CHEST

The Aging Lung
Is Lung Health Good Health for Older Adults?

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The prevalence of lung conditions, such as COPD and pulmonary fibrosis, and lung infections, such as pneumonia, increases sharply with age. The physiologic, cellular, and immunologic changes that occur during aging contribute to the development of lung disease. Studies of age-related changes in physiology and function are not only key to preventing or ameliorating disease, they are also essential for understanding healthy aging. Individuals with good lung function live longer, healthier lives, although the mechanisms by which this scenario occurs are not understood. The present article reviews changes in the aging lung that facilitate development of disease and the evidence supporting the idea that robust lung function reduces the risk of developing chronic inflammatory conditions that occur with age. CHEST 2018; ■(■):■-■

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Longitudinal studies on aging generally arrive at the same disturbing conclusion: the groundwork of whether a person will age well, or age poorly, begins early in life. By the time we are in our second or third decade, biological aging and chronological aging do not proceed in step.[1] Some biologic measures are more predictive of whether an individual will have a life of relatively good health, or develop chronic diseases, become frail, and die early. Intriguingly, lung function seems to play a significant role in healthy aging.[2,3]

Physiologic changes to the lungs contribute to changes in lung function and susceptibility to disease (Table 1).[4-11] Lung diseases such as COPD and pulmonary fibrosis increase with age, as does the incidence of pneumonia.[12] In some cases, such as pulmonary fibrosis, the development of disease is clearly linked to cellular senescence as mutations in genes associated with premature aging increase the risk of developing disease, and the hallmarks of cellular senescence, such as mitochondrial dysfunction, are clearly evident.[13-16] In contrast to pulmonary fibrosis, mutations in genes associated with cellular senescence are not associated with an increased risk of COPD,[3] and although hallmarks of cellular stress and senescence are evident once the disease is clinically apparent, these factors seem to be a consequence rather than a cause of COPD. The prevailing theory is that COPD results in age-related changes in lung capacity that are more evident in those whose initial lung capacity was low and which can be accelerated by cellular stressors such as pollution, particulates, or the unparalleled senescence-inducing properties

ABBREVIATIONS: AEC1 = alveolar epithelial type 1 cell; AEC2 = alveolar epithelial type 2 cell; ECM = extracellular matrix protein; ER = endoplasmic reticulum

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TABLE 1] Physiologic Changes to the Lungs and Related Changes in Lung Function and Susceptibility to Disease

Measures of Lung Function	Changes With Age	Reference
Total lung volume	No change	4, 5
Alveoli (number)	No change	6
Alveoli (size)	Increases	7
Alveoli (elasticity)	Decreases	4
Functional residual capacity	Increases due to changes in elasticity and enlargement of airways	8
The volume of air remaining at the end of expiration		
End-expiratory lung volume	Increases due to changes in elasticity and enlargement of airways	8
The volume of air remaining at the end of passive expiration (functional residual capacity) in addition to the increase in lung volume by applied positive end-expiratory pressure		
Apparent diffusion coefficient	Increases due to airspace enlargement	7
Diffusion of a gas is restricted by the boundaries of the alveoli		
FEV_1/FVC	Decreases due to changes in elasticity, airspace enlargement, and other physiologic changes (eg, body mass composition) that occur with age	9, 10
The ratio of FEV_1 over the FVC (the amount of air that can be forcibly exhaled after taking the deepest breath possible)		
Airspace wall surface area per unit volume of lung tissue	Decreases due to airspace enlargement	11

of cigarette smoke.[17,18] Although the role of cellular senescence in COPD is not as clear, prematurely senescent mice develop features (eg, pronounced airspace enlargement) that normally would only be observed in extreme old age. This finding provides further evidence that cellular senescence contributes to both age- and disease-related changes in the lungs.[19,20] Immunosenescence is also an important feature of the aging lung. A significant portion of the cells of the lung are resident immune cells, and the near-constant contact with circulating immune cells means that immunosenescence affects lung aging and disease progression. The present article reviews age-related changes in the lung and discusses how these factors might contribute to both disease and healthy aging (Fig 1).

Physiologic Changes in the Aging Lung

Although the number of alveoli, alveolar ducts, and capillary segments are stable once adulthood is reached[6] and total lung volume remains the same,[4,5] physiologic changes in the aging lung occur that decrease functional capacity. For example, alveolar and alveolar-capillary surface area increases[6] while elasticity decreases,[4] resulting in an increase in resting functional residual capacity and an increase in end-expiratory lung volume.[8] In healthy older adults, these functional changes may only be felt during exercise or extreme exertion,[21,22] but age-related changes in capacity must be accounted for when diagnosing lung disease. Determining what "normal" lung function is in older adults has proven challenging. Some measurements of lung function such as airspace wall surface area per unit volume of lung tissue (millimeters squared per cubic millimeters) appear to decrease in a linear manner with age and be fairly consistent between the sexes.[11] Other measures such as the apparent diffusion coefficient, which increases as the alveoli become larger, seem to grow in a linear manner with age. These changes are not uniform over the entire lung, however, with diffusion being highest in the larger alveoli of the apical lung and

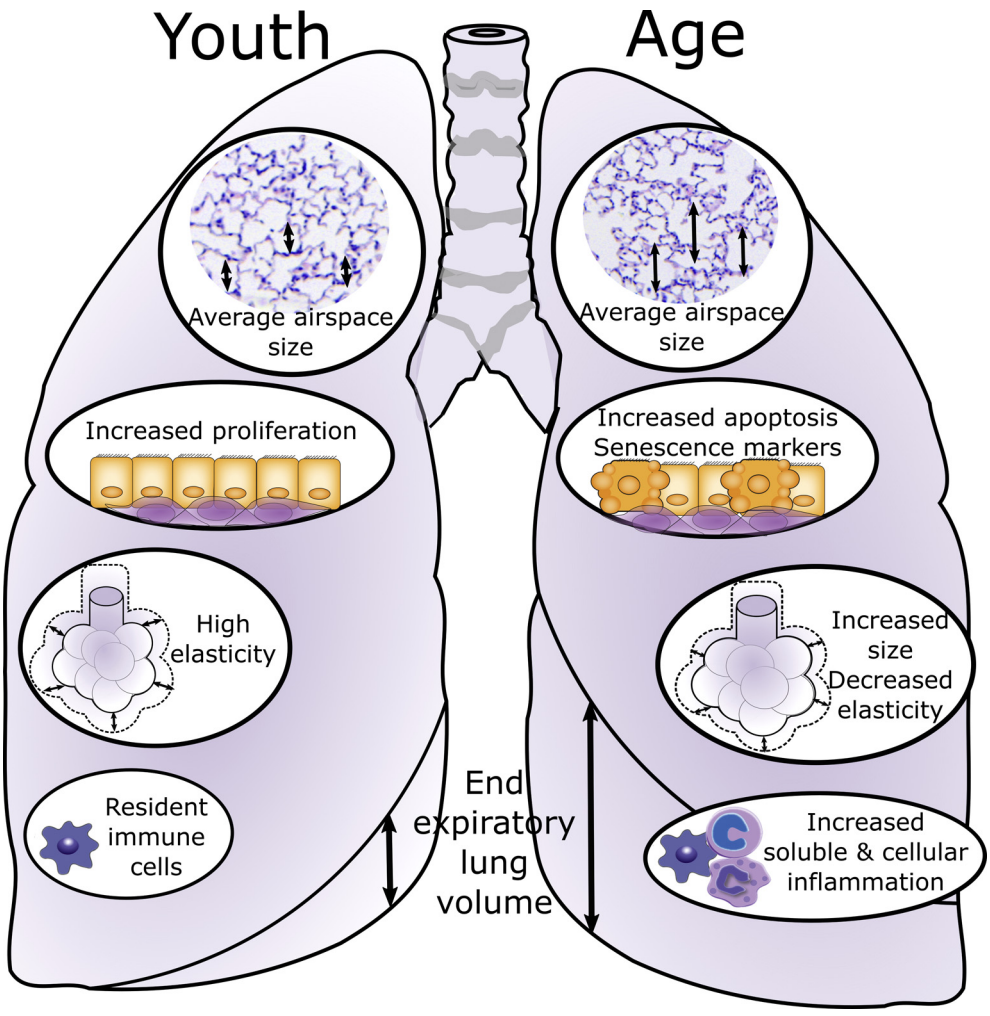

Figure 1 – *Changes in the aging lung. With age, physiologic changes such as airspace enlargement and decreased elasticity of the alveoli collectively contribute to reduced forced and end-expiratory lung volume. Concurrently, increased cellular senescence of fibroblasts and epithelial cells results in reduced resilience to injury and predisposes to fibrotic scarring. Age-associated inflammation includes elevated levels of inflammatory mediators and cytokines (soluble inflammation), as well as increased numbers of immune cells such as neutrophils, even in the absence of infection (cellular inflammation). Resident immune cells such as macrophages are less effective at resolving infections and may contribute to lung remodeling.*

lowest in the basal region of the lung.[7] This scenario indicates that although there may be global increases in apparent diffusion coefficient with age, the lung does not age uniformly.

In contrast, developing reference intervals for some age-related changes such as FEV_1 and FVC have been problematic. There is some controversy as to whether FVC (the amount of air that can be forcibly exhaled after taking the deepest breath possible) and FEV_1, or the ratio of FEV_1/FVC, change in a linear manner with age; the general consensus, however, is that reference values inferred from younger populations are inaccurate when applied to older adults and can lead to a misdiagnosis of COPD.[9,23,24] Reference values for FVC and FEV_1 have been challenging to establish due to differences attributable to height, weight, sex, and ethnicity.[9,25,26] This issue is further compounded when studying older adults as the relative contribution of height, weight (or more specifically, body composition), and sex to lung capacity seems to be different in older (aged $>$ 65 years) adults compared with younger adults.[26,27] In some studies, "normal" values seem to increase slightly higher in the "oldest old" (ie, those aged $>$ 85 years).[28] As with many studies in aging, this finding is likely attributed to the "survivor effect" wherein only those with the most physiologic reserves survive past age 85 years in good enough health to be included in such studies.

Cellular Changes in the Aging Lung

The list of insults our lungs will face over the course of an average life includes particulates, ozone, aerosols, infections (and possibly overexuberant immune

responses), allergens, and pollutants. Some people will have longer lists that will include, by choice or by chance, cigarette smoke, radiation, drugs and medications, mechanical injury, and exposure to industrial pollutants. Consequently, tissue repair is of paramount importance in the lungs as we age. Inappropriate or ineffective repair can lead to scarring (ie, fibrosis/dysplasia) or remodeling (eg, emphysema, COPD). Tissue repair and remodeling are orchestrated by epithelial cells, immune cells, fibroblasts, and progenitor cells,[29] all of which undergo age-related changes that affect function.

Alveolar Epithelial Cells

The alveolar epithelium consists of alveolar epithelial type 1 cells (AEC1s) and type 2 cells (AEC2s), although the relative proportion of these cells is the subject of debate.[30-33] Squamous AEC1s are flat and constitute approximately 95% of the surface area of the lung but account for a minor proportion of the total cell population. AEC1s closely interact with the alveolar capillary system and are the primary site for gas exchange. AEC2s are believed to be the long-lived progenitors of AEC1s that also produce surfactants.[34] Minor insults to the lung epithelium will result in destruction of AEC1s with subsequent re-epithelialization by AEC2; however, if these insults are not resolved, epithelial cells may experience endoplasmic reticulum (ER) stress which results in accumulation of immune cells that, in the best-case scenario, stimulate apoptotic cell death of the stressed epithelial cell and replenishment by AEC2s. In the worst-case scenario, aberrant or excessive immune involvement can create a cytokine environment that favors fibroblast proliferation and subsequent fibrosis or remodeling that leads to airway expansion.[29]

Age-related changes in AECs, in conjunction with changes in the cytokine environment of the aging lung, likely contribute to susceptibility to lung infection as well as dysregulated repair responses.[29] Senescent epithelial cells bind more *Streptococcus pneumoniae* due to increased expression of proteins that the bacteria co-opt for cell entry[35]; however, despite higher bacterial burdens, inflammatory signaling is muted in the lungs of aged mice.[36] This increased propensity to bind bacteria coupled with changes in epithelial turnover is believed to contribute to the slower rate of resolution of infection observed in older adults recovering from pneumonia.

The ratio of proliferating to apoptotic AECs seems to decrease with age, even in the absence of insult or injury,[37] which seems to favor apoptotic responses and higher levels of ER stress subsequent to challenge with fibrogenic agents.[38] There is less evidence of ER stress in the aging lung in the absence of disease,[39] but there is ample evidence of ER stress in structural or immune cells in the context of COPD or pulmonary fibrosis.[38,40,41] Once lung disease (ie, COPD, pulmonary fibrosis, lung cancer) is present, elevated levels of the senescence marker $p16^{INK4a}$ and shorter telomere length, a cardinal sign of cellular senescence, is apparent in AECs.[34,42] Exogenous insults such as bleomycin and cigarette smoke increase expression of these markers,[42-45] and the degree of AEC senescence correlates with lung function[42]; however, the degree to which AEC senescence contributes to disease is not clear. Senescence-accelerated mice developed more pronounced bleomycin-induced fibrosis,[46] implying that senescence contributes to fibrosis. In contrast, ablating senescent epithelial cells in mice exposed to cigarette smoke does not blunt the development of a COPD/emphysema type phenotype.[47] Further research disentangling the role of cellular senescence in the initiation or acceleration of lung disease is warranted.

Fibroblasts

Fibroblasts are found throughout the interstitium of the lungs and between epithelial and endothelial layers. They support the growth of epithelial cells through secretion of extracellular matrix protein (ECM). Changes in secretion of collagen contribute to age-related changes in elasticity and airspace enlargement (as reviewed by Skloot[48]). During disease or experimental insult, fibroblasts from older individuals or mice produce more collagen, fibronectin, and matrix metalloproteinases, which contribute to the severity of disease[49,50] and display all the hallmark signs of senescence (eg, telomere shortening, expression of senescence markers, decreased proliferative ability).[15,51]

The cross-talk between cells and structure has been elegantly shown in studies comparing acellularized lungs (ie, those in which all the cells have been denuded but the ECM remains) from patients with idiopathic pulmonary fibrosis and healthy control subjects. Fibroblasts seeding fibrotic lungs take on a pro-fibrotic phenotype by expressing more α-smooth muscle actin, collagen, laminin, and fibronectin.[52] In the fibrotic lung, structure clearly dictates function.

Although the evidence of cellular senescence in pulmonary fibrosis and other age-related lung disease is unequivocal, it is not clear to what degree alterations in

fibroblast localization, function, or ECM production change during the course of aging but in the absence of disease. Fibroblasts that have been rendered senescent in vitro have been shown to alter epithelial cell characteristics and modify lung morphology in an organoid culture system,[53] which presumably occurs in vivo as well. Because age is the major risk factor for lung disease, it makes intuitive sense that subtle changes in fibroblast senescence and ECM production would contribute to both age-related changes in lung elasticity and function and development of disease; however, evidence of age-related fibroblast senescence is not usually observed in the absence of experimental insult or disease.[49,50]

Leukocytes

Resident, recruited, and transient immune cells contribute to a significant percentage of the total cells in the lung.[54] Leukocytes follow subtly different aging trajectories due to differences in origin (embryonic or bone marrow-derived), lineage (lymphoid or myeloid), and immune experience. Immunosenescence of specific immune populations in the aging lung has been reviewed in detail elsewhere.[55-57] Collectively, it is apparent that immunosenescence contributes to susceptibility to infection, to increased damage during insults, and to impaired or aberrant wound healing. One underappreciated aspect of immunosenescence is an increase in systemic inflammation. Age-associated inflammation or "inflamm-aging" is the gradual increase in inflammatory cytokines in the circulation and tissues.[58] Elevated levels of cytokines and innate cells such as neutrophils are found in the lungs of older adults and aged mice,[59] but these cells are less functional due to chronic exposure to inflammatory cytokines.[36,60-62] This immune infiltration may result from signals from senescent structural cells. When epithelial cells, specifically AEC2s, overexpress tumor necrosis factor, mice develop a pulmonary fibrosis-like phenotype with increased deposition of collagen, enlargement of airspaces, and, importantly, increased recruitment of T cells. This outcome implies that in addition to a primary insult that might induce fibrosis, a gradual increase in immune infiltration and remodeling due to age-associated inflammation contributes to lung remodeling.[63]

Immunosenescence and age-associated inflammation contribute to both susceptibility to and severity of influenza and pneumonia. With age, the ratio of naive vs terminally differentiated T cells decreases, as does the ability to mount robust antibody responses by B cells, which collectively contribute to susceptibility to infections.[64] Having higher than age-average levels of inflammatory cytokines in the circulation increases the risk of developing pneumonia in older adults.[65] Although a robust inflammatory response generally protects against infections, high levels of circulating inflammatory cytokines during pneumonia in the elderly are associated with more severe disease and higher mortality.[66] In fact, a meta-analysis reported that combining antibiotics with immunosuppressive steroids improved outcomes in elderly patients hospitalized for pneumonia.[67] Chronic exposure to low levels of cytokines, and especially tumor necrosis factor alpha, alters the development, migratory potential, and responsiveness of monocytes and macrophages to microbe-associated molecular patterns.[36,60,61] Lung macrophages have alterations in their ability to regulate inflammation, which can result in hyporesponsiveness to infection[68] or hyperresponsiveness to lung injury.[69]

Although the degree to which age-related changes in the lung ECM contribute to changes in leukocyte numbers or function is not clear, any detrimental age-related changes are likely compounded by those in the peripheral immune system. As an example, older mice have more fibrocytes in the bone marrow, and more of these are recruited to the lung during a bleomycin challenge,[49] thus mimicking observations observed in patients with fibrosis.[70] Studies in mice show that recruited inflammatory monocytes, which increase in number and have enhanced recruitment to sites of inflammation with age,[61] contribute to the pathology of fibrosis more than resident macrophages.[71,72] Circulating innate cells such as monocytes and macrophages seem to be particularly sensitive to the effects of age-associated inflammation,[73] which alters their development, phenotype, and function. As a result, increasing numbers of less mature myeloid cells enter the circulation and have hyperinflammatory responses when they encounter inflammatory stimuli, yet have altered chemotaxis and phagocytosis.[61,62,74,75] These impairments are exaggerated in older adults with lung disease.[76-80]

The Relationship Between Lung Health and Other Age-Related Diseases

Maximum lung capacity is generally reached in one's mid-twenties and remains stable for a decade, or in a fortunate few, for 2 decades. Lung capacity begins to decline in mid-life. This decline is steeper for those with lung disease and for smokers; however, even among

those who have never smoked, there is considerable variation in both maximal lung capacity and the subsequent rate of decline.[81,82] The observation that having above-average lung capacity is a predictor of good health and that lower-than-average lung capacity is a harbinger of poor health or premature death is attributed to the inventor of the spirometer, John Hutchison, in 1846[83] and has been confirmed many times since then.[2,3,84-86] Intriguingly, individuals whose FEV_1 and FVC are at the lower end of the normal range develop many of the "diseases of age" (eg, cardiovascular disease, type 2 diabetes, cognitive decline) earlier than those with more robust lung function. As an example, in one longitudinal study, individuals who developed type 2 diabetes had lower FEV_1 and FVC more than a decade before they developed clinically apparent diabetes.[87] This observation that decreased lung function precedes development of diabetes (or, in some cases, even elevated blood glucose levels) has been replicated in cross-sectional[88,89] and longitudinal[88,90-92] studies and is independent of smoking, age, and sex. It is important to note that it is not the rate of decline that differs between those who will go on to develop diabetes and those who will not but rather their lung function when they are apparently healthy. Although a number of explanations between lung function and metabolic dysregulation have been proposed, there is no clear mechanism linking insulin resistance or hyperglycemia to lung capacity or function.[88,93,94] A plausible explanation for the observation that lower lung capacity and function precedes type 2 diabetes is that lower lung function is an accelerant in the aging process.

Type 2 diabetes is one of the common "diseases of age," as are cardiovascular disease, autoimmunity, and dementia. The risk of having one of these chronic conditions increases the risk, sometimes dramatically, of developing another chronic condition.[95] Only a small percentage of individuals in their forties will have more than one chronic condition but almost everyone in their eighties will have more than one.[96] The rate at which we develop these conditions is proportionate to our rate of biological aging; thus, if low lung function is an accelerant to the aging process, it should be a predictor of developing any of these age-related conditions. Consistent with this scenario, a study of middle-aged (40-70 years of age) adults found that lower FEV_1 and FVC at baseline correlated with lower cognitive function and an increased risk of being hospitalized for dementia in the 10-year follow-up period.[97] As with the studies linking lower lung function to type 2 diabetes, there was no change in the rate of decline in lung function between the cognitively intact vs those with impairment. Other longitudinal studies have confirmed that robust lung function in mid-life correlates with higher cognitive ability later in life.[98,99]

One of the major predictors of whether someone ages well or poorly is their level of what is called "age-associated inflammation." With age, levels of inflammatory markers in the serum and tissues increase, and individuals with higher-than-age-average levels have higher all-cause mortality than those with lower-than-age-average levels.[100] The genesis of age-associated inflammation is the topic of some debate, but irrespective of the cause, it is well documented that those in the top tertile of age-associated inflammation have higher rates of chronic inflammatory conditions and are at increased risk of developing lung diseases and pneumonia.[101] Intriguingly, lung function and age-associated inflammation seem to be inversely correlated. Common clinical measures of age-associated inflammation (eg, C-reactive protein, fibrinogen) correlate strongly with FEV_1 and FVC.[102-104] There are conflicting reports on whether increased levels of systemic inflammation are predictive of declining lung function[105,106] or whether they are merely higher in individuals with lower lung capacity.[107,108] Consistent with a role of inflammation as a driver of declining lung function, there is a strong correlation between having higher-than-age-average levels of inflammatory cytokines and developing respiratory problems such as shortness of breath.[109]

In contrast, it has been proposed that lower lung function may precede systemic inflammation. Although this theory has not been rigorously tested, longitudinal studies have found correlations between lung function and levels of inflammatory markers at a follow-up visit.[103,104] If having low lung capacity promotes systemic inflammation, then individuals with low lung function should be at increased risk of developing other chronic inflammatory diseases. Unsurprisingly, low FVC is associated with increased cardiovascular events,[103] but surprisingly, it also precedes development of other age-related conditions such as osteoporosis[110] and cognitive decline.[111] Consistent with the idea that inflammation drives lower lung function, even children with inflammatory diseases such as juvenile arthritis or type 1 diabetes have lower lung function.[112,113] Although further longitudinal studies are required to determine the directionality of this relationship, it is well

documented that in individuals with COPD, levels of inflammation are higher and proportionate to disease severity,[114] and that individuals with COPD develop other age-related conditions and cognitive decline faster than their disease-free counterparts.[115-117]

How age-associated inflammation impairs lung function (or vice versa) is not known; however, the lungs are exposed to a steady stream of microbes, pollutants, dust, and allergens. With age, innate immune cells tend to mount hyperinflammatory responses to microbes and microbial components that are slower to resolve than in younger individuals.[61] Conceivably, this process could contribute to the development of age-associated inflammation. The liver usually clears microbial products that emanate from the gut; blood from the lungs, however, enters the circulation directly, and any microbial products or inflammatory mediators therein will be dispersed in the central circulation. In addition to longitudinal studies in humans, mouse models in which age-associated inflammation can be either genetically or pharmacologically enhanced or ablated[60] will be required to understand causality.

Lung Health Is Good Health for Older Adults

Lung health is intimately associated with good health in older adults. Robust lung function correlates with a higher basal metabolic rate, which is associated with keeping trim in our later years,[118] and with activity and physical performance.[119] As discussed earlier, having lung disease or pneumonia can accelerate the development of other, seemingly unrelated chronic conditions. Collectively, the data are clear—healthy lungs contribute to a long and healthy life—but how can we capitalize on this information? Although the data on which modifiable risk factors contribute to health and longevity are relatively simple (avoid smoke, eat well, exercise, manage any chronic conditions as well as you are able, get enough sleep, and maintain a robust social network to stave off loneliness), adherence is not as high as it should be. Perhaps by changing the messaging to include specific health advice on the role of healthy lungs in staving off some of the most feared conditions of aging while building communities that are conducive to the simplest and least expensive way to improve lung health (eg, walking) are the way to add "life to our years, rather than years to our life."[120,121]

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