Relationship of senescence of pulmonary system to chronic obstructive pulmonary disease in the advanced life

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Summary Chronic obstructive pulmonary disease (COPD) is a major worldwide health problem. There exists a relationship between COPD and increased oxidative stress, and oxidants may be involved in lung damage during the course of COPD. Polymorphonuclear (PMN) cell recruitment at lung level plays an important role in free radical overproduction, impact inflammatory processes and may alter oxidant–antioxidant balance. Biological aging is thought to be influenced by free radical generation, aging, and the diseases. All the components of the respiratory system are affected by aging. Nutrition, smoking habits and sleep-related disorders also affect the respiratory system. Whether these changes are due to aging or associated with aging is a matter of debate. Since alterations caused by aging and cigarette smoke in lungs of various species were informed to be partly simulated with age-related alterations in human lung, the effects of oxidative agents and antioxidative parameters on both COPD and aging were evaluated. © 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The recent reports regarding the effects of age and cigarette smoke on alterations in the lungs of the various species inform that these changes in the lungs exposed to cigarette smoke were partly simulated with age-related alterations in human lung. Therefore, the effects of oxidative agents and antioxidative parameters on both chronic obstructive pulmonary disease (COPD) and aging have been evaluated in this report.

Aging, usually defined as a normal physiologic process, traditionally has been excluded from the domain of disease because it is ‘normal’; disease is usually considered ‘abnormal’. Conceptually, this distinction seems clear until the concept of ‘injury’ is introduced; some pathologists have defined disease as the result of injury. Aging appears to be the result of the accumulation of small, imperceptible injuries. In this context, the distinction between aging and disease remains unclear (1).

COPD: HYPOTHESES, PATHOGENESIS, AND RISK FACTORS

COPD is a major worldwide health problem and has an increasing prevalence and mortality. It is rare before the age of 40 and the prevalence of it increases progressively until 60–70 year of age (2–5).

The incidence, prevalence and health-related costs of COPD are increasing. Likewise, mortality from COPD has risen. In 1991 in the United States, COPD was the fourth leading cause of death after heart disease, cancer and stroke and the mortality rate had increased by nearly 33% over 1979 figures. In contrast, mortality
from causes such as heart disease and stroke has declined (6–11). This is an unbelievable and frightening fact in today’s developing world and should be handled with great and immediate attention.

COPD is a heterogeneous collection of conditions that can affect various structures within the lung in a number of different ways. As a whole, COPD is characterized by a single physiologic feature: limitation of expiratory airflow. A number of diseases can lead to this physiologic abnormality. In general, COPD embraces asthma, chronic bronchitis and emphysema (7).

Significant overlaps exist in signs and symptoms among these three major diseases of airflow obstruction. These relationships have been summarized as a non-proportional Venn Diagram (3,8).

HYPOTHESES
Three hypotheses for the relationship between inflammation and airway tissue remodeling in the development of fixed airflow limitation have been introduced so far. It seems reasonable to consider these hypotheses not as competing, but rather as complementary. In this regard, an inciting etiology, for example cigarette smoking or infection, leads to airway inflammation. In the Dutch hypothesis, this inflammatory process can lead to airway hyperreactivity. In the British hypothesis, it can lead to mucus hypersecretion, and these various processes may eventually contribute to the development of fixed airflow limitation. American hypothesis might be that the inflammatory process directly leads to airway remodeling and airflow limitation independently of airway hyperreactivity or mucus hypersecretion (7).

PATHOGENESIS OF COPD
Upon exposure to tobacco smoke, air pollution and other environmental factors, continual bronchial irritation and inflammation, and breakdown of elastin in connective tissue of lungs contribute to the development of chronic bronchitis and emphysema, respectively. Chronic bronchitis, characterized by bronchial edema, hypersecretion of mucus, chronic productive cough and bronchospasm and emphysema, characterized by destruction of alveolar septa and airway instability may lead to the common symptoms of airway obstruction, air trapping, dyspnea and frequent infections which in turn result in abnormal ventilation–perfusion ratio, hypoxemia and hypoventilation (7).

RISK FACTORS FOR COPD
Tobacco smoking is undoubtedly the main cause of COPD, and accounts for 80–90% of the risk of developing COPD. Therefore, encouragement and support in smoking cessation is the best way to help the patient with COPD (9).

In addition to cigarette smoke, occupational exposures, and α1-protease inhibitor deficiency, etiologies that have been definitely linked to the development of COPD, a number of other factors are likely associated with the clinical manifestations and progression of COPD. These presumed risk factors include α1-antitrypsin deficiency, air pollution, passive smoke exposure, respiratory virus infection, recurrent bronchopulmonary infections, lower birth weight, a history of severe childhood respiratory infections, socio-economic factors, nutrition, alcohol ingestion, age, gender, poorly defined familial factors, mucus hypersecretion and airway hyperresponsiveness (7,12).

AGING AND THE PULMONARY SYSTEM
All the components of the respiratory system are affected by aging, though at different rates. However, whether these changes are due to aging or associated with aging is a matter of debate. Nutrition, smoking habits and sleep-related disorders also affect the respiratory system.

Less is known about structure and function of the lungs in the very young and the elderly, but a few normal physiologic (developmental and degenerative) changes are known to occur from birth to old age. An understanding of these changes is needed to provide appropriate care and to differentiate between normal alterations and disease. Normal alterations associated with advancing age include; loss of elastic recoil, stiffening of the chest wall, alterations in gas exchange, diminished ventilatory reserves, abnormal ventilation–perfusion ratio, reduction in respiratory muscle strength and endurance, increased residual volume (RV) and functional residual capacity (FRC), decreased vital capacity (VC) and forced expiratory volume (FEV,1) (13).

HYPOTHESIS
The most striking relationship is between cigarette smoking and COPD. Nearly 85–90% of all COPD patients are smokers. These results suggest that about 10–15% of COPD patients develop disease from the causes other than cigarette smoking (2,14,15). At this moment, the point which makes the discussion interesting is that only 10–20% of cigarette smokers develop symptomatic COPD, implying undue susceptibility compared with the remainder of the population at large (14). That means not all of the cigarette smokers develop COPD. Therefore, it may be plausible to suggest that even for the cigarette smokers – if all the other risk factors are properly handled – COPD may not be the unavoidable conclusion.
COPD is associated with significantly lower levels of FEV₁ and FVC. There is also loss of lung elastic recoil due to inflammation and alveolar wall destruction. Decreased lung function is frequent. Abnormal ventilation-perfusion ratio, hypoxemia, hypoventilation are the final elements associated with pathogenesis of COPD. The chronic airway obstruction is due to a combination of airway disease, which particularly affects small airways, and loss of lung elasticity due to enzymatic destruction of the lung parenchyma. In patients with COPD, there is an imbalance between proteases that digest elastin and those that protect against this (1).

This information indicates the close similarity in the alterations of the structure and function of the lungs between aging and COPD.

Because pulmonary function declines with aging, everything must be done to prevent any additional functional loss caused by COPD. Indeed, elderly cigarette smokers who develop COPD may lose as much as 80 ml of FEV₁/yr compared with 33 ml/yr for non-smokers (16).

A number of investigators have implicated oxidant-antioxidant imbalance, like protease-antiprotease imbalance in the pathogenesis of smoking-induced COPD. Therefore, both protease-antiprotease balance and oxidant-antioxidant balances are important factors to be considered.

The contribution of iron has become increasingly meaningful in understanding the development of COPD. Iron deposition in the lung has been shown to be associated with tissue injury and fibrosis. Iron accumulates in the lungs of smokers and patients with various pulmonary diseases as well as occupational diseases and during alveolar hemorrhage or hyperoxic lung injury (17).

It is also interesting to note that iron in the lung increases with age (18). Progressive increases in iron occurred as a function of aging in men and in postmenopausal women—intriguingly, at the time when COPD worsens in both sexes (2,19).

The diet is a rich source of antioxidants such as vitamins C, E and β-carotene that protect against damage mediated by reactive oxidants (20). One SD decrease in vitamin C intake in a general population sample is associated with a difference in FEV₁, approximately equivalent to 5-pack yr. smoking (21). Vitamin C intake is also found to be negatively associated with a history of bronchitis and wheezing in a population-based study (22). It is also suggested that for every extra milligram increase in vitamin E in the daily diet, FEV₁ increased by an estimated 42 ml and FVC by an estimated 54 ml (20).

In an experimental study performed on senescence-accelerated mice (SAM), good models for studying physiologic and/or pathologic aging; the effects of chronic cigarette smoke inhalation and age on the function and morphology of lungs have been investigated. Alterations observed suggested that the effect of age might be greater than that of the small burden of tobacco smoke on the lung alterations. In the aged SAM, there were no differences in function and structure between tobacco-exposed and air-exposed mice (23).

Finally, reports suggesting that only 10–20% of cigarette smokers develop COPD, the absence of demonstrable risk factors in the individual for developing COPD or lung cancer should not deter physicians from persuading smokers to quit the habit (2,14).

Reduced lung function is common among the elderly and is usually associated with the presence of respiratory symptoms. Aside from tobacco smoking other determinants must also operate. The development of COPD in only 10–20% of cigarette smokers also suggested that the removal of some possible risk factors might prevent the development of symptomatic COPD in spite of cigarette smoking. It has been shown that antioxidants in the lung have a protective role against oxidative damage (20). Supplementation of individual’s diet with antioxidant vitamins, living in the areas devoid of air pollution, lack of exposure to respiratory infections earlier in life, high socio-economic status, avoiding passive smoking are some of the positive factors improving the health status of the individuals.

TESTING THE HYPOTHESIS

The hypothesis can be tested by assessing the effects of each risk factor on the spirometric tests in the wide-scowed studies performed on large numbers of healthy elderly populations as well as the patients with COPD. However, first of all, the definition of the symptoms of the disease should be made clearly. The distinction between the different groups composing COPD patient groups should be a clear-cut one. The overlaps observed in Venn Diagram should be removed. A detailed classification is required. Then, narrow ranges of age for COPD patients should be established. Closely resembling COPD patients should be grouped and if the only significant difference between the groups becomes the age, it will then be possible to clearly see the alterations due to senescence.

REFERENCES


