



Normative aging of the respiratory system

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Clinicians are familiar with the prevalent and interacting diseases commonly encountered in geriatric patients but are less aware of the specific normal physiologic changes that may determine the presence or absence of reported symptoms, level of function, or an apparently aberrant test result. Many geriatric patients have interactions between the respiratory system and other organ systems. Even with healthy lungs the common age-associated morbidity of spinal osteoporosis with loss of height profoundly influences lung volume, oxygenation, and exercise capacity. Neurologic conditions may affect the swallowing mechanism, leading to aspiration of oropharyngeal contents, which presents as signs and symptoms localized to the upper airways, lung parenchyma, or as unsuspected radiographic findings [1]. Likewise, the only indicators of heart failure or esophageal reflux disease may be reported or observed dyspnea [2] or a cough [3]. The most obvious reason to define the normal age-related changes of the respiratory system, those that occur predictably after normal development in the absence of established disease or toxic exposure, is to accurately interpret symptoms, signs, and diagnostic studies in older adults and to avoid inappropriate attempts to medicalize normal phenomena [4,5].

For the respiratory system, more than other organ systems, there are many limitations to distinguishing a solely age-related change in physiology, accurately predicting a rate of decline or defining age-appropriate norms. Current knowledge is limited by the lack of representation of the oldest adults in the data sets of physiology researchers [6–10]. Some studies have determined a regression equation for age-related decline from a cohort whose oldest participant would not be eligible for Medicare [11–13] or from the data of one 80-year-old participant [14,15]. Whereas most geriatric patients are women, early aging studies included only men [7,16–18]. In general, physiology studies have found greater variability and skew in a given measurement between older participants compared with a given measurement between younger patients [8,9,19–21]. Even in the

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absence of disease older adults are more different from each other than are younger adults, contributing to difficulties in establishing a normal range for advanced age. Furthermore, conclusions have been made about normal aging from cohorts that did not exclude participants with occult disease, cigarette exposure, or symptoms indicative of subclinical illness [12,16,22–26]. In support of rigorous exclusion criteria the Cardiovascular Health Study found that hypertension, lower extremity edema, and diabetes were independently associated with a lower level of lung function and participants with these characteristics were eliminated from the “healthy group” for defining normal limits of lung function [4].

An assessment of inherent methodologic biases is necessary for clinical application of a study’s result. Cross-sectional studies use age as the independent variable and the physiologic measure as the dependent variable. Defining a line from the data points represents differences in the level of the physiologic measure at different ages; however, it is not a measure of a rate of change with time and therefore the normal aging process [13,20,27]. Determining the best-fit line across the age range of the participants infers that all differences between the younger and geriatric participants are caused by the process of aging when they may be from delayed development in childhood or toxic exposures in youth [7, 28,29]. This cohort effect is the most significant bias of cross-sectional studies. People born within a defined time period are exposed to a set of influences such as childhood infectious epidemics, nutritional deficiencies, occupational hazards, and environmental pollution, which may differ in successive generations. The effect of these adverse influences on maximal development in youth and a later rate of decline cannot be separated from the aging process in cross-sectional surveys [30,31]. In addition, the older members of the cohort are healthy enough to have survived and participated, whereas those born in the same time period who were lost as potential participants because of a rapid decline in organ function are unrealized to the researchers. This survivor effect underestimates the age-specific rate of change [8,20,21,31]. In contrast, longitudinal assessment detects change for a given individual between measure periods and is the only way of quantifying nonlinear rates of change and different rates of change at different ages [13,21,31,32]. The limitations of longitudinal methods are period effects of changes in technology and instrument calibration [21,31], revisions in disease definition, and attrition of participants [20,21,29].

There are significant differences in reporting and clinical interpretation of lung function tests compared with other common diagnostic tests. Measurement of bone mineral density is reported as an absolute value. The interpretation is based on the patient’s distance from the mean in standard deviations compared with two different curves: one of 30-year-old women and another of age-matched women. In most instances, the diagnosis of disease and prescription of treatment is based on comparison to 30-year-old women. For example, bone mineral density below a threshold in an older woman is not accepted as normal because it has predictive value for the clinical outcome of subsequent fracture. This is different from lung function tests, which are a set of performance-based measures also

reported as absolute values but interpreted as a percentage of predicted performance for the interrelated characteristics of gender, height, and age. The predicted value is not a biologic norm but, like bone mineral density, is simply the mean value derived from testing a selected cohort of healthy people [4,28,33]. The use of a fixed percent predicted instead of standard deviation will overclassify those farther from the mean (100% of predicted) as abnormal when in fact these patients' values may still be within two standard deviations. This situation occurs with advanced age and shorter height [6,8,9,27,28,33]. Last, even after adjusting for shorter height in older adults, worse absolute values on lung function tests are, to a degree, accepted as a normal age-related phenomenon because they have not been linked to a treatable clinical outcome.

There is evidence for age-related cellular, histologic, and structural changes in the respiratory system, which contribute to the detectable changes in organ system function. Some of these changes may result in alteration of symptoms, diagnostic criteria, response to treatment, and also impact the overall functioning of an older adult. This article reviews the data on the normal age-related changes of the respiratory system in the absence of disease.

Structure

Cellular

A small cross-sectional study of subjects with normal spirometry found age-related differences in the cell populations of bronchoalveolar lavage (BAL) fluid, presumably reflective of changes in the epithelial lining of the lungs. The older subjects (mean age, 74 years; range, 70–80 years) had a higher percentage of neutrophils (40% versus 10%, $P < 0.005$) and a lower percentage of macrophages (32% versus 67%, $P < 0.0001$) as compared with the younger group (mean age, 27 years; range, 19–34 years) [34]. Another study found a similar age-associated increase in neutrophils in BAL samples, with higher levels of interleukin-8, neutrophil elastase, and a variety of antiproteases [35]. The clinical relevance of cellular and inflammatory differences with age remains to be determined, but these differences may contribute to an altered risk for lower respiratory tract infection and to histologic changes of lung parenchyma.

Tissue composition

There are two age-related changes in tissue composition that may have a significant effect on compliance (ie, change in volume for a given change in pressure) of the lung and thorax [36,37]. A study of 45 right middle lobe autopsy samples of patients who were described as “did not die of lung disease,” found an age-related increase in the ratio of elastin to collagen ($r = 0.73$) measured in grams per dry weight [38]. Although alterations in the quantity of connective

tissue does not imply an alteration in the structure and alignment of these fibers, a decrease in collagen content may contribute to increased lung compliance, reduced expiratory airway diameter, or airflow limitation. Another gross change in tissue composition is calcification of the cartilaginous articulations of the spine, ribs, and sternum, which is associated with age on chest radiographs [39]. Unfortunately, these changes in tissue composition have not been linked to in vivo studies of compliance.

Anatomic

The term *senile emphysema*, found in the medical literature of the early 20th century [18,24], was used to describe changes in the shape and compliance of the thorax [24] and consistent observations of airspace enlargement with age [40]. The influence of smoking, occupational illness, and inhaled pollutants on lung histology were not considered when these changes were attributed to normal aging. The term senile emphysema was formally abandoned because the age-appropriate upper limit of normal for airspace diameter had not been defined and because a tendency toward emphysematous histology could not be related to the clinical entity of chronic obstructive lung disease [41].

A qualitative progression to histologic emphysematous changes will never be proven with longitudinal study because this would require serial biopsies, but similar descriptions persist in cross-sectional studies done with improved exclusion criteria. A study of airspace size relative to age in subjects aged 21 to 93 years found airspace enlargement in the older subjects [42]. Although this study did not characterize occupational exposure, a lifelong history of nonsmoking was determined from medical records or relatives of the patients represented by 16 autopsy specimens and 22 surgical specimens. The surgical samples were obtained during resection of tumors, which were primary or secondary malignancies (10), carcinoid (5), congenital, or benign lesions (7). Twelve samples from the autopsy specimens were taken from the apex to the base of the lung and six blocks were analyzed from each lobe of the surgical specimens. An electronic scanner was used to measure the airspace surface area to volume ratio, which was found to be negatively correlated with age ($r = -0.78$, $P < 0.001$).

There is also radiologic evidence for emphysematous change with age. A sample of 88 asymptomatic subjects aged 20 to 80 years who had no history of pulmonary disease or pulmonary symptoms were studied with inspiratory and expiratory CT [43]. Half of the participants also had lung function tests. There was a higher frequency of air trapping with age and the percentage of lung volume involved was moderately and significantly correlated with age ($r = 0.523$, $P < 0.001$) and negatively correlated with the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC; $r = -0.438$, $P < 0.002$). Conclusions from these results are limited because some of the participants were smokers and smoking history was not reported by age.

Function

There are complex interrelated changes in lung and chest wall mechanics and muscle function, which contribute to changes in lung volumes and ventilatory flow rates. Studies of lung function in relation to age are carried out for two purposes: to determine reference values for pulmonary function laboratories [4,6,9] and for a scientific definition of the normal rate of change with the aging process [13,20,29,32]. Studies to “predict” performance for clinical testing derive regression equations from a cross-section of the healthiest members of a population who represent a normal level of function at a given age [7,28]. In comparison, those studies done to determine the rate of change with normal aging are done by serial longitudinal assessment. These data are not used as the comparison standard in clinical testing because longitudinal studies use individual rates of change to calculate a mean for specific birth cohorts [31].

Ventilation depends on neurologic control and muscle strength to move the rib cage during inspiration and elastic recoil of the lungs during expiration. The diaphragm, scalenes, and external intercostal muscles are used during ambient inspiration. Effortful inspiration during exercise or inspiration to total lung capacity (TLC) additionally recruits accessory muscles, such as the sternocleidomastoid and trapezii. In contrast, expiration during ambient breathing is mostly a function of the passive recoil of the lungs, but expiration below functional residual capacity (FRC) involves the abdominal recti and internal intercostal muscles.

In clinical practice lung function tests might be ordered in an elderly patient with persistent dyspnea, despite maximal treatment of cardiac disease, to clarify symptoms observed in a patient with dementia [44] or to assess the risk of bronchoconstriction with β -adrenergic antagonists in a patient with a remote history of wheezing [45]. They might also be ordered to diagnose asthma in a patient with an isolated symptom of cough [3] or to monitor adverse effects of drugs with pulmonary toxicity [46]. Lung function tests would be less helpful in following the progression of chronic lung disease because of marked lack of precision of the measurements and little ability to influence a symptom-driven treatment plan [28,47].

Muscle function

Because of simultaneous changes in the mechanical properties of the lung and chest wall and the interdependence of muscle groups, it is difficult to precisely quantify age-related changes of specific respiratory muscles [48]. Estimates are additionally confounded by nutrition, fitness, and lung volumes [48,49].

Maximal inspiratory pressure (MIP), pressure at the mouth against a closed valve, is clinically used to assess muscle strength, primarily of the diaphragm in patients with neurologic and muscular diseases. All studies that included participants of advanced age have been done to establish reference values and not to evaluate the normal aging process. These cross-sectional surveys have revealed high interindividual variability probably because of the interactions of

patient performance and technician instruction. A study of 504 subjects without acute or chronic illness who ranged in age from 18 to 82 years, all of whom had normal spirometry and body mass index, found age to be an independent predictor of MIP ($r = -0.24, P < 0.05$) [25]. This study included smokers and concluded that the acceptable normal range is wide.

Muscle strength is also assessed by maximal voluntary ventilation (MVV), which is breathing at maximal tidal volume (V_T) and respiratory rate for 12 seconds. MVV has been shown to be lower in older endurance athletes (mean age, 65 years) compared with younger men of similar fitness (mean age, 24 years) [50]. A significantly lower value in MVV adjusted for height was also found in a cross-sectional analysis of male participants from the Baltimore Longitudinal Study [17] and a mean decrease of 12% was detected over a 6-year longitudinal study of 18 highly fit older people [20].

Lung-thorax mechanics

Compliance of the total respiratory system has two components with opposing effects. Compliance of the lungs determines the force and rate of expiration and compliance of the thorax determines the elastic work of breathing during inspiration. These forces are equal and opposite at FRC and therefore determine this volume. Lung compliance is the change in volume relative to the difference between alveolar and pleural pressure (ie, the transpulmonary pressure). Thoracic compliance is the change in volume relative to the difference between pleural and body surface pressure [37].

Early studies with significant methodologic limitations have shown a lower thoracic and higher lung compliance with older age in convenience samples that included smokers [12,24]. These results were later confirmed in several studies that rigorously excluded occult disease and smokers [14,51,52]. Specifically, a subgroup of 42 male participants from the Baltimore Longitudinal Study, aged 24 to 78 years, had a lower total lung-thorax and thoracic compliance, which was considered to be the cause of the higher FRC and residual volume (RV) with age [17]. Another study compared six women aged 60 to 69 years with men and women in their 20s and similarly found a higher lung compliance in the older women [53]. Several researchers have suggested that a higher lung compliance is the main contributing factor to age-related changes in expiratory flow rates [52,53].

Lung volumes and ventilatory flow rates

The cohort effect for lung volumes is exemplified by the observation that FEV_1 and vital capacity (VC) have generally improved with spirometric study of successive cohorts from the early 20th century [7,13]. This is analogous to an increase in life expectancy during the same time period and is because of improved nutrition and reduced exposure to infection and environmental toxins, all of which determine maximal growth during youth and rate of decline during

adulthood. Because of this, the American Thoracic Society and others have suggested that prediction equations for determining norms of lung function tests be revised for future cohorts [9,28,29].

There are problems with precision and accuracy in lung function tests. Precision is affected by instrument calibration, patient performance, and the influence of a technician, which result in measurable day-to-day variation and a learning effect. The accuracy of lung function tests is unknown. There has never been a study of interobserver agreement for the interpretation of lung function tests with calculation of κ scores and there are no known positive predictive values for determining the diagnoses of obstructive or restrictive lung diseases [28].

Studies have shown remarkable consistency in the qualitative changes of lung volumes with age. Because all lung volumes are dependent on body size, particularly height and chest circumference, they increase during childhood to the point of maximal development. After adjustment for height TLC does not change as an individual ages [20]. Both FRC and RV are greater in cross-sectional studies [17,52,53], and an increase in RV can be measured longitudinally even in highly fit older people [20]. Dynamic lung volumes are commonly assessed with spirometry, which clinically reflects airway function but is also dependent on volume. There is thought to be a period of plateau in VC and FEV₁ during early adulthood followed by a decline. Similar to the previously noted cohort effect for greater VC, the age at which FEV₁ begins to decline has been shifted to older ages with study of successive birth cohorts. Cross-sectional studies estimate the beginning of the decline to the early 20s [6,8], but longitudinal data from well-defined cohorts found that FEV₁ does not begin to decline until about the age of 36 years for both men and women [29,32]. The decline in FVC is estimated to start in the mid-30s [13,33], with the most precise estimate being 39 years (95% confidence interval [CI], 34–43 years) [13]. The ratio of FEV₁ to FVC is lower in older healthy people [6,8,53]; therefore, the use of 80% as the lower limit of normal will result in overdiagnosis of obstructive airway disease in older adults [5,28]. Data collected from the Cardiovascular Health Study have suggested that the lower limit of normal for FEV₁/FVC should be 64% to 56% for persons aged 65 to 85 years [4].

Because longitudinal data show that the rate of decline is nonlinear [29,33], many researchers suggest that a single regression equation is not sufficient to describe all phases of development and aging [8,29]. There is possibly an accelerated rate of decline in FEV₁ after age 70 [8,20], but little reliable data after this age. Determining a precise rate of change is difficult because of marked intraindividual variability [5,8,28,31,33,46], estimated at 125 mL between tests [30], which is considered to “far exceed its expected annual decline” [29]. Because a loss of an equal quantity of lung volume or flow rate has an entirely different clinical implication for persons beginning with a higher or lower level, Dockery et al [33] have suggested that the rate of decline in FEV₁ or FVC might be best expressed as the proportion of the maximal attainable for a given height rather than as a constant annual rate of decline for persons of all sizes.

Dyspnea and control of breathing

The sensation of dyspnea and control of breathing are complex phenomena involving the mechanical properties of the lung and chest wall, central carbon dioxide (CO₂) and hydrogen ion chemoreceptors, peripheral oxygen (O₂) chemoreceptors, and central nervous system integration.

Nonasthmatic older participants (mean age, 67 years; range, 60–76 years) were compared with younger participants (mean age, 28 years; range, 20–36 years) using a 4-point scale for perception of bronchoconstriction with methacholine challenge testing [54]. Despite similar levels of decline in FEV₁ between the older and younger participants (16.3% ± 1.3% versus 13.7% ± 1.7%), the older group ranked less discomfort than the young group for the sensation of dyspnea (1.53 ± 0.17 versus 2.76 ± 0.22, $P = 0.004$). This study also demonstrated the same findings for groups of younger and older asthmatics. Whereas the mechanism for this difference is unknown, the clinical implications are that older people may not perceive or report symptoms of dyspnea even with significant bronchoconstriction.

A study designed to determine the mechanism for previously reported lower ventilatory response to hypoxia and hypercapnia with age [55] also measured age-related changes in compliance and muscle strength [14]. Significant differences were found in a comparison of 10 older adults (mean age, 73 years; range, 65–79 years) to 9 younger adults (mean age, 24 years; range, 22–29 years). None of the participants had cardiopulmonary or cerebrovascular disease and all were lifelong nonsmokers with normal physical examinations, lung function tests, and chest radiographs. Using rebreathing methods with measurement of end-tidal CO₂, oximetry, and occlusion pressure at the mouth as a measure of neuromuscular output, participants were studied under two test conditions: progressive hypoxia to a saturation of 70% to 75%, with end-tidal CO₂ held constant at the individual's resting value, and progressive hypercapnia to an end-tidal CO₂ of 65 mm Hg under hyperoxic conditions. There were several differences between the older and younger participants. Despite equivalent mean body surface areas, the mean VC was significantly lower in the older subjects (3.34 ± 0.89 L versus 4.30 ± 0.91 L, $P < 0.001$). Lung and chest wall compliance were not assessed separately, but total respiratory compliance was lower in the older group (72.8 ± 22.5 L/cm H₂O versus 99.3 ± 32.7 L/cm H₂O, $P < 0.001$). The same was found for MIP (70.1 ± 12.1 cm H₂O versus 92.5 ± 19.8 cm H₂O, $P < 0.001$). The older participants had a significantly lower ventilatory response to both hypoxia and hypercapnia. At an oxygen saturation of 75%, the mean minute ventilation (V_E) was 20.9 ± 2.3 L/minute in the older subjects compared with 30.3 ± 2.8 L/minute in the younger subjects ($P < 0.01$), with mean inspiratory occlusion pressures of 3.4 ± 0.5 cm H₂O and 7.0 ± 1.2 cm H₂O ($P < 0.005$), respectively. The mean V_E at an end-tidal CO₂ of 65 mm Hg was 1.15 ± 0.16 L/minute in the older participants compared with 2.17 ± 0.38 L/minute in the younger participants ($P < 0.01$), with mean occlusion pressure of 5.6 ± 0.8 cm H₂O and 9.7 ± 0.9 cm H₂O, respectively ($P < 0.01$). There was no

difference in respiratory rate between the groups to either of the test conditions. The researchers concluded that the lower total compliance and lower muscle strength in the older participants were not large enough to explain the differences in response to hypoxia and hypercapnia. Because the occlusion pressure response to both hypercapnia and hypoxemia were reduced by a similar magnitude an alteration in central nervous system efferent control was thought to be from the lower response of the older participants. The clinical significance of these results is unknown.

Cough reflex

Distinct from the symptom of cough is the function of a reflex cough. A small-scale study comparing a group of 20 older participants (mean age, 83 years) with 20 younger subjects (mean age, 27 years) used nebulized distilled water as a cough stimulant and saline as a control [56]. All participants were lifelong nonsmokers with technically adequate FEV₁ performance on spirometry and without recent upper respiratory infection. The reflex was quantified as cough frequency during the 30 seconds after the inhalation. The mean cough frequency for the older group was 5.87 (95% CI, 2.82–8.92) compared with 15.4 (95% CI, 11.0–19.8) in the younger group. Several possible mechanisms for a lower frequency of reflex cough with age were suggested: a higher stimulus threshold of the laryngeal and bronchial vagal afferents, an altered central perception of bronchoconstriction, or alterations in central integration of the cough mechanism. The clinical significance of these results remains to be determined.

Gas exchange

Exchange of CO₂ and O₂ is dependent on alveolar ventilation, alveolar perfusion, and diffusion through the alveolar-capillary membrane. Changes in ventilation-perfusion matching, shunt perfusion, and the components of the alveolar-capillary membrane tend to promote a lower arterial partial pressure of oxygen (PaO₂) and a wider alveolar-arterial oxygen gradient (A-a DO₂) with age.

Ventilation-perfusion matching

Cross-sectional studies show an age-associated larger dead-space ventilation [18,57] and a larger physiologic shunt measured as closing volume by single-breath nitrogen washout [9,51]. Likewise, dead-space ventilation and shunt perfusion have been demonstrated to increase progressively with age in longitudinal assessment [20].

Dead-space ventilation was reported in a case series of 18 apparently disease-free men aged between 62 and 82 years who had a mean VC of 2.53 L (range, 1.35–3.7 L). These subjects had normal mean values for arterial partial pressure of carbon dioxide (PCO₂) (38 mm Hg) and PaO₂ (108 mm Hg). Whereas the mean

V_T was normal (491 L; range, 390–696 L), the respiratory rate and mean V_E were both high, 19 per minute (range, 12–28/minute) and 9.32 L (range, 5.95–13.33 L), respectively. Total dead space measured by exhaled CO_2 was higher, 235 mL compared with a predicted value for young adults of 150 mL [18]. Another study selected “normal” hospitalized patients who had cardiovascular and dyspeptic diseases and calculated that the percentage of V_T that is physiologic dead space was greater in participants aged 61 to 75 years (32%) compared with younger participants aged 15 to 20 years (13%) [26]. When these same subjects were given 100% oxygen, the older participants also had a greater measured shunt fraction compared with the younger subjects. A longitudinal study discussed later measured a progressive increase in dead-space ventilation during exercise in highly fit elderly subjects over a 6-year period [20].

The alveolar-capillary membrane

The alveolar-capillary membrane, the anatomic pathway through which oxygen and carbon dioxide must diffuse, is studied by use of the diffusing capacity of carbon monoxide (DL_{CO}). Diffusion of gases is directly proportional to alveolar cross-sectional area and inversely proportional to the diffusion distance or thickness of the alveolar-capillary membrane. Because DL_{CO} is dependent on alveolar ventilation and lung volume, it is measured at TLC and normalized for alveolar ventilation (DL_{CO}/V_A). The best evidence of the effects of age on DL_{CO} is from a cross-sectional study, which rigorously excluded participants with occult disease and included six older participants aged 69 to 85 years. This study found a lower DL_{CO}/V_A in older participants [10]. Because the value is normalized for V_A it suggests that the lower level is caused by alterations in components of the alveolar-capillary membrane other than loss of alveolar surface area, but these data are limited because of a small number of subjects.

Blood gas values

The previously described data suggest there is a physiologic basis for a lower PaO_2 and wider A-a DO_2 with age. Even the studies that did not exclude occult illness have not shown any age-related difference in CO_2 exchange with age; therefore, respiratory acidosis is always a pathologic finding [15,18,26].

A precise estimate and rate of decline in arterial PaO_2 or precise age-corrected value cannot be determined from the limited cross-sectional studies. There are several published formulas to adjust PaO_2 and A-a DO_2 for age, which have been widely reproduced in print and electronic handbooks [58,59]. The review and use of the original data that generated these formulas reveals several shortcomings. The following results for age-adjusted PO_2 would be obtained for an 85-year-old person:

1. $PO_2 = 104.2 - 0.27 (\text{age}) = 81 \text{ mm Hg}$ [26]
2. $PO_2 = 100.1 - 0.325 (\text{age}) = 72 \text{ mm Hg}$ [60]
3. $PO_2 = 109 - 0.43 (\text{age}) = 75 \text{ mm Hg}$ [15]

The first equation is from a study that enrolled patients hospitalized with cardiovascular disease aged 15 to 75 years. The second equation is unreferenced in a review article [60], which indicates that the lower limit of normal would be 90% of the calculated value—in this case, a PaO₂ of 64 mm Hg. The third study used a rural population and rigorously excluded participants with clinical, laboratory, or radiologic evidence of heart, lung, thyroid, hematologic, and liver disease, but included an unknown number of participants older than 60 years [15]. Similarly, using formulas to determine an age-adjusted A-a DO₂ would yield the following results for an 85-year-old person:

1. A-a DO₂ = 2.5 + 0.21 (age) = 20 [26]
2. A-a DO₂ = 4 + (age/4) = 25 [61]
3. A-a DO₂ = 1.4 + 0.43 (age) = 37.9 [15]

The reference for the first formula is from the previously mentioned study that did not exclude people with overt or occult cardiopulmonary diseases. The second is an unreferenced response in a question-and-answer section of a medical journal, which implies that the formula is valid between the ages of 20 and 60 years [61]. In clinical practice an arterial blood gas test is performed in a patient with illness in anticipation of an abnormal value. The study by Sorbini et al [15], which reported on a population not exposed to urban pollution, clearly supports a lower oxygenation with age but cannot reliably be used to disregard a lower PaO₂ or wider A-a DO₂ as age appropriate for a sick or symptomatic individual in the absence of a previously measured value during health. Whereas the study included 152 male and female participants who ranged in age from 14 to 84 years, there is apparently a single participant older than 80 years and no confidence intervals are provided. This equation does not account for the significant individual variation in normal values at advanced age and may lead to a clinical situation of discounting pathologic hypoxemia because of age.

Autonomic system

Age-related changes in response to pharmacologic stimulation of the autonomic system of bronchial smooth muscle may alter the presenting symptoms of lung diseases, affect the predictive value of diagnostic tests, or determine the efficacy of treatment.

The cholinergic system

Methacholine is used during spirometry to precipitate bronchoconstriction and support the pretest clinical impression of asthma. The effects of age on the methacholine bronchoconstrictive response were reported from the control group from a longitudinal study of asthma [62]. Participants were rigorously excluded based on characteristics that might result in a hypersensitive response, such as a

history of asthma, emphysema, chronic bronchitis, allergic rhinitis, eczema, or smoking; a recent respiratory infection; or a physical examination that yielded abnormal results. The cumulative dose of methacholine required to reduce FEV₁ by 20% for the 148 subjects, who ranged in age from 5 to 86 years, yielded a hyperbolic curve, with younger and older participants having a greater bronchoconstrictive response to methacholine; however, there was a wide variation at both ends of the age range. The Normative Aging Study found that 161 of the never-smoking participants (mean age, 62 years; range, 41–84 years) had a significant response to methacholine testing without symptoms of wheeze or cough and concluded that a positive methacholine challenge test in an asymptomatic person is of unknown clinical significance [63]. There are no data to suggest any age-related difference in response to inhaled anticholinergic medications.

The adrenergic system

For the cardiovascular system an age-related resistance to the chronotropic effect of β -adrenergic agonists has been demonstrated [64,65]. The models used to study age-related changes of the β -adrenergic system in lung tissue have included *ex vivo* comparisons of blood lymphocytes obtained from younger and older subjects [66] and study of lung fibroblasts “aged by replication” *in vitro* [67]. There has been no direct assessment of an age-associated alteration in the pharmacodynamic response of bronchial smooth muscle to either β -adrenergic agonists or antagonists.

Exercise capacity

There is no evidence that the normal changes in lung volumes or FEV₁ described previously correlate with an alteration in performance of activities of daily living or contribute to symptoms in day-to-day life. They may become relevant in situations of increased ventilatory requirements, such as exercise, or possibly during the physiologic demands of medical or surgical illness.

Exercise capacity is measured with maximum oxygen consumption (VO_{2 max}), but this is confounded by fitness and habitual physical activity. One way to distinguish age-related from fitness-related changes is to study elderly master athletes. Several studies of this type have shown that training is a stronger determinant to lung function and VO_{2 max} than age [20,50]. A 6-year longitudinal study of 18 highly fit, nonsmoking men and women aged 62 to 82 years, 8 of whom were competitive runners, was able to detect the positive effects of fitness but also an age-related decline [20]. The mean VO_{2 max} was 45.3 ± 1.7 mL/kg per minute at baseline compared with a mean age-predicted value of 20 mL/kg per minute. Six years later, the mean VO_{2 max} had declined to 40.3 ± 2.1 mL/kg per minute ($P < 0.05$). At the 6-year repeat testing, there were no changes in mean TLC, FRC, FEV₁/FVC, or DL_{CO}; however, all participants had an 11% decrease in VC, and 15 had a 13% increase in RV. All flow rates at the initial evaluation

were 103% to 109% of predicted values, but over the 6-year period, FEV₁ declined by 13% in all participants. The worsening of VC, RV, and FEV₁ was not related to the individual subject's VO_{2 max} at the baseline, but the magnitude of the change was directly related to his or her age at the first evaluation. At the 6-year evaluation the V_E had decreased from 106.4 ± 4.5 L/minute to 98.8 ± 6.2 L/minute at a work intensity of 60% VO_{2 max} and steady-state CO₂ production, therefore supporting an increase in dead-space ventilation. The magnitude of these changes was greater than that predicted by the regression equations from cross-sectional data.

Similar findings were obtained from a study of men, which compared younger (24 ± 4 years) and older (65 ± 3 years) endurance athletes to untrained younger (27 ± 3 years) and older (66 ± 5 years) participants on measures of oxygen consumption and lung volumes [50]. Similar to the longitudinal study, the older athletes had a mean VO_{2 max} of 50.0 ± 4.9 mL/kg per minute, compared with 27.0 ± 2.2 mL/kg per minute in the untrained older participants (*P* < 0.05). In comparison, the younger athletes had a mean VO_{2 max} of 66.8 ± 6.0 mL/kg per minute, relative to 44.0 ± 4.3 mL/kg per minute for the untrained younger participants. There was no difference between the two older groups in lung volumes. Both older groups had lower VC and FEV₁ and higher RV compared with the younger groups. These studies support the theory that training alters, but does not prevent, the age-specific decline in pulmonary function, but a component of the usual “deterioration” is a result of deconditioning and sedentary habits.

Summary

An absolute quantified normal rate of change and normal range of functions of the respiratory system applicable to all older adults as they age is elusive. Like life expectancy, which is dependent on a cohort effect, the norms of respiratory system function are related to the birth cohort to which a given individual belongs and the age at which the parameter is assessed. No single rate of change can express normal across all age ranges even for those individuals in apparently good health [29]. Analogous to defining risk factors for a disease, determining that a change in anatomy or physiology is not disease requires stringent prospective evaluation for the absence of occult disease and known risk factors for disease prior to concluding that the alteration is inevitable with the normal aging process [19,31]. Additional limitations in quantifying the norms of respiratory function with age are the lack of participation of the oldest adults in studies and the lack of precision and accuracy in these performance-based measurements.

The data, although limited, do support a qualitative emphysematous change in lung histology and lung-thorax mechanics. This change plus altered lung volumes influence oxygenation and oxygen consumption. There is no evidence that the changes in the respiratory system with aging impact day-to-day function of older adults, but they may become evident under circumstances when physiologic demand reaches the limits of supply. Despite changes in cholinergic and

adrenergic receptor functioning, there is no evidence to suggest altering prescribing these classes of medications for older people.

Pioneer physiologists asked the original question “Is there a difference in this measurement for older people?” Researchers in pulmonary medicine, pathology, radiology, epidemiology, and public health have continued to revise the question toward the clinical implications while studying the aging process from their respective viewpoints. Clinicians who need to develop an integrated care plan should neither rely on formulas to “normalize” a measurement for age nor assume that a established predictive value of a diagnostic test done in young adults can be automatically applied to geriatric patients [4]. Rather, the clinical situation should consider that the variability in normal is greater with older age and that all diagnostic tests and care plans should be considered in the context of the patient’s symptoms [5].

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Appendix. Age-related changes in respiratory function

Parameter	Change	Study design and participant age range
Airspace size	Larger	Cross-sectional 21–93 y (<i>n</i> = 6 > 80 y) [42]
Maximal inspiratory pressure	Lower	Cross-sectional 18–82 y (<i>n</i> = 34 > 70 y) [25] 19–80 y (<i>n</i> = 10 > 65 y) [14]
Maximal voluntary ventilation	Decreases	Longitudinal 62–82 y (<i>n</i> = 18 for 6-y period) [20]
Lung compliance	Higher	Cross-sectional 20–82 y (<i>n</i> = 17 > 60 y) [51] 25–75 y (<i>n</i> = 19 > 63 y) [52] 19–80 y (<i>n</i> = 10 > 65 y) [14]
Thoracic compliance	Lower	Cross-sectional 24–78 y (<i>n</i> = 12 > 60 y) [17]
Total compliance	Lower	Cross-sectional 24–78 y (<i>n</i> = 12 > 60 y) [17] 24–79 y (<i>n</i> = 10 > 64 y) [14]

Parameter	Change	Study design and participant age range
Forced vital capacity	Decreases	Longitudinal 25–74 y ($n = 1311 > 64$ y for 3-y period) [33] 20–60 y (for 11-y period) [13]
Forced expiratory volume in 1 s	Decreases	Longitudinal 20–67 y ($n = 172 > 60$ y) [29] 62–82 y ($n = 18$ for 6-y period) [20]
Total lung capacity	Unchanged	Longitudinal 62–82 y ($n = 18$ for 6-y period) [20]
Residual volume	Increases	Longitudinal 62–82 y ($n = 18$ for 6-y period) [20]
Dead-space ventilation	Increases	Longitudinal 62–82 y ($n = 18$ for 6-y period) [20]
Shunt perfusion	Increases	Longitudinal 62–82 y ($n = 18$ for 6-y period) [20]
Diffusion capacity CO/alveolar ventilation	Lower	Cross-sectional 20–85 y, $n = 6 > 68$ y [10]
Arterial partial pressure CO ₂	Unchanged	Cross-sectional 14–84 y ($n = 11 > 70$ y) [15]
Arterial partial pressure O ₂	Lower	Cross-sectional 14–84 y ($n = 11 > 70$ y) [15]
Maximum oxygen consumption	Decreases	Longitudinal 62–82 y ($n = 18$ for 6-y period) [20]

References

- [1] Kikuchi R, Watabe N, Konno T, et al. High incidence of silent aspiration in elderly patients with community acquired pneumonia. *Am J Respir Crit Care Med* 1994;150:251–3.
- [2] Tresch DD. Management of the older patient with acute myocardial infarction: differences in clinical presentation between older and younger patients. *J Am Geriatr Soc* 1998; 46:1157–62.
- [3] Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;119:977–83.
- [4] Enright PL, Kronmal RA, Higgins M, et al. Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular Health Study. *Am Rev Respir Dis* 1993;147:125–33.
- [5] Sobol BJ, Weinheimer B. Assessment of ventilatory abnormality in the asymptomatic subject: an exercise in futility. *Thorax* 1966;21:445–9.
- [6] Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–64.
- [7] Glindmeyer HW, Diem JE, Jones RN, et al. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. *Am Rev Respir Dis* 1982;125:544–8.
- [8] Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725–34.

- [9] Roberts CM, MacRae KD, Winning AJ, et al. Reference values and prediction equations for normal lung function in a non-smoking white urban population. *Thorax* 1991;46:643–50.
- [10] Stam H, Hrachovina V, Stijnen T, et al. Diffusing capacity dependent on lung volume and age in normal subjects. *J Appl Physiol* 1994;76:2356–63.
- [11] Astrand I, Astrand PO, Hallback I, et al. Reduction in maximal oxygen uptake with age. *J Appl Physiol* 1973;35:649–53.
- [12] Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. *J Appl Physiol* 1968;25:664–71.
- [13] Van Pelt W, Borsboom GJJM, Rijcken B, et al. Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. *Am J Respir Crit Care Med* 1994;149:1218–26.
- [14] Peterson DD, Pack AI, Silage DA, et al. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. *Am Rev Respir Dis* 1981;124:387–91.
- [15] Sorbini CA, Grassi V, Solinas E, et al. Arterial oxygen tension in relation to age in health subjects. *Respiration* 1968;25:3–13.
- [16] Kanber GJ, King FW, Eschar YR, et al. The alveolar-arterial oxygen gradient in young and elderly men during air and oxygen breathing. *Am Rev Respir Dis* 1968;97:376–81.
- [17] Mittman C, Edelman NH, Norris AH, et al. Relationship between chest wall and pulmonary compliance with age. *J Appl Physiol* 1965;20:1211–6.
- [18] Tenney SM, Miller RM. Dead space ventilation in old age. *J Appl Physiol* 1956;9:321–7.
- [19] Costa PT, McCrea RR. Design and analysis of aging studies. In: Masoro EJ, editor. *Handbook of physiology*. New York: Oxford University Press; 1995. p. 25–34.
- [20] McClaran SR, Babcock MA, Pegelow DF, et al. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *J Appl Physiol* 1995;78:1957–68.
- [21] Ware JH, Dockery DW, Louis TA, et al. Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. *Am J Epidemiol* 1990;132:685–700.
- [22] Babb TG, Rodarte JR. Mechanism of reduced maximal expiratory flow with aging. *J Appl Physiol* 2000;89:505–11.
- [23] DeLorey DS, Babb TG. Progressive mechanical ventilatory constraints with aging. *Am J Respir Crit Care Med* 1999;160:169–77.
- [24] Frank NR, Mead J, Ferris BG. The mechanical behavior of the lungs in healthy elderly persons. *J Clin Invest* 1957;36:1680–7.
- [25] Hautmann H, Hefele S, Schotten K, et al. Maximal inspiratory mouth pressures (PIMAX) in healthy subjects—what is the lower limit of normal? *Respir Med* 2000;94:689–93.
- [26] Mellegaard K. The alveolar-arterial oxygen difference: its size and components in normal men. *Acta Physiol Scand* 1966;67:10–20.
- [27] Kerstjens HAM, Rijcken B, Schouten JP, et al. Decline of FEV₁ by age and smoking status: facts, figures, and fallacies. *Thorax* 1997;52:820–7.
- [28] The American Thoracic Society. Lung function testing: selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991;144:1202–18.
- [29] Burrows B, Lebowitz MD, Camilli AE, et al. Longitudinal changes in forced expiratory volume in one second in adults. *Am Rev Respir Dis* 1986;133:974–80.
- [30] Glindmeyer HW, Jones RN, Diem JE, et al. Useful and extraneous variability in longitudinal assessment of lung function. *Chest* 1987;92:877–82.
- [31] Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. *Am J Respir Crit Care Med* 1996;154:S208–11.
- [32] Tager IB, Segal MR, Speizer FE, et al. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;138:837–49.
- [33] Dockery DW, Ware JH, Ferris BG, et al. Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult, never smokers in six U.S. cities. *Am Rev Respir Dis* 1985;131:511–20.
- [34] Thompson AB, Scholer SG, Daughton DM, et al. Altered epithelial lining fluid parameters in old normal individuals. *J Gerontol* 1992;47:M171–6.

- [35] Meyer KC, Rosenthal NS, Soergel P, et al. Neutrophils and low-grade inflammation in the seemingly normal lung. *Mech Ageing Dev* 1998;104:169–81.
- [36] Hoppin FG, Stothert JC, Greaves IA, et al. Lung recoil: elastic and rheological properties. In: Fishman AP, editor. *Handbook of physiology*. Vol. 3. Bethesda, MD: American Physiology Society; 1986. p. 195–212.
- [37] Smith JC, Loring SH. Passive mechanical properties of the chest wall. In: Fishman AP, editor. *Handbook of physiology*. Vol. 3. Bethesda, MD: American Physiology Society; 1986. p. 429–42.
- [38] Pierce JA. Age related changes in the fibrous proteins of the lungs. *Arch Environ Health* 1963;6:50–4.
- [39] Teale C, Romaniuk C, Mulley G. Calcification on chest radiographs: the association with age. *Age Ageing* 1989;18:333–6.
- [40] Wright RR. Elastic tissue of normal and emphysematous lungs. A tridimensional histologic study. *Am J Pathol* 1961;39:355–63.
- [41] Fletcher C, Gilson JG, Hugh-Jones P, et al. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. A report of the conclusions of a CIBA guest symposium. *Thorax* 1959;14:286–99.
- [42] Gillooly M, Lamb D. Airspace size in lungs of lifelong non-smokers: effect of age and sex. *Thorax* 1993;48:39–43.
- [43] Lee KW, Chung SY, Yang I, et al. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects. *Radiology* 2000;214:831–6.
- [44] Connolly MJ, Jarvis EH, Hendrick DJ. Late-onset asthma in a demented elderly patient. The value of methacholine challenge in diagnosis. *J Am Geriatr Soc* 1990;38:539–41.
- [45] Connolly MJ. Obstructive airways disease: a hidden disability in the aged. *Age Ageing* 1996;25:265–7.
- [46] Crapo RO. Pulmonary-function testing. *N Engl J Med* 1994;331:25–30.
- [47] Guyatt GH, Townsend M, Nogradi S, et al. Acute response to bronchodilator, an imperfect guide for bronchodilator therapy in chronic airflow limitation. *Arch Intern Med* 1988;148:1949–52.
- [48] Tolep K, Kelsen SG. Effects of aging on respiratory skeletal muscles. *Clin Chest Med* 1993;14:363–78.
- [49] Enright PL, Kronmal RA, Manolio TA, et al. Respiratory muscle strength in the elderly. *Am J Respir Crit Care Med* 1994;149:430–8.
- [50] Hagberg JM, Yerg JE, Seals DR. Pulmonary function in young and older athletes and untrained men. *J Appl Physiol* 1988;65:101–5.
- [51] Begin R, Renzetti AD, Bigler AH, et al. Flow and age dependence of airway closure and dynamic compliance. *J Appl Physiol* 1975;38:199–206.
- [52] Knudson RJ, Clark DF, Kennedy TC, et al. Effect of aging alone on mechanical properties of the normal adult human lung. *J Appl Physiol* 1977;43:1054–62.
- [53] Gibson GJ, Pride NB, O’Cain C, et al. Sex and age differences in pulmonary mechanics in normal nonsmoking subjects. *J Appl Physiol* 1976;41:20–5.
- [54] Connolly MJ, Crowley JJ, Charan NB, et al. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992;47:410–3.
- [55] Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnea with aging in normal men. *J Clin Invest* 1973;52:1812–9.
- [56] Newnham DM, Hamilton SJC. Sensitivity of the cough reflex in young and elderly subjects. *Age Ageing* 1997;26:185–8.
- [57] Brischetto MJ, Millman RP, Peterson DD, et al. Effect of aging on ventilatory response to exercise and CO₂. *J Appl Physiol* 1984;56:1143–50.
- [58] Mahler DA, Rosiello RA, Loke J. The aging lung. *Clin Geriatr Med* 1986;2:215–25.
- [59] Raffin TA. Indications for arterial blood gas analysis. In: Cox HC, editor. *Common diagnostic tests. Use and interpretation*. 2nd edition. Philadelphia: American College of Physicians; 1990. p. 102.

- [60] Knudson RJ. How aging affects the normal lung. *J Respir Dis* 1981;2:74–84.
- [61] Skorodin MS. Respiratory disease and A-a gradient measurement. *JAMA* 1984;252:1344.
- [62] Hopp RJ, Bewtra A, Nair NM, et al. The effect of age on methacholine response. *J Allergy Clin Immunol* 1985;76:609–13.
- [63] Sparrow D, O'Connor G, Colton T, et al. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The normative aging study. *Am Rev Respir Dis* 1987;135:1255–60.
- [64] Stessman J, Eliakin R, Cahan C, et al. Deterioration of beta-receptor-adenylate cyclase function in elderly, hospitalized patients. *J Gerontol* 1984;39:667–72.
- [65] Vestal RE, Wood AJJ, Shand DG. Reduced β -adrenoceptor sensitivity in the elderly. *Clin Pharmacol Ther* 1979;26:181–5.
- [66] Davis PB, Byard PJ. Beta-adrenergic responses and airway reactivity in healthy adults. *Mech Ageing Dev* 1990;54:29–42.
- [67] Kilfeather SA, Collins D, McCormack P, et al. The effect of in vitro aging on human lung fibroblast beta-adrenergic receptor density, coupling and response. *Mech Ageing Dev* 1992;63:247–56.