Aging, tobacco use and lung damages

Le vieillissement, la consommation tabagique et les dégâts pulmonaires

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Abstract

The main two functions of the lung are the respiratory functions, dependent on ventilatory mechanics and gas exchange, and the non-respiratory functions such as metabolic, immunological, and endocrine ones. Lung aging is secondary to the age-dependent impairment of one or more of these functions.

Tobacco use accelerates lung aging and touches biological, structural and respiratory and non-respiratory functions. These changes contribute to the development of chronic pulmonary diseases and predispose to pulmonary infections in older individuals.

The knowledge of these changes is very useful for better management of elderly. Lung health in aging can be improved by strategies that slow the age-related decline in lung function by acting on the environmental parameters. It is also possible to improve lung development in children and to strengthen the lungs' resistance to environmental challenges and thus to extrinsic lung aging.

Key words : extrinsic lung aging, FEV1, pulmonary static volumes, ACE2, immunosenescence.

Résumé

Les deux principales fonctions du poumon sont la fonction respiratoire, qui correspond à la mécanique ventilatoire et les échanges gazeux, et les fonctions non respiratoires, métaboliques, immunologiques et endocriniennes. Le vieillissement pulmonaire est secondaire à l'altération, liée à l'âge, d'une ou plusieurs de ces fonctions. Le tabagisme accélère le vieillissement pulmonaire et touche les fonctions biologiques, structurelles, respiratoires et non respiratoires. Ces changements contribuent au développement de maladies pulmonaires chroniques et prédisposent aux infections pulmonaires chez les personnes âgées. La connaissance de ces changements est très utile pour une meilleure prise en charge des personnes âgées. La santé pulmonaire dans le vieillissement peut être améliorée par des stratégies qui ralentissent le déclin de la fonction pulmonaire lié à l'âge en agissant sur les paramètres environnementaux. Il est également possible d'améliorer le développement pulmonaire chez l'enfant et de renforcer la résistance des poumons aux défis environnementaux et donc au vieillissement pulmonaire extrinsèque.

Mots-clefs : ventilation alvéolaire, muscles respiratoires, DLCO, Récepteur β2, tabagisme.

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INTRODUCTION

The main two functions of the lung are the respiratory functions, dependent on ventilatory mechanics and gas exchange, and the non-respiratory functions such as metabolic, immunological, and endocrine ones. Lung aging is secondary to the age-dependent impairment of one or more of these functions (1). Aging is the major risk factor for many chronic and fatal human diseases known as age-related diseases (2).

Lung aging has an intrinsic origin by affecting the cell: cell division itself can be affected by aging in addition to chromosomal deletions (3). L'opez-Ot'ın et al. (3) proposed nine features of intrinsic aging: genomic instability, telomere attrition, cellular senescence, epigenetic alterations, loss of proteostasis, deregulation of nutrient sensing, mitochondrial dysfunction, stem cell depletion, and altered cellular and intercellular communication. This physiological lung aging can be accelerated by extrinsic or environmental factors (eg; occupational exposure, air pollution, smoking...) (4) and in these conditions it can lead to the early development of chronic obstructive pulmonary disease (COPD) especially since the main risk factor for extrinsic aging is smoking (2). Wu et al. (5) showed that after Balb/c mice were chronically exposed to various concentrations of cigarette smoke, lung function was impaired, lung tissue senescence was increased, and the senescence-associated secretory phenotype in bronchoalveolar lavage fluid was increased. It is notable that there are several similarities between the pathologic and physiologic features of normal aging in the lung and COPD (6,7). The objective of this update was to gain insight into the effect of aging when associated with smoking on the respiratory system.

RESPIRATORY FUNCTIONS, AGING, AND TOBACCO SMOKE

Figure 1 exposes all the structures and functions of the respiratory system that may be affected by intrinsic or physiological aging.

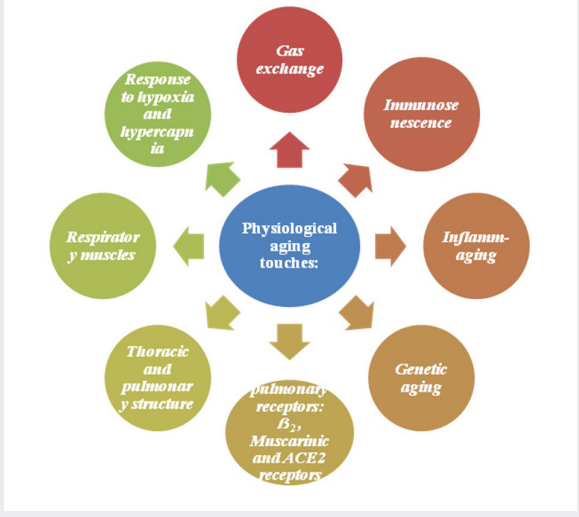

Figure 1. The physiological aging of the lung : ACE2: Angiotensin converting enzyme 2

Pulmonary mechanical function, aging, and tobacco smoke

In the elderly, there are several predictive factors for decline in lung function, represented by falling ventilatory flow rates and lung volumes, such as: male sex, ethnicity, certain metabolic pathologies (eg; diabetes mellitus) and smoking (7). Thus, all these factors are responsible for a significant variability in lung function in healthy elderly people and make it difficult to establish a range of values defining "normal function" (8).

There is a progressive age-related decline in lung function, with forced expiratory volume in one second (FEV1) decreasing by approximately 30 ml per year in both men and women, while forced vital capacity (FVC) begins to decrease later and at a slower rate of about 20 ml per year, resulting in a decrease in the FEV1/FVC ratio (1,9,10). Consistent with the morphological findings described previously, residual volume (RV) and functional residual capacity (FRC) increase with age (Figure 2).

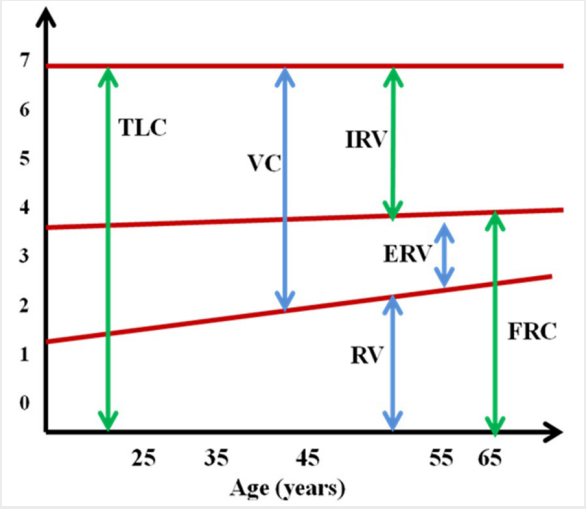

Figure 2. Static lung volumes and capacities according to age: TLC: Total lung capacity, VC: Vital capacity, IRV: Inspiratory reserve volume, ERV: Expiratory reserve volume, RV: Residual volume, FRC: Functional residual capacity

The main mechanism of the fall in pulmonary volumes and flows is represented by changes in the elasticity of the mechanical ventilatory system (the thoraco-pulmonary tissues). As a result, an increase in the pulmonary relaxation volume (ie; FRC) is noticeable with a decrease in the caliber of the small bronchi linked to an increase in the elastic forces of retraction of the pulmonary parenchyma (1,11) (Figure 3).

In aged people, structural changes of the chest wall represented by narrowing of the intervertebral disk spaces is observed and causes kyphosis or curvature of the spine. This curvature creates a smaller chest cavity and so small lung volume (ie; restrictive defect) (1,12, 13).

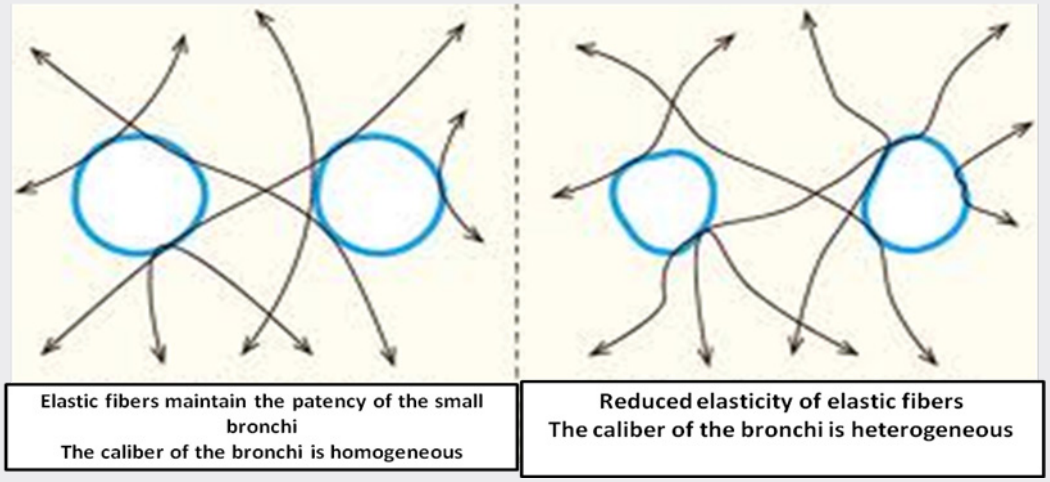

Figure 3. Decrease in the caliber of the small bronchi linked to reduced elasticity of elastic fibers

The decrease of FEV1 with age is variable from one subject to another. Environmental factors and in particular smoking accelerates the FEV1 fall from 30 to 60 mL/year in non-COPD smokers (14). When COPD is established, FEV1 decreases from 60 to 90 mL/year, and sometimes even more than 100 mL/year (14-17). The classic epidemiological studies of Fletcher and Peto (18) considered that, in susceptible cigarette smokers who develop COPD, there is an accelerated decline in lung function with the age of 50-100 mL/year of FEV1 (18).

Thoracic and pulmonary structure, aging and tobacco use

With age, several morphologic changes in the chest wall and lung parenchyma reduce respiratory efficiency. Indeed, lung aging is characterized by an increase in alveolar size, without inflammation or destruction of the alveolar wall (19). As described in emphysema, lung aging is manifested by a decrease in density and an increase in diameter of the membranous bronchioles, but unlike emphysema, there are no differences in alveolar attachment (19).

Experimental studies have shown that smoking can permanently alter the structure of the lungs and thus lung function, through a mechanism of parenchymal and bronchial inflammation related to oxidative stress (20). This increases the risk of chronic respiratory diseases such as COPD and accelerates lung aging (21).

Respiratory muscles, aging and tobacco use

The decrease in respiratory muscle strength with age is related to changes in the structure of the striated skeletal muscles, and particularly the main respiratory muscle: the diaphragm. Indeed, from the age of 50 years, the maximum inspiratory and expiratory pressures, which explore the function of the respiratory muscles, begin to decrease (11, 22).

Chlif et al. (22), comparing a group of old endurance trained athletes with a group of young athletes, showed that with age a lower inspiratory muscle performance is evidenced by a higher tension-time index during exercise in the group of old trained athletes. This change appears to be less marked in older men with lifelong endurance training compared to sedentary older subjects (22). With age, the decrease of skeletal muscle strength and endurance is noted and these changes can be explained by sarcopenia (3).

When studying the effect of smoking on muscle function, it has been shown that the muscles of non symptomatic smokers are weaker and less resistant to fatigue than those of nonsmokers (23). Although the physical inactivity of many smokers contributes to some of the alterations observed in skeletal muscle, exposure to cigarette smoke can also induce skeletal muscle dysfunction. It is the local and systemic inflammation induced by oxidative stress secondary to the components of cigarette smoke that promotes proteolysis and inhibits protein synthesis at the cellular level, resulting in a loss of muscle mass (ie; sarcopenia) (3).

Reduced skeletal muscle contractile endurance in smokers may result from a decrease in oxygen delivery to mitochondria and the ability of mitochondria to generate ATP due to the interaction of carbon monoxide with hemoglobin, myoglobin, and respiratory chain components (24, 25). Winther Petersen et al. (26) found a deteriorating effect of smoking on respiratory muscle strength with a positive dose response relationship.

Besides stimulating protein degradation, smoke exposure may also inhibit anabolic pathways. Muscle protein synthesis, as assessed by the incorporation of labeled leucine, is decreased in the quadriceps muscle of smokers (26), which was associated with an increased expression of myostatin (26). Myostatin inhibits muscle growth by inactivation of protein kinase B (also known as Akt),a promoter of protein synthesis, and by hampering muscle cell renewal (27).

All of these muscular effects of smoking when present in an elderly subject will be responsible for severe impairment of muscle function that may induce motor disability.

Gas exchange, aging and tabacco use

Gas exchange across the alveolar capillary membrane is measured by carbon monoxide diffusion capacity (DLCO). Age-related changes in the pulmonary circulation result in increased pulmonary artery systolic pressure, increased ventilation-perfusion mismatch (A/Q.), and a progressive decrease in DLCO in the elderly (8, 28, 29).

Previous work has demonstrated an age-related increase in A/Q. mismatch, characterized by a heterogeneous distribution of lung units with high and low A/Q. ratios: this is age-related A/Q. mismatch (30).

The age-related increase in A/Q. inequality may coexist with a decrease in DLCO. The decrease in DLCO may be due to a decrease in alveolar surface area and pulmonary capillary density (31).

Smoking accelerates the aging of the lung parenchyma. Indeed, the amount of smoking (ie; pack-years) was negatively correlated with DLCO as a percentage of theoretical value (32). Zhang et al. (32) showed that nonsmokers with COPD had less gas exchange impairment and a lower prevalence of emphysema than smokers with COPD (32).

Response to hypoxia and hypercapnia, aging and tobacco use

The ventilator response to low oxygen tension or high carbon dioxide tension is markedly impaired in the elderly. Kronenberg and Drage (33) studied 8 young and 8 healthy elderly subjects and noted a 50% reduction in response to hypoxia and 40% reduction in response to hypercapnia. The likely explanation for the reduced response is the age-related decline in efferent neural output to respiratory muscles during hypoxic or hypercapnic states. This hypothesis is supported by the fact that older adults generate lower occlusion pressure compared with younger individuals during these states (28).

Hildebrandt et al. (34) showed that the hypoxic ventilatory response is significantly reduced in smokers when studied after a night of abstinence from cigarettes, i.e., after nicotine elimination (34). This hypoxic ventilatory response depends on the oxygen chemosensitivity of the carotid body, which is part of the crucial regulatory reflexes of oxygen homeostasis (34).

NON RESPIRATORY FUNCTIONS, AGING AND TOBACCO USE

The lungs perform several important non-respiratory functions. The lungs are a vascular reservoir of the body, a filter for blood-borne substances, a defense barrier against inhaled substances (ie; mucociliary escalator, immune function), a defense against inhaled chemicals, and perform several endocrine and metabolic functions (ie; isolated pulmonary neuroendocrine cells and innervated cell groups).

Nitric oxide (NO) is one of the metabolic mediators produced by lung cells. As demonstrated by Rouatbi et al. (35) lung aging alters exhaled nitric oxide values and smoking accelerates this decrease by inhibiting the enzyme NO synthase (Figure 4) (35).

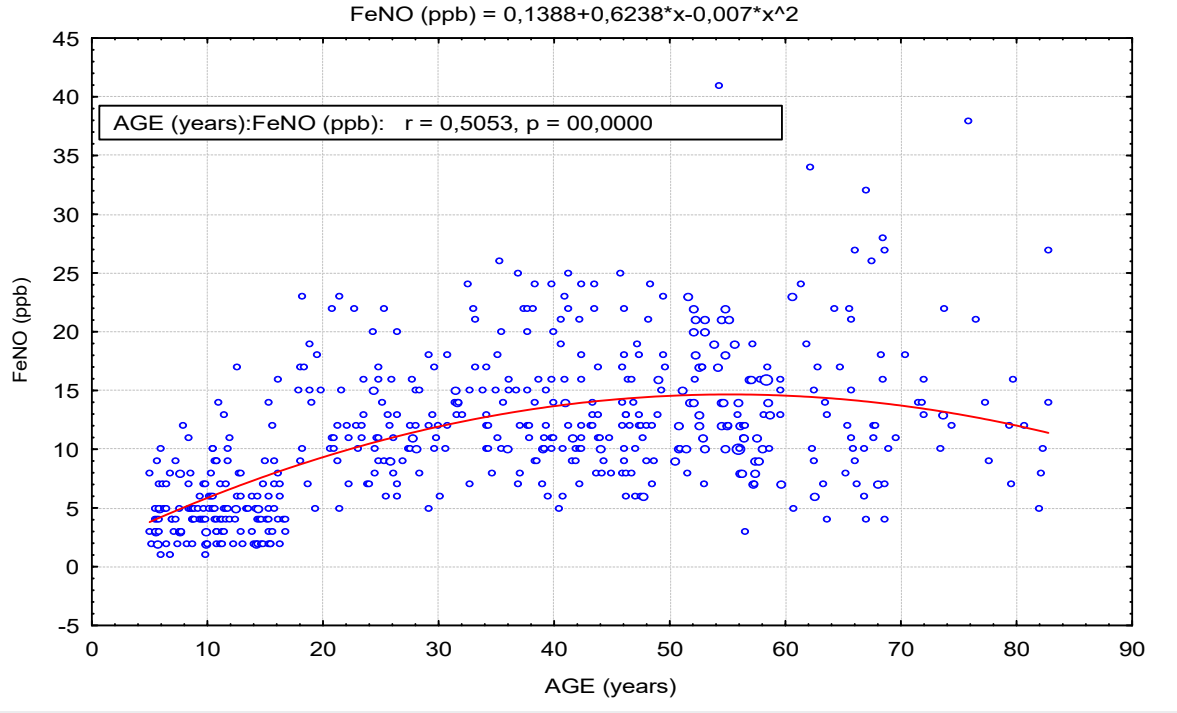

Figure 4. The effect of aging on the fraction of exhaled nitric oxide (FeNO) values (28)

Lung Immunosenescence and Tobacco use

The immune system also undergoes an aging process termed immunosenescence. Both innate immunity and adaptive immunity are affected by aging (36). Aging innate immune cells, such as neutrophils, macrophages, dendritic cells, and natural killer cells, undergo a functional decline in phagocytosis, chemotaxis, their ability to secrete inflammatory cytokines, antigen-presenting capacity, and bactericidal ability (37-40). Declining function of innate immune cells with aging also contributes to the dysregulation of the adaptive immune system via molecular cross-talk (41).

Humoral immune function also changes significantly with age; these changes include decreased antibody responses and diminished production of high-affinity antibodies related to defective surface immunoglobulin/B-cell receptor affinity decreased signaling, and reduced B-cell proliferation (42). There is also a loss of naïve B-cells and an increase in memory cells with age, resulting in a reduced ability to respond to new antigens (43).

The decline in immunity associated with age and/or smoking is a critical mechanism for the development of COPD (16).

Inflammation, aging and tobacco use

In the elderly, levels of pro-inflammatory mediators, C-reactive protein, interleukins (IL) (eg; IL-1β, IL-6 and IL-8), and tumor necrosis factor (eg; TNF-α), are elevated with a simultaneously hypersensitive immune system to specific antigens. The combination of these phenomena in elderly subjects is termed “inflamm-aging” (44). The suggested serious consequences of this “inflamm-aging” are represented by cardiovascular disorders and COPD in elderly patients (45, 46).

Genetic aging and tobacco use

The genetic factor influences the intrinsic aging of the respiratory system: this is physiological aging.

Smoking significantly disrupts 18 genes related to aging of the small airway epithelium. In an independent cohort of male subjects, smoking significantly reduced telomere length in the small airway epithelium of smokers by 14% compared with nonsmokers. These data provide biological evidence that smoking accelerates aging of the small airway epithelium (47).

Lung biochemical structure, aging and tobacco use

β- adrenoreceptor

β2-adrenergic receptors are present in the bronchial smooth muscle cell. They are an important therapeutic target in bronchial diseases: asthma or COPD. Stimulation of the β-adrenoreceptor by an agonist or antagonist is mediated by the production of cyclic adenosine monophosphate (AMP). The β-adrenoreceptor can exist in two physiological states: high or low affinity. The density of β-receptors remains unchanged throughout life, but it is the affinity of these receptors that decreases with age (48). This reduction in high-affinity receptor represents a functional uncoupling of the receptor from the adenyl cyclase complex and an impairment of receptor-mediated adenyl cyclase activity (49).

Vestal et al. (50) demonstrated reduced β-adrenoceptor sensitivity in elderly smokers by studying the relationship between isoproterenolol resistance and age in smokers and nonsmokers (50).

β2-adrenergic receptors are important targets in the treatment of COPD. Hu et al. (51) suggest that increased circulating β2-adrenergic receptor auto-antibodies are associated with smoking-related emphysema (49).

Muscarinic receptor

Pulmonary muscarinic receptors are present at the bronchial smooth muscle cell and neuron. There are three subtypes of muscarinic receptors: M1, M2 and M3. These receptors are a therapeutic target for chronic respiratory diseases. Data on age-related changes in pulmonary muscarinic receptors in humans are limited. A study of age-related changes in muscarinic receptors in guinea pigs showed no change in receptor density but noted a significant reduction in high-affinity agonist binding sites in old tissue compared to young tissue. Changes in muscuranic receptor subtypes and G protein receptor coupling with senescence were noted (52).

Kistemaker et al. (53), in their study of the effects of muscarinic receptor subtypes on cigarette smoke-induced airway inflammation in mice, found a pro-inflammatory role for the M3 muscarinic receptor in cigarette smoke-induced neutrophilia and cytokine release, but an anti-inflammatory role for the M1 and M2 receptors (53).

Angiotensin-converting enzyme 2 (ACE2)

ACE2 was predominantly expressed in alveolar epithelium (alveolar cells type 2), bronchiolar epithelium, endothelium, and smooth muscle cells of pulmonary vessels. However, ACE2 was not detected in the bronchiolar smooth muscle cells (54). ACE2 expression is dramatically reduced with aging in both genders (55). So the elderly may be at increased risk of serious infections by coronavirus disease 19 (COVID-19), decompensation of chronic diseases, addiction, and death (54-57).

Cigarette smoke causes a dose-dependent upregulation of ACE2, in rodents and human lungs. Thus chronic smoke exposure triggers a protective expansion of mucus-secreting goblet cells and a concomitant increase in ACE2 expression(56) (Figure 5).

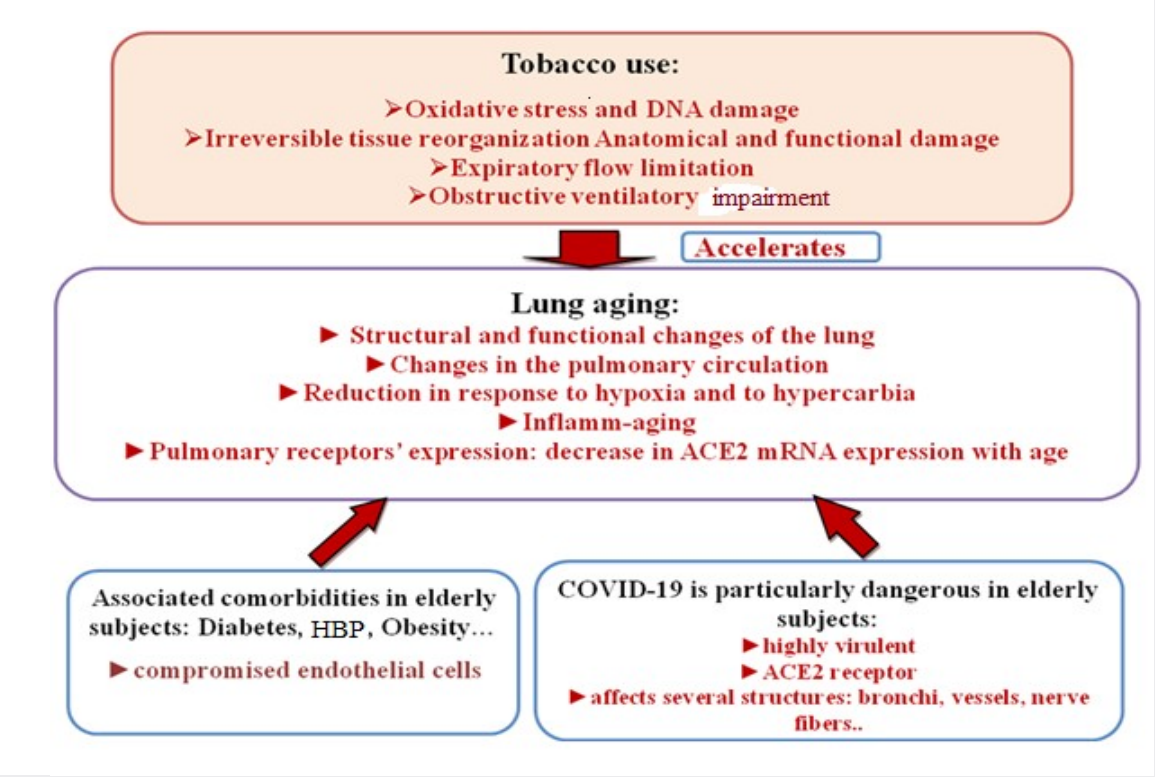

Figure 4. The effect of aging on the fraction of exhaled nitric oxide (FeNO) values (28) Figure 5. Factors influencing premature lung aging:

ACE2: Angiotensin converting enzyme2, COVID-19: Coronavirus disease 19, DNA: Deoxyribonucleic acid, HBP: High blood pressure, mRNA: messenger ribonucleic acid.

EXPLORATION OF LUNG AGING

Lung aging can be explored by several methods: spirometry and measure of FEV1, Fletcher curve, and lung age calculation (18, 58, 59). Graphics (Fletcher Curve (18)) displays more effective than FEV1 results, and lung age resonates more than FEV1 alone. These tools are used in smoking cessation counseling (19).

CONCLUSION

Tobacco use accelerates lung aging and touches biological, structural, and respiratory and non respiratory functions. These changes contribute to the development of chronic pulmonary diseases and predispose to pulmonary infections in older individuals. Knowledge of these changes is very useful for better management of elderly.

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