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Aging and asthma: pathophysiological mechanisms

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Asthma is common in all age groups and emerges as significant problem for elderly people (1–5). It is often underperceived, underdiagnosed, and undertreated (6, 7). There are several reports of acute, severe asthma in this age group (8, 9).

From the clinical perspective, asthma in an elderly person may be difficult to diagnose because of lower sensitivity to symptoms, nonspecific presentation, and the frequently confounding effect of comorbidity. The latter can, in turn, increase the severity of the clinical picture and make treatment more difficult (10, 11). Other important issues concerning the treatment of asthma in the elderly relate to changes in pharmacokinetics, a higher risk of untoward effects, and poorer compliance. An important aspect of this phenomenon is the limited ability of this age group to use inhalers (12). Polypharmacy is inherent in treating older people and accurate drug histories are essential for identifying those in whom concurrent treatment may induce bronchospasm or may interact with asthma medication.

Morphologic and physiologic abnormalities have been observed in the aging human lung (13). A decrease in mucociliary function, dilatation of the air spaces, loss of elastic recoil, loss of elastin fibers, diminished diffusion capacity, and evidence of low grade inflammation of the respiratory tract have all been found in elderly people. These changes have superimposed effects on those induced by the asthma-related chronic inflammation of

the airways, and cannot be without effect on the evolution of the remodeling process in the airways (14–21).

Aging also has a profound effect on the immune system and cells that have a regulatory role in asthma (22). A decline in humoral immunity has been documented in older people (23). Advanced age has also been shown to be associated with an increased vulnerability to infectious agents (24). These specific events may depend on many age-related changes in various organ systems, such as environmental factors, nutritional status, and the frequent presence of multiple chronic debilitating diseases. However, it is still unclear whether, and to what extent, immunosenescence plays a role in the increased susceptibility to inflammatory agents involved in the pathogenesis of asthma, and in the dynamics of development of structural airway changes.

Effect of age on immune cells and functions

T lymphocytes

Aging is associated with a decline in immune function in humans and animals. The primary defects appear to reside in the T-cell compartment (23). Progressive atrophy of the thymus gland occurs with aging, and thymic hormone activity in serum is undetectable in people over 60 years of age (22, 25, 26). Although the thymus involutes, there is little or no decline in blood T cells in older individuals

(27, 28). However, the ability to generate a cell-mediated immune response has been shown to diminish with age (29, 30). T cells from aged donors have an impaired proliferative response whether they are cultured with accessory cells from young or aged donors, leading to a progressive reduction in antigen-driven lymphocyte proliferation.

There are several potential causes involved in such a phenomenon. In aged individuals, the sum of $CD4^+$ lymphocytes and $CD8^+$ lymphocytes substantially exceeds the total number of $CD3^+$ lymphocytes. This finding, which differs from what is observed in young individuals, implies that either $CD4^+$ or $CD8^+$ may be $CD3^-$, or that $CD3^+$ cells can be, at the same time, $CD4^+$ and $CD8^+$. This latter phenotype is consistent with a thymocyte-like pattern of surface marker expression, whereas the former is similar to immature cord blood cells that can be $CD8^+$ or $CD3^-$. It seems, therefore, that aging is associated with an expansion of the pool of undifferentiated lymphocytes. There is a potential explanation for these findings: as the thymus involutes with aging, T cells cannot undergo thymic differentiation, so they maintain a less mature phenotype that is responsible for the reduced responsiveness of T lymphocytes to inflammatory and infectious factors (Fig. 1).

In addition, several important T cell functions appear to be lost in aging lungs. After influenza infection, aged mice have prolonged viral shedding that is presumably due to lower anti-influenza class I-restricted $CD8^+$ cytotoxic T lymphocyte (CTL) activity. An age-related delay in recovery from influenza virus infection has also been shown (31). Several mechanisms seem to be involved, including decreased anti-influenza class II-restricted CTL activity, pulmonary interferon(IFN)-gamma levels, and serum neutralizing antibodies. Taken together, these findings suggest a loss of $CD4^+$ T cell function with aging, and may explain the progressive loss of immunoallergic reactions (such as in the lungs and the skin) found in elderly people.

Again, an animal model has been used to study this phenomenon. Sensitized Brown Norway rats are known

to develop eosinophilic bronchial inflammation and airway hyperresponsiveness after antigen exposure. However, in the past it has been shown that sensitized aged rats of the same strain fail to develop such allergic inflammation. This animal model has been used to understand the mechanisms underlying the phenomenon, showing decreased expression of Th2-type cytokine transcripts in aged animals. The age-associated changes in cytokine profile were found to be not restricted to bronchoalveolar lavage (BAL) cells, but a general feature of lymphocytes, as shown by examination of popliteal lymph nodes draining the site of sensitization. These findings suggest that decreased allergic inflammation in aged animals can be attributed to age-dependent impairment of Th2 generation in response to antigen (23).

In contrast to the aforementioned studies, recent evidence has also suggested possible active involvement of T lymphocytes in the airways of elderly people. Meyer et al. performed BAL on discontinuous age groups (20–36, 45–55, and 65–78-year-olds) of clinically normal volunteer subjects. They measured immunoglobulins (IgG, IgA, IgM), albumin, and interleukins (IL-6 and IL-10). Bronchoalveolar cell profiles, cell surface antigen expression, and superoxide anion production were also measured. A significant increase in total cell concentration, neutrophils, and BAL immunoglobulin content was observed in the oldest age group compared with the youngest age group. Mean lymphocyte subset ratios ($CD4^+/CD8^+$) were significantly increased in blood, and to a greater degree in BAL, for the oldest vs youngest age groups. Similarly, BAL-derived cells displayed significantly increased phorbolmyristate acetate-stimulated release of superoxide anion for the oldest vs the youngest subject group, and mean BAL IL-6 concentrations were significantly elevated in the oldest age group compared to the youngest.

Taken together these observations suggest that altered inflammatory cell profiles and low-grade inflammation exist in the lower respiratory tracts of many asymptomatic, clinically normal volunteers of advanced age. However, it is still unknown whether such age-related low-grade inflammation represents a background that favors development of exaggerated immune and inflammatory responses in elderly people affected by asthma or other chronic inflammatory diseases of the airways.

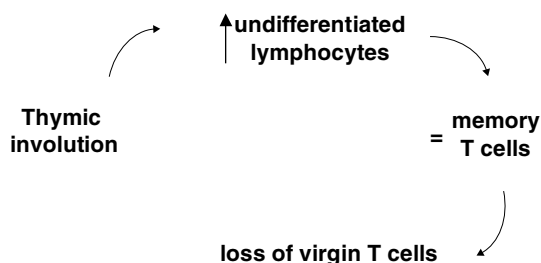


Figure 1. The potential effects of aging on lymphocyte differentiation. Thymic involution in elderly subjects leads to a decrease of differentiated and naive T cells, without major changes of memory T cells.

Mast cells and basophils

The regulation of tissue mast cell numbers depends on both the rate of production of mast cell precursors from bone marrow and the length of survival of mature mast cells within tissues.

In experiments with aged mice, isolated peritoneal mast cells showed a considerable decrease in *Fc*-gamma-RIIB/III expression and higher degranulation, as compared to peritoneal mast cells derived from young mice.

Basophil-bound IgE increased rapidly and reached adult levels during childhood in atopic individuals, while it gradually increased with advancing age in parallel with serum IgE in normal controls (33).

The annual change in basophil count has been directly related to change in the methacholine dose-response slope, suggesting that inflammatory mechanisms involving the basophil may be important for development of increasing nonspecific airway responsiveness during aging (34).

Macrophages

While defects in acquired humoral and T-cell-mediated immunity may exist, increased susceptibility to infection in the elderly is more likely related to defects in the constitutive functioning of macrophages and granulocytes (35).

Alveolar macrophages are the resident cellular defenders of the lung and provide first-line defence for smaller bronchioles and alveolar spaces. In the majority of studies, mononuclear phagocyte chemotaxis, adherence, and phagocytosis appear to be unaffected by aging. However, a decrease in monocyte phagocytosis of glutaraldehyde-treated red blood cells and of *Candida albicans* was seen when aged donors were compared with younger ones (36).

Alveolar macrophages can also participate in specific immune responses, and may function as accessory cells. However, although macrophages can process and present antigen, express major histocompatibility complex (MHC), and elaborate appropriate mediators, these cells bind resting T cells rather poorly and are weak antigen-presenting cells (37, 38). It appears that by combining macrophages with nonadherent leukocytes from donors of various ages and assessing proliferation, the antigen processing and presentation to T cells is not diminished by aging (39). No difference was found in the normal proliferative response of T cells from young donors if they were cultured with adherent cells from aged donors or from young donors. Therefore, mononuclear phagocytes from normal donors are not impaired in their ability to facilitate the proliferative response to T cells.

Neutrophils

Polymorphonuclear neutrophils have long been regarded as a terminal differentiated cell, incapable of protein synthesis, and fulfilling a role in inflammation via phagocytosis. Neutrophils can release oxygen free radicals and cytokines such as IL-1, tumor necrosis factor (TNF)- α and IL-6 (40–42). They also release a wide variety of enzymes including elastase (43) which, besides degrading elastin and other extracellular matrix (ECM) proteins (44), may affect bronchial epithelium (45), activate fibroblasts, and stimulate mucous gland secretion. Neutrophils have been involved in acute and chronic injury of the lung.

Many neutrophil functions appear to be altered in the elderly, including chemotaxis (46, 47) and reduced CD16 expression and phagocytosis (48). In addition, a progressive decrease in superoxide anion production associated with a decline of opsonized particles has been found (49). We recently evaluated induced sputum samples from elderly asthmatic subjects and found that the number of neutrophils significantly correlated with the levels of both active and total elastase, which were both higher than the levels measured in control nonasthmatic people. The increased ability of neutrophils isolated from elderly asthmatics to produce increased amount of elastase may play an important role in the pathogenesis of loss of elastic recoil and of elastin fibers in the aging lung.

Recently the number of neutrophils in the lower respiratory tract has been evaluated in healthy, clinically normal individuals of more advanced age. Using BAL in three discontinuous age groups (group I, 19–36 years; group II, 45–55 years; group III, 64–83 years), it was found that neutrophils, IL-8, and neutrophil elastase complexed to α_1 -antiprotease were significantly elevated in the oldest vs the youngest age group. This cross-sectional investigation suggests that low-grade inflammation exists in the air spaces of many clinically normal, older people (50) (Fig. 2).

Eosinophils

Evidence obtained using an animal model has shown that aging is associated with a defect in eosinophil accumulation in sites exposed to antigen, probably because of an age-dependent alteration in T cells, leading to reduced IL-5 production (52).

Epithelial cells

For many years bronchial epithelial cells were considered to act mainly as a barrier, participating in mucociliary clearance, and the removal of noxious agents. More recently, epithelial cells were found to participate in inflammatory reactions also by releasing eicosanoids, peptidases, matrix proteins, cytokines and nitric oxide (NO), as well as by performing an immune function through their capacity to express human leukocyte antigen HLA-DR and to present antigen.

There are many studies evaluating morphological and functional abnormalities of bronchial epithelial cells in elderly asthmatic people. However, a prominent feature seems to be a progressive reduction in mucociliary clearance rate in the healthy aged population, compared with that found in the young (53). Although not yet explored, it is likely that this specific function is further reduced in elderly people suffering from chronic inflammation of the airways. If so, this may lead to increased accumulation of mucus in the airways, leading to reduced airway baseline caliber, and to greater susceptibility to viral and/or bacterial infections.

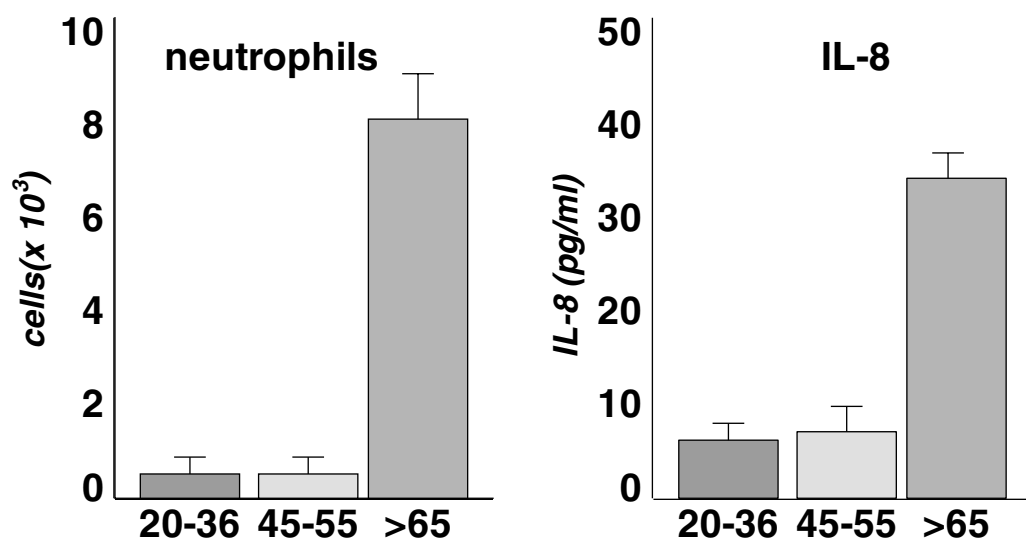


Figure 2. The figure shows that the number of neutrophils and levels of interleukin-8 are significantly elevated in the oldest vs youngest age group (51).

Immune response in aging

Immunosenescence is a state of disregulated immune function that contributes to the increased susceptibility to infection in the elderly (54). Immune-system alterations during aging are complex and pleiotropic, suggestive of remodeling or altered regulation, rather than simple immune deficiency (55). The most dramatic age-related changes occur within the T cell compartment, the arm of the immune system that protects against pathogens and tumors. However, there is no compelling scientific evidence to show that these changes are directly relevant to the common infections seen in the aged population (24).

Innate immunity, the first line of defence that precedes the antigen-specific T and B cell responses, also undergoes changes with age (48). Some of the immune effects associated with aging are secondary to overall changes of the organism, such as alterations in the viscosity of cell membranes and proteolytic cellular machinery.

Respiratory tract infections, particularly pneumonia, are a leading cause of death in persons 65 years or older in both developed and developing countries. Because many attributes of immunity wane with advancing age, the elderly may be more susceptible to respiratory infections, even if they appear to be in good health. A decline in the ability of lymphoid tissues to mount an antigen-specific response (adaptive immunity) to specific microorganisms, such as the influenza virus or *Streptococcus pneumoniae*, is thought to be an important factor in increasing susceptibility to respiratory tract infection with advancing age. However, abnormalities in innate immunity may also contribute to increased susceptibility to respiratory infections, and have been poorly characterized in the elderly (56).

Increased serum levels of inflammatory mediators are another hallmark of aging (57), suggestive either of regulatory defects, or of an ongoing attack on subclinical neoplastic disease or infection (55). There is evidence that advanced age is associated with disregulation of apoptosis (58). Several studies have shown age-related changes in the levels of proteins and factors that regulate apoptosis.

Immune response in aging asthma sufferers

Immune response in the airways of elderly asthma sufferers has not been consistently investigated to date. However, based on evidence accumulated in healthy individuals, some speculations can be made. First of all, the disregulation of the immune system, and of T-lymphocytes in particular, is a condition that may predispose the airways of asthmatic people to viral and/or bacterial infections. Infections, which could also be favored by changes in bronchial epithelium of elderly people, may contribute to amplification of the inflammatory response in the airways of asthmatic subjects. The development of an exaggerated inflammatory process in the airways may also be sustained by the increased influx of neutrophils that characterizes the aging lung. This may lead to increased neutrophil activation and to the release of mediators, such as elastase and free radicals, that have the potential to damage airway tissues and to promote their remodeling. Therefore it may be suggested that in the elderly low-grade inflammation, mainly sustained by a neutrophilic component, could favor the development of more severe clinical asthma phenotypes (Fig. 3) (59–61). This might explain why elderly people with longstanding asthma have more severe airway obstruction than those with recently acquired disease (62–64).

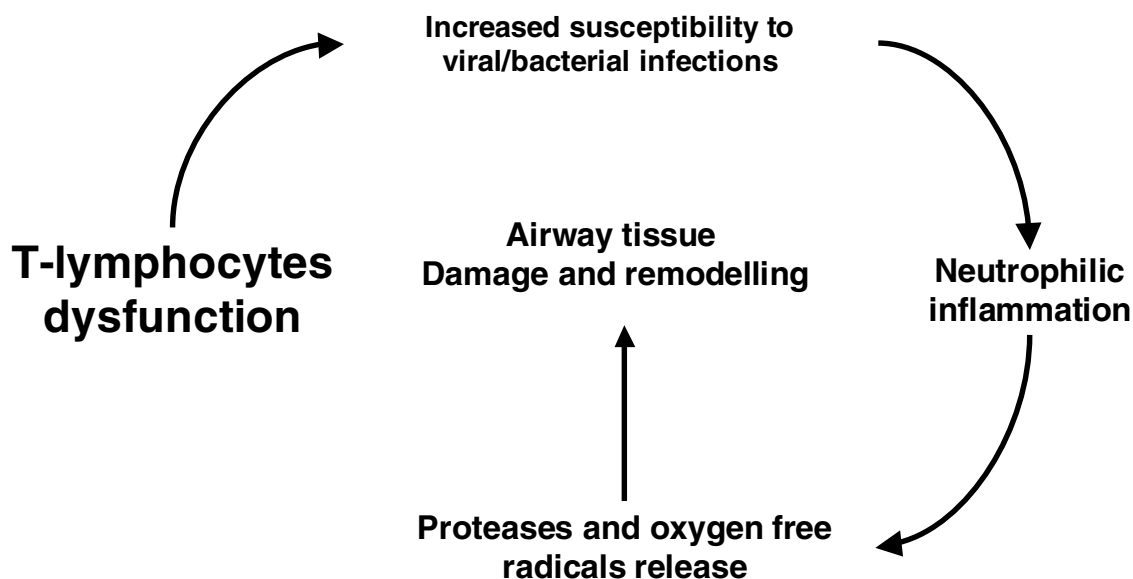


Figure 3. Theoretical consequences of T-lymphocyte dysfunction in elderly asthmatic people. T-lymphocyte dysfunction may have important consequences in the airways of asthmatic subjects, such as increased susceptibility to infections, and enhanced neutrophil recruitment. The end result of this might be the excessive release of protease and oxygen free radicals, leading to airway inflammation and remodeling.

Effect of aging on allergic hypersensitivity and allergic diseases

Allergic diseases (clinical conditions sustained by immunologic mechanisms) (65) such as allergic asthma, allergic rhinitis, and allergic atopic eczema/dermatitis syndrome (AEDS) usually begin in childhood or early-adult life. Detection of IgE-mediated allergy becomes less frequent with age, and symptoms tend to decrease (66). Aging may therefore represent an interesting *in vivo* model for studying the waning of allergic diseases. Information about age-dependent immunologic phenomena is available.

Serum IgE levels and antigen-specific IgE production both decline (67–69), which may explain the age-dependent decline in allergic diseases. The reduction in total IgE levels in aged people may be associated with reduced basophil activation. Numerous reports have dealt with age-related changes in the cytokine profile of T cells stimulated with nonspecific stimulants in a variety of species (70–73). Defective *in vivo* induction of functional type-2 cytokine responses was found in aged mice (74). Skin test reactivity to histamine also declines with age (75).

However, even if IgE-mediated allergy may be down-regulated in elderly asthmatics, allergy may be a common feature, and can be present in 75% of them (76).

Effect of aging on tissue remodeling

During adult life, asthma is often associated with an increase in the rate of decline in forced expiratory volume

in one second (FEV₁) (14–21). However, symptoms may remain unchanged while lung function deteriorates (77). In middle-aged and elderly smokers it is difficult, in some individuals, to separate chronic bronchitis and asthma by means of FEV₁ (78, 79) and by response to bronchodilators (79). Bronchial hyperresponsiveness appears to be inconstantly associated with an increased rate of decline of lung function (19, 80), and with FEV_{25-75%}/FVC values (34).

It is likely that airway remodeling may be responsible for some of the functional abnormalities found in elderly asthmatic people. In particular, alterations of ECM homeostasis may contribute to progressive reduction of the airway baseline caliber. Lung collagen levels are determined by a balance between synthesis and degradation. It is known that these processes have high rates in young animals, but very little evidence has been accumulated as yet for aging lungs. Mays et al. (82, 83) reported age-related changes in lung collagen synthesis and degradation in rats at five ages, from 1 month to 2 years. They showed that lung collagen synthesis and degradation occur throughout life, and that degradative pathways may play important roles in regulating collagen production during growth, particularly during aging.

Airway remodeling and natural history of asthma

The natural history of lung growth and senescence in individuals with asthma is still poorly known. Lung growth appears to be relatively normal in most children with asthma, but is reduced throughout childhood and

adolescence in those with severe and persistent symptoms (18). It is not known whether this reflects a failure to reach full growth in relation to bronchoconstriction or congenitally small lungs (81). Little is known about the influence of the degree of bronchial obstruction and the outcome of asthma in children. Approximately 50% of children with asthma still have respiratory symptoms in adult life (84).

Although there are no longitudinal studies starting in infancy, it is supposed that decline in lung function may start at a very early stage in the natural history of the disease (85).

An increase in the rate of decline in FEV_1 can also occur during adult life in asthmatics, particularly in middle-aged and elderly smokers, making a differentiation between chronic bronchitis and asthma by means of FEV_1 (86).

Interestingly, decreased lung density (as shown by CT scan), which has been shown to represent emphysematous change in individuals with chronic obstructive pulmonary disease, has recently been shown to correlate with aging in nonsmoking asthmatics, thus offering a new tool for understanding aging-related functional and structural changes in the lungs (87). However this decline appears to be highly heterogeneous between patients, seemingly minimal in some and quite extensive in others, and similar to those with COPD. Loss of pulmonary function during a lifetime does not seem to increase constantly, but stepwise. The decline in FEV_1 with aging is strongly influenced by other factors, such as smoking habit, or cockroach allergen levels in the home, which has been shown to be an independent risk factor for accelerated impairment in FEV_1 (88).

Effect of aging on lung function

Healthy subjects

Aging *per se* is associated with important physiological changes that, in turn, lead to a decrease in lung performance. Modifications in pulmonary mechanics, gas exchange, respiratory control, and airway responsiveness have been described in elderly people, and contribute to the characterization of the asthma phenotype for this age. In particular, age-related physiological changes that may have important implications upon the handling of resistive loads, may be grouped into three phenomena

- 1) decrease in strength of respiratory muscles
- 2) decrease in lung recoil, and
- 3) increase in stiffness of the chest wall (Fig. 4).

The strength of the diaphragm has been shown to be moderately reduced in elderly people (89), perhaps as a part of age-associated alterations in skeletal muscle function (90). The poor nutritional status often seen in the elderly could also explain impaired performance of

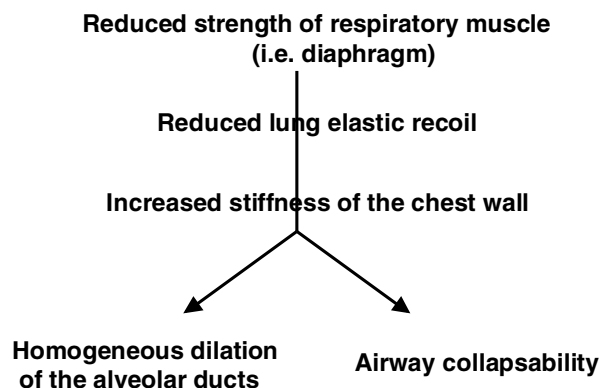


Figure 4. Age-related physiological changes can be grouped into three phenomena (1): decrease in strength of respiratory muscles (2), decrease in lung recoil, and (3) increased stiffness of the chest wall.

respiratory muscles. Indeed, Enright et al. (91) showed that maximal inspiratory and expiratory pressures (MIP and MEP), which are reliable measurements of overall respiratory muscle strength, significantly correlated with bodyweight and body mass index. This study also reported that, in the elderly population, normal inspiratory and expiratory pressure values were below the clinical thresholds for occurrence of respiratory muscle dysfunction. Moreover, increases in the main diameters of the chest and the kyphotic curvature of the spine may affect the force-generating capacity of the diaphragm (92).

The loss of elastic recoil in the lung is mainly due to structural changes in the elastic properties of the lungs (93–95). Aging processes have been shown to induce a rearrangement, rather than an actual decrease, in the lungs' connective fiber network (96), which is more prominent around the alveolar spaces. This phenomenon results in homogeneous dilatation of the alveolar ducts, similar to emphysema, so leading to the misleading definition of “senile emphysema” (93). Semantic issues aside, the aforementioned alterations are markedly different from the irregular distribution of air space enlargement associated with destruction in emphysema.

Finally, calcifications of costal cartilage and rib-vertebral articulations, together with changes in the shape of the thorax related to osteoporosis, cause increased stiffness of the chest wall, thus blunting its tendency to expand outwards. As a result, chest-wall compliance decreases with age.

Decreasing elastic recoil and stiffening of the chest wall with age have a profound impact on lung volume. Remodeling of the connective network that surrounds the small airways is responsible for the tendency to collapsibility with premature closure of the airways, even in tidal breathing. As a result, air-trapping occurs with

increase in residual volume (RV), which is also determined by the reduced chest-wall compliance and the overall diminished strength of the respiratory muscles. Despite expectation, total lung capacity (TLC) does not change throughout life; hence, vital capacity (VC) decreases accordingly to about 75% of its best value. In addition, diminished elastic recoil accounts for increases in functional residual capacity (FRC), which represents the volume level at which the inward lung elastic recoil is balanced by the outward elastic recoil of the chest wall. The main consequence lies in the fact that elderly people breathe at higher lung volumes than younger subjects, imposing an additional load to respiratory muscles.

The age-related changes in airway–parenchyma interdependence, with consequent premature closure of terminal airways, mainly affect the distribution of ventilation with respect to perfusion, with consequent reduction of the ventilation/perfusion ratio (low V/Q) (97). This is one of the major factors responsible for diminished arterial oxygen tension and reduced transfer capacity of the lungs for carbon monoxide (TLCO). Reduction of the alveolar surface area is also thought to explain reduction in TLCO (97).

Although spirometry becomes increasingly difficult with aging, spirometric performance is feasible in 90% of the elderly population (99), and rigorous quality control has been shown to ensure reliable data in the majority of subjects (100). Various spirometric outcomes, i.e. FVC and FEV₁, may be strongly influenced by reduction in muscular strength and, to greater extent, by decreased lung elastic recoil, which provides the driving pressure. An interesting functional pattern in the elderly is characterized by the development of airflow obstruction at small lung volumes. This is to be referred to the dynamic compression of the airways, normally limited by forces generated by lung elastic recoil. In older lungs, where elastic recoil is reduced, the dynamic compression takes place earlier in the expiratory event, with consequent collapse of peripheral airways and airflow limitation.

Asthma sufferers

Nonspecific hyperresponsiveness is a central feature of asthma and a potential risk factor for the development and progression of the disease. In the Normative Aging Study (101), nonspecific airway responsiveness was shown to increase with advancing age, as suggested by previous observations (18, 102, 103). Interestingly, the prechallenge level of pulmonary function was shown to predict the response to methacholine, suggesting that geometric factors, rather than biological mechanisms, could be primarily responsible for the increased airway responsiveness in this age. On the other hand, there is evidence that bronchial reactivity does not diminish with age (104). An important limitation to the interpretation

and comparison of data is caused by the paucity of data for older people; as a result, the relationship between age and airway responsiveness needs to be further clarified.

Aging has been associated with a reduced acute response to bronchodilators (105–107), most likely attributed to age-related decline in β -receptor function (109), or loss of β -receptors with aging (108). The reduced sensitivity to bronchodilators in the elderly has been shown to persist even after adjustment for FEV₁ levels (107).

Effect of aging on clinical manifestations of asthma

The aforementioned physiological changes of aging have a significant impact on the clinical appearance of asthma in the elderly and become relevant to the diagnosis and treatment of the disease at this age. Also noteworthy are the other factors contributing to the complexity of asthma in the elderly, including blunted perception of mechanical and chemical loads (110–112), the reduced responsiveness of chemoreceptors to hypoxia (113), and the lack of awareness about deterioration of airway function (114).

The main consequence of physiologic age-related alteration of lung mechanics lies in the fact that some characteristics of asthma are determined by a complex interaction of multiple phenomena, some of which are yet to be established. The clinical hallmark of asthma is airflow obstruction that responds clinically and spirometrically to a bronchodilator. This pattern is less typical in the elderly, making it harder to distinguish from other diseases such as chronic bronchitis and emphysema. Yet differential diagnosis of these diseases is the main step in providing appropriate care to elderly asthma sufferers. Overall, the clinical phenotype of asthma in the elderly is not markedly different from that of younger patients, although some observations have confirmed that elderly asthmatics seem to experience more severe disease (79).

Another factor to consider when evaluating asthma in the elderly is the duration of the disease. In this respect, the aged lung is affected by time-related external factors, such as tobacco smoke and occupational stimuli. When patients are divided into early-onset disease and late-onset disease, however, the groups are clinically indistinguishable (1).

Duration of asthma is associated with the degree of airflow limitation and hyperinflation, and these abnormalities can become irreversible over time, perhaps reflecting distal airway and/or parenchymal changes as well as proximal airway remodeling (15).

Cigarette smoking is a well-known health hazard, with great importance to people suffering from asthma (115, 116). In many elderly asthmatic people, COPD is associated with asthma.

Conclusions

Asthma is common in all age groups and emerges as a significant problem for elderly. Morphologic and physiologic abnormalities have been observed in the aging human lung, such as a decreased mucociliary function, dilatation of the air spaces, loss of elastic recoil and of elastin fibers, diminished diffusion capacity, and evidence of low-grade inflammation of the respiratory tract. These changes may superimpose their effects upon those induced by asthma-related chronic inflammation of the airways, and cannot be without effecting the evolution of the remodeling process within the airways.

Aging also has a profound effect on the immune system and the cells that have a regulatory role in asthma, such as T lymphocytes, neutrophils and epithelial cells. Clinically, these aging-related changes may be responsible for the development of specific airway responsiveness and reduced responsiveness to anti-asthma drugs.

Taken together, these observations confirm that asthma in the elderly is a complex phenomenon because the aging-associated alterations in lung function render the symptomatology peculiar at this age. This emphasizes the fact that a correct functional approach of asthma in the elderly should be made to avoid misdiagnosis and to provide the best attainable treatment.

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