in epidemiologic and pediatric studies, in spite of its attractive simplicity, performed poorly in the detection of COPD in older subjects compared with FOT or spirometry, with a higher coefficient of variation than FOT [58]. The negative expiratory pressure technique (NEP), which does not require a forced expiratory maneuver, is useful to detect flow limitation [59]. The test involves applying negative pressure at the mouth during a tidal expiration. When the NEP elicits an increase in flow throughout the expiration, patients are not flow limited. In contrast, when patients do not have an increase in flow during most or part of the tidal expiration on application of NEP, they are considered flow limited. This technique has significant limitations, as it underestimated the presence of COPD without resting flow limitation in a study of 26 adults ages 42 to 87 (mean 65 ± 10 years) and, therefore, cannot be considered a substitute for spirometric screening for COPD [59].

For assessment of respiratory muscle performance, SNIP and MIP and MEP are feasible in older subjects, although SNIP tends to be easier to perform and better tolerated than MIP; these tests show an important learning effect and must be repeated at least five (MIP and MEP) to 10 (SNIP) times [60,61]. Reported coefficients of variation for MIP and MEP in healthy elderly subjects are, respectively, 10.2% and 12.8% [62].

Plethysmographic measurement of lung volumes seldom is required in this age group and, to the author’s knowledge, no specific reference values are available for subjects over age 70.

### Lung volumes

The major determinants of static lung volumes are the elastic recoil of the chest wall and that of the lung parenchyma. Loss of elastic recoil of the lung parenchyma and, to a lesser degree, decrease in respiratory muscle performance result in an increase in residual volume (RV): RV increases (air-trapping) by approximately 50% between ages 20 and 70 (see Fig. 2). Conversely, there is a progressive decrease in vital capacity to approximately 75% of best values. Because of the increased stiffness of the chest wall, the age-related diminished elastic recoil of the lungs is counterbalanced by an increased elastic load from the chest wall; total lung capacity (TLC) thus remains fairly constant throughout life [63]. Increased elastic recoil of the chest wall and diminished elastic recoil of the lung parenchyma also explain the increase in FRC (ie, elderly subjects breathe at higher lung volumes than younger subjects) (see Figs. 1 and 2) [63].

The closing volume (ie, the volume at which small airways in dependent regions of the lung begin to close during expiration) increases with age. Premature closure of terminal airways is related to a loss of supporting tissues around the airways. The closing volume begins to exceed the supine FRC at approximately 44 years of age and to exceed the sitting FRC at approximately 65 years of age [64]. Closing volume may reach 55% to 60% of TLC and equal FRC; as such, normal tidal breathing may occur with a significant proportion of peripheral airways not contributing to gas exchange (low ventilation-perfusion ratio [V/Q] zones). Although this is sug-
suggested as an important mechanism for the age-related decrease in \( \text{PaO}_2 \), increase in alveolar-arterial difference in partial pressure of oxygen (\( \text{PaO}_2 - \text{PaO}_2 \)), and decrease in carbon monoxide transfer, measurement of V/Q inequality using the multiple inert gas elimination technique (MIGET) fails to show a significant increase in low V/Q areas with aging in 64 subjects ages 18 to 71 [65].

**Spirometry**

Forced expiratory volumes increase with growth up to the age of approximately 18. According to European Community for Coal and Steel data, no significant changes occur in forced expiratory volume in 1 second (FEV\(_1\)) or forced vital capacity (FVC) between the ages of 18 and 25 [66]. After this plateau, FEV\(_1\) and FVC start to decrease, although more recent studies excluding smokers suggest a later start of FEV\(_1\) and FVC decline in nonsmokers [67]. Cross-sectional and longitudinal studies show an accelerated decline in FEV\(_1\) and FVC with age; the rate of decline is greater in cross-sectional versus longitudinal studies and in men versus women and more rapid in patients who have increased airway reactivity [63]. The age-related decrease in FEV\(_1\) and FVC initially was considered linear, but more recent studies—including subjects ages 18 to 74—suggest that the decline may be nonlinear and accelerates with aging [68–71].

Regression equations, based on extrapolations from groups of younger subjects, tend to overestimate predicted values for FEV\(_1\), FVC, and FEV\(_1\)/FVC in elderly subjects [67]. Few studies report results obtained in large samples of elderly subjects. Ericsson and Irnell, for example, report measurements performed on 264 normal “elderly” subjects, none of whom was older than 71 years of age [72]. Fowler and colleagues studied 182 Londoners over age 60, but only 44 subjects were over age 75 and 23 were over 80 [73]. The three largest studies (all cross-sectional) reporting spirometric data from healthy elderly subjects were published by Milne and Williamson, Enright and colleagues, and DuWayne Schmidt and colleagues [52,74,75]. DuWayne Schmidt and colleagues included patients ages 20 to 94 and found that decline in FEV\(_1\) and FVC with age was linear (−31 mL/year in men and −27 mL/year in women). Values for FEV\(_1\)/FVC were stable in young adults and decreased in women over age 55 and in men over age 60 to 70 to 75% range [75]. The study by Milne and Williamson includes a large number of active or former smokers, and 20% of subjects had regular cough and phlegm; thus, it is unreliable [52].

Enright and colleagues selected 777 healthy nonobese, never-smokers ages 65 to 85 who had no history of lung disease from 5201 ambulatory elderly participants of the Cardiovascular Health Study; estimation of annual decline for FEV\(_1\) was 32 mL/year in women and 27 mL/year for men and, for FVC, 33 mL/year in women and 20 mL/year in men (Box 1) [13,74,108,113,117]. Regression equations suggest a linear relationship between age and decline in FEV\(_1\) and FVC in this study [73]. In summary, the average yearly decline of FEV\(_1\) and FVC is approximately 30 mL/year, although it may be overestimated by cross-sectional studies. Whether or not decline of forced expiratory volumes with age is linear remains controversial, and longitudinal studies of older nonsmoking subjects are required to clarify this issue.

According to published reference values for FEV\(_1\)/FVC, using a threshold value of FEV\(_1\)/FVC less than 70% for defining the presence of airway obstruction, as suggested by the Global Initiative for Chronic Lung Diseases (GOLD) Workshop Summary, may lead to overdiagnosis of COPD. This is illustrated by a Norwegian study of forced expiratory volumes in 71 asymptomatic never-smokers, ages 70 or older; according to GOLD criteria, 25% had stage I COPD and 10% stage II; for subjects older than 80, results were, respectively, 32% and 18% [76]. Using the regression equations published by Enright and colleagues, normal values for FEV\(_1\)/FVC are less than 70% for men ages 80 and older and women ages 92 and older (see Box 1) [74].

**Flow-volume curves and peak expiratory flow**

Fowler and colleagues report characteristic modifications in the expiratory flow-volume curve with aging (Fig. 3) [73]. The changes in expiratory flow-volume suggested alterations in the small peripheral airways, with an obstructive pattern present even in lifetime nonsmokers, suggesting that this pattern may be normal in old age. Similar results are reported by Babb and Rodarte, who compared expiratory flow rates in 17 younger adults (ages 35–45) with those of 19 older adults (ages 65–75); in this study, decline in peak expiratory flow (PEF) in the older group is proportional to loss of lung elastic recoil [77]. Changes in peripheral airways and loss of supporting tissue around the airways (“senile lung”) (discussed previously) are plausible explanations for these findings.

Although PEF rates tend to decrease with age, the variability in predicted peak flow values is large, and prediction equations are, therefore, not reliable [78,79]. PEF lability (maximal difference in PEF
per mean PEF) is shown to correlate with a diagnosis of asthma in younger subjects. Although middle-aged and older persons seem to be successful in providing a measure of PEF reliably at home, older age per se was a factor of increased variability in longitudinal monitoring of ambulatory PEF (independent predictor of higher PEF lability) [80]. In a study of 1223 subjects (mean age 66, range 43–80), Enright and colleagues report an upper limit of normal of 16% for PEF lability in older patients [80]. Another study

### Box 1. Regression equations for pulmonary function test variables in older subjects

**Spirometry: men**

\[
\begin{align*}
\text{FEV}_1 (\text{liters}) &= (0.0378 \times \text{height}_{\text{cm}}) - (0.0271 \times \text{age}_{\text{years}}) - 1.73; \text{LLN} = -0.84 \\
\text{FVC} &= (0.0567 \times \text{height}_{\text{cm}}) - (0.0206 \times \text{age}_{\text{years}}) - 4.37; \text{LLN} = -1.12 \\
\text{FEV}_1/\text{FVC}\% &= (-0.294 \times \text{age}_{\text{years}}) + 93.8; \text{LLN} = -11.7
\end{align*}
\]

**Spirometry: women**

\[
\begin{align*}
\text{FEV}_1 (\text{liters}) &= (0.0281 \times \text{height}_{\text{cm}}) - (0.0325 \times \text{age}_{\text{years}}) - 0.09; \text{LLN} = -0.48 \\
\text{FVC} &= (0.0365 \times \text{height}_{\text{cm}}) - (0.0330 \times \text{age}_{\text{years}}) - 0.70; \text{LLN} = -0.64 \\
\text{FEV}_1/\text{FVC}\% &= (-0.242 \times \text{age}_{\text{years}}) + 92.3; \text{LLN} = -9.3
\end{align*}
\]

**Maximal mouth inspiratory and maximal mouth expiratory pressures: men**

\[
\begin{align*}
\text{MIP} (\text{cm H}_2\text{O}) &= (0.131 \times \text{weight}_{\text{lb}}) - (1.27 \times \text{age}_{\text{years}}) + 153; \text{LLN} = -41 \\
\text{MEP} (\text{cm H}_2\text{O}) &= (0.25 \times \text{weight}_{\text{lb}}) - (2.95 \times \text{age}_{\text{years}}) + 347; \text{LLN} = -71
\end{align*}
\]

**Maximal mouth inspiratory and maximal mouth expiratory pressures: women**

\[
\begin{align*}
\text{MIP} (\text{cm H}_2\text{O}) &= (0.133 \times \text{weight}_{\text{lb}}) - (0.805 \times \text{age}_{\text{years}}) + 96; \text{LLN} = -32 \\
\text{MIP} (\text{cm H}_2\text{O}) &= (0.344 \times \text{weight}_{\text{lb}}) - (2.12 \times \text{age}_{\text{years}}) + 219; \text{LLN} = -52
\end{align*}
\]

**6-minute walk test: men (n = 117; ages 40 to 80)**

\[
\text{6MWD}_{\text{meters}} = (7.57 \times \text{height}_{\text{cm}}) - (5.02 \times \text{age}_{\text{years}}) - 309 \text{ m}; \text{LLN} = -153 \text{ m}
\]

**6-minute walk test: women (n = 173, ages 40 to 80)**

\[
\text{6MWD}_{\text{meters}} = (2.11 \times \text{height}_{\text{cm}}) - (2.29 \times \text{weight}_{\text{kg}}) - (5.78 \times \text{age}_{\text{years}}) + 667 \text{ m}; \text{LLN} = -139 \text{ m}
\]

**Maximal heart rate (n = 18712)**

Maximal heart rate = 208 – (0.7 × age)

**Maximal oxygen consumption (n = 100; ages 15 to 71)**

\[
\text{VO}_{2\text{max}} (\text{L/min}) = (0.046 \times \text{height}_{\text{cm}}) - (0.021 \times \text{age}_{\text{years}}) - 0.62 (0: \text{male}; 1: \text{female}) - 4.31 \text{ L}; \text{LLN} = -0.89 \text{ L}
\]

**Abbreviations:** LLN, lower limit of normal (mean − 1.96 SD); 6MWD, distance walked during a 6-minute test.
by the same group, based on a larger community sample of 4581 persons ages 65 and older, reports an upper limit of normal of 29% for PEF lability. A cut-off value of 30% for PEF lability, therefore, is recommended in older subjects for the diagnosis of asthma [78].

No specific changes are noted regarding the inspiratory flow curves, although maximal inspiratory flow values decrease with aging. Because lung deposition of inhaled drugs is flow dependent with available powder-inhaling devices, determination of maximal inspiratory flow-volume curves in Londoners aged 60 years and over. Thorax 1987;42:173–82.) by the same group, based on a larger community sample of 4581 persons ages 65 and older, reports an upper limit of normal of 29% for PEF lability. A cut-off value of 30% for PEF lability, therefore, is recommended in older subjects for the diagnosis of asthma [78].

Airway resistance and conductance

When adjusted for lung volume, age has no significant effect on airway resistance. Peripheral airways contribute marginally to the total resistance of the airways and, therefore, changes in the peripheral airways are not reflected by changes in airway resistance [63]. Using the FOT, Pasker and colleagues find a weak impact of age on resistance and reactance, with opposite effects according to sex; the investigators consider the relationship between FOT measurements and age clinically irrelevant [83].

Respiratory muscle testing

Respiratory muscle weakness may lead to shortness of breath, reduced exercise tolerance, and, in more severe cases, alveolar hypventilation and respiratory failure. The overall strength of respiratory muscles can be measured noninvasively by recording MIP and MEP or by measuring SNIP [61,84]. These measurements can be performed easily at bedside [61,84]. Inspiratory pressures are measured at FRC or at RV. Expiratory pressures usually are measured at TLC. As discussed previously, the learning effect for MIP, MEP, and SNIP measurements is important, with significant increases over at least five consecutive maneuvers [13,61]. Values greater than or equal to 80 cm H2O (in men) or 70 cm H2O (in women) for MIP or greater than or equal to 70 cm H2O in men and 60 cm H2O in women for SNIP exclude clinically relevant respiratory muscle weakness [85].

Available reference values for these measurements show a decrease with age of respiratory muscle strength (see Table 1 and Box 1) [13–16]. Enright and colleagues measured MIP and MEP in ambulatory subjects ages greater than or equal to 65; normal values for women ages greater than or equal to 65 and males ages greater than or equal to 75 are below the aforementioned threshold for clinically relevant respiratory muscle dysfunction [13]. Nutritional status (body weight, bioelectric impedance, and body mass index) and peripheral muscle strength (handgrip) correlate significantly with MIP and MEP values [13]. Other investigators find values in the same range for MIP, MEP, or SNIP [15,16,86]. The decrease in respiratory muscle strength likely is relevant in elderly patients in clinical situations where an additional load is placed on the respiratory muscles, such as pneumonia or left ventricular failure [35,36]. The effects of poor nutritional status and CHF on respiratory muscle strength are discussed previously.

Gas exchange

Changes in arterial oxygen tension and ventilation-perfusion relationships

Wagner and coworkers, using the MIGET, report an increase, with aging, in V/Q imbalance, with a rise
in units with a high V/Q (wasted ventilation or physiologic dead space) and in units with a low V/Q (shunt or venous admixture) [87,88]. The decrease in \( P_aO_2 \) with age is described as a consequence of this increased heterogeneity of V/Q and, in particular, of the increase in units with a low V/Q (dependent parts of the lung, poorly ventilated during tidal breathing, as reflected by an increased closing volume) [87]. These conclusions are based, however, on a small number of observations. More recently, Cardus and coworkers described the age-related changes in V/Q distribution in 64 healthy subjects ages 18 to 71 [65]. Although there was a slight increase in V/Q mismatch in older patients, shunt and low V/Q areas did not exceed 3% of total cardiac output, and decrease in \( P_aO_2 \) observed in healthy subjects, with the following regression equation: \( P_aO_2 = 109 - (0.43 \times \text{age}) \) (the fact that patients were supine during arterial sampling probably explains lower \( P_aO_2 \) values obtained from this regression) [92]. More recently, Cerveri and coworkers suggest that the decrease in \( P_aO_2 \) with aging is not linear [93]. In their study, arterial blood gas tests were analyzed in 194 non-smoking subjects ages 40 to 90. Stratifying the results by 5-year age intervals, the investigators found a clear decline in \( P_aO_2 \) up to 70 to 74 years of age, followed by a slight rise in \( P_aO_2 \) from ages 75 to 90. For healthy patients older than 75, \( P_aO_2 \) was not correlated with age; mean values reported were \( 83 \pm 9 \text{ mm Hg} \) (11.1 ± 1.2 kPa), and fifth percentile was at 68.4 mm Hg (9.2 kPa) [93].

A modest increase in the \( P_aO_2 - P_aO_2 \) with age is expected because of the previously described increase in V/Q heterogeneity. According to Sorbini and coworkers [92], the highest normal value for the \( P_aO_2 - P_aO_2 \) at a certain age is given by the equation: \( P_aO_2 - P_aO_2 \) (mm Hg) \( \leq 1.4 \pm 0.43 \times \text{age} \) (years). High values obtained by this equation (ie, 4.8 kPa [36 mm Hg] for 80 years of age) also may result from the supine position of subjects at time of sampling. More recent studies find no significant relationship between age and \( P_aO_2 - P_aO_2 \); however, values reported are well above normal values for younger adults (ie, 3.2 ± 1.4 kPa [24 ± 10 mm Hg] [90] and 4.4 ± 0.6 kPa [33 ± 4.5 mm Hg] [91]).

**Carbon monoxide transfer factor**

Flattening of the internal surface of the alveoli (ductectasia) in the elderly is associated with a reduction in alveolar surface (75 m² at the age of 30 years versus 60 m² at age 70 years, a reduction of 0.27 m²·year⁻¹) [63]. Because of loss of alveolar surface area, decreased density of lung capillaries, decline in pulmonary capillary blood volume, and increased V/Q heterogeneity, it is estimated that, even in healthy nonsmokers, there is a yearly decline in the diffusing capacity of the lung for carbon monoxide (DL\(_{CO}\)) of 0.2 to 0.32 mL·min⁻¹·mmHg⁻¹ from middle ages and onward in men and a decrease of 0.06 to 0.18 mL·min⁻¹·mmHg⁻¹ in women [91,94]. Guénard and Marthan determined, in a population of 74 healthy subjects aged 69 to 104, the following regression equation for transfer capacity of the lung for carbon monoxide (T\(_{\text{LCO}}\)) versus age (age explaining 29% of the variance of T\(_{\text{LCO}}\)): T\(_{\text{LCO}}\) (mL·min⁻¹·kPa⁻¹)=126 - 0.9 \times \text{age} \text{ (years); } r=0.54, P<0.001) [91].

**Regulation of breathing**

**Aging and ventilatory responses**

Aging is associated with a marked attenuation in ventilatory responses to hypoxia and hypercapnia [95–97]. Kronenberg and Drage compared the
responses to hypercapnia and hypoxia in eight healthy young men (22–30 years old) with those of eight older men (64–73 years old) [95]. In the older subjects, ventilatory response to hypoxia was four times less than that of the younger group; response to hypercapnia was decreased by 58%. Mouth occlusion pressure (P0.1), an index of respiratory drive, is the inspiratory pressure generated at the mouth when occluding the airway 0.1 second after the beginning of inspiration. Peterson and colleagues describe, in subjects ages 65 to 79, a 50% reduction in the response to isocapnic hypoxia and a 60% reduction in that to hyperoxic hypercapnia measured by P0.1 compared with younger subjects [97]. More recently, however, two studies cast doubt on the age-related decrease in hypocapnic ventilatory response. Smith and colleagues studied two groups of nonsmoking male subjects, ages 30 ± 7 and 73 ± 3, who were submitted to 20 minutes of acute isocapnic hypoxia; ventilatory responses and increment in neuromuscular drive were similar in both groups [98]. Similarly, Pokorski and Markzak compare the ventilatory response to isocapnic hypoxia in 19 women ages 71 ± 1 to 16 younger women and find no significant difference between groups in slopes of the ΔVE (ventilation) to ∆SaO2 (arterial oxygen saturation) ratio and ΔP0.1/ ∆SaO2 [99].

The importance of the decrease in ventilatory response to hypercapnia in older subjects also is unsettled: as in the study by Kronenberg and Drage, Brischetto and colleagues report a reduction in the slope of the ventilatory response to hypercapnia in older subjects (−67%) versus a younger control group [95,96]. Rubin and coworkers, however, in a comparative study of ventilatory response and P0.1 response to hypercapnia, fail to disclose significant differences between older (n=10, ages over 60) versus younger adults (n=18, ages under 30) [100].

Thus, although some studies suggest that there is an age-related decline in the ability to integrate information received from sensors (peripheral and central chemoreceptors and mechanoreceptors) and generate appropriate neural activity, further investigations are needed to clarify this issue.

Aging also is associated with a decreased perception of added resistive or elastic loads [57,101,102]. Older subjects have a lower perception of methacholine-induced bronchoconstriction than younger subjects. Although available evidence yields conflicting results, blunting of the response to hypoxia and hypercapnia and lower ability to perceive bronchoconstriction may represent a partial loss of important protective mechanisms (alarm signals).

During sleep

The prevalence of sleep-disordered breathing increases in elderly subjects. In middle-aged populations, the prevalence of the obstructive sleep apnea syndrome (OSAS), using an apnea/hypopnea index (AHI) of 15 events·h⁻¹ as a cut-off value, is approximately 4% in women and 9% in men [103]. In older subjects, however, 13% to 62% of elderly subjects suffer from OSAS with an AHI greater than 10 events per hour [104]. Sleep-disordered breathing may be associated with impairment in cognitive function and is reported to be more frequent in Alzheimer’s disease [105]. As discussed previously, aging is associated with a diminished perception of added resistive loads, such as that generated by bronchoconstriction or upper airway collapse. Indeed, respiratory effort in response to upper airway occlusion in elderly patients is decreased compared with younger subjects. Krieger and coworkers recorded esophageal pressure during sleep in 116 patients who had OSAS (AHI>20) and showed that indexes of respiratory effort were reduced significantly in older compared with younger patients (inspiratory effort at end of apnea: maximal esophageal pressure 40 ± 2 versus 56 ± 3 cm H2O) [106]. The lesser increase in respiratory effort in older patients may result from a decrease in respiratory drive and respiratory muscle performance. In spite of the fact that indexes of respiratory effort during apneic episodes were lower in older individuals, mean apnea duration was not prolonged significantly in older patients (28.3 ± 0.7 s versus 30.4 ± 0.9 s), and postapneic SaO2 was higher in older individuals.

Ventilatory response to exercise

Performance during the 6-minute walk test

In subjects who do not have significant osteoarticular or neuromuscular limitation, the 6-minute walk test is a widely used standardized measurement for evaluating physical function; results of a 6-minute walk test are useful to quantify physical limitation and monitor progression of disease in chronic obstructive or restrictive disorders, CHF, or pulmonary vascular diseases; performance is correlated with health-related quality-of-life scores and predictive of morbidity and mortality in disorders, such as pulmonary hypertension or CHF [107]. There is a 15% learning effect when tests are performed on two successive days. Coefficient of variation is 8%. Enright and Sherrill established reference equations...
for the 6-minute walk test from results collected in 290 healthy subjects ages 40 to 80 (see Box 1) [108]. Predicted values for distance walked decrease linearly with age, with a difference of approximately 200 meters between the ages of 40 and 80 years. Mean baseline SaO₂ was stable at 96%. The 6-minute walk test is a submaximal exercise test (peak VO₂max during a 6-minute walk is approximately 80% of VO₂max during maximal exercise testing); thus, potentially it is less sensitive for the detection of cardiac or pulmonary disorders.

Maximal oxygen consumption and aging

The ability to perform physical tasks declines with advancing age. VO₂max, expressed in L · min⁻¹, reaches a peak between 20 and 30 years of age. Longitudinal and cross-sectional studies thereafter show a decrease in VO₂max at an estimated rate of 9% to 10% per decade or year (see Box 1) [109–114]. The ventilatory threshold also decreases with age, although less rapidly than VO₂max [115]. The decrease in VO₂max is more pronounced in sedentary subjects than in those remaining physically active [109]. In fact, loss in VO₂max is attenuated in fit elderly individuals and may not be significant clinically. VO₂max of older trained athletes is shown to be higher than that of middle-aged untrained men [116]. Thigh muscular mass also has a positive impact on VO₂max [113]. The Fick equation gives the relationship between cardiac output, peripheral oxygen extraction ([Ca – Cv]O₂), and oxygen consumption per unit time (VO₂): VO₂ = cardiac output × [Ca – Cv]O₂. Maximal heart rate (HR) in healthy adults decreases with age: Tanaka and colleagues, in a recent meta-analysis compiling data from 18,712 subjects, show that maximal HR is independent of sex and level of physical activity and is predicted mainly by age alone; they computed the equation, maximal HR = 208 - 0.7 × age (r = −0.90 versus age), which gives slightly higher values than the commonly used predictive equation, maximal HR = 220 - age [117]. Factors limiting VO₂ in older subjects are reduced maximal HR (resulting from a decrease in sensitivity of cardiac β-adrenergic receptors), decreased left ventricular ejection fraction, reduced maximal cardiac output, and reduced peripheral muscle mass. Fleg and Lakatta measured 24-hour urinary creatinine excretion, an index of muscle mass, in 184 healthy nonobese volunteers, aged 22 to 87, who performed a maximal treadmill exercise [118]. VO₂max showed a strong negative linear relationship with age. When VO₂max was normalized for creatinine excretion, a large portion of the age-associated decline in VO₂max was explained by the loss of muscle mass [118].

Ventilation and exercise

Ventilation during exercise in the elderly is associated with more abdominal contribution than in young adults and a concomitant change in respiratory pattern (higher rate and lower tidal volume), which may result from increased stiffness of the thoracic cage.

When compared with younger subjects, initial ventilatory (and circulatory) responses to exercise are slowed in the elderly. Although respiratory frequency increases rapidly, rise in tidal volume and total ventilation is delayed [119].

In contrast to the previously discussed decreased response to hypercapnia at rest, elderly subjects seem more responsive than younger subjects to carbon dioxide during exercise. Poulin and colleagues demonstrate, in a sample of 224 subjects aged 56 to 85, that, for a given carbon dioxide production (VCO₂), the ventilatory response (VE/VCO₂) increases with aging [120]. Similarly, Inbar and co-workers find a 14% increase in VE/VCO₂ and a 13% increase in VE/VO₂ between the ages of 20 and 70, in a large cross-sectional study of 1424 healthy subjects [114]. This also was reported by Brischetto and colleagues [95]. In both of these studies, this response was related neither to oxygen desaturation nor to increased metabolic acidosis; Prioux and colleagues, however, show that, above the anaerobic threshold, older subjects had, for a given carbon dioxide production, higher lactate concentrations [121]. A higher dead space–to–tidal volume ratio in elderly subjects most probably is contributive to the higher VE/VCO₂ ratio. In agreement with this hypothesis is the observation of a higher difference between end-tidal and arterial carbon dioxide tensions (PaCO₂) in older subjects and the increase in V/Q heterogeneity with aging (described previously) [65,114]. In itself, this may increase dyspnea for a given workload. Indeed, for a given VE, the oxygen cost of breathing is higher in elderly subjects.

Response to exercise training

Pulmonary rehabilitation programs are shown to improve exercise capacity in older patients who have COPD. A retrospective study by Couser and co-workers compares the impact of a 2-month rehabilitation program in 28 subjects ages 75 years and older versus 56 subjects aged less than 75. Improvement in 12-minute walking distance was significantly
higher in the older patient group (+167 m; 38% increase) than in the younger group (+107 m; 23% increase) [122].

Aerobic training also is feasible in older healthy individuals and results in significant, although often modest, improvements in VO₂peak in older subjects. For instance, Malbut and colleagues studied the effects of a 6-month aerobic training program on maximal aerobic power of 26 healthy elderly people (79 to 91 years) [123]. After training, VO₂max increased by 15% in women but not in men. Another study of 22 sedentary subjects (aged 80 to 92) shows, after 6 months of moderate-intensity aerobic exercise training, an improvement in exercise test duration (+33%) and peak VO₂ (+9%) [124]. Training programs of 4 to 12 months, in older individuals, show average increases in VO₂max of 8.5% to 25% [125–128].

Summary

Compliance of the chest wall and the respiratory system and lung elastic recoil decrease with aging, resulting in static air trapping (increased RV), increased FRC, and increased work of breathing. Respiratory muscle function also is affected by aging, either as a consequence of geometric changes in the rib cage, nutritional status (lean body mass, body weight), cardiac function, or through the age-related reduction in peripheral muscle mass and function, referred to as sarcopenia. In subjects 80 years of age and older, values of MIP may reach critically low values; this may result in alveolar hypoventilation or respiratory failure in clinical situations such as left-sided heart failure or pneumonia. Expiratory flow rates also decrease with aging, with characteristic changes in the flow-volume curves suggesting increased collapsibility of peripheral airways.

Gas exchange is remarkably well preserved at rest and during exertion in spite of a reduced alveolar surface area and increased ventilation-perfusion heterogeneity. In fact, in older athletes who have regular physical training, the respiratory system remains capable of adapting to high levels of exercise. In sedentary individuals, however, VO₂max decreases regularly with aging, whereas work of breathing, at a given level of ventilation, increases. Decreased sensitivity of respiratory centers to hypoxia or hypercapnia may result in a diminished ventilatory response in case of acute disease, such as heart failure, infection, or aggravated airway obstruction, although published data as to the ventilatory response to hypoxia in the elderly are inconclusive. Furthermore, blunted perception of added resistive loads (ie, bronchoconstriction) and diminished physical activity may result in a lesser awareness of respiratory disease and delay diagnosis.

References

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