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REVIEW

Airway bacterial colonization: The missing link between COPD and cardiovascular events?

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Summary
Background: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide and, according to the World Health Organization, its prevalence will double by 2020. COPD is a chronic inflammatory disease of the lung characterized by poorly reversible airflow limitation and, frequently, by extrapulmonary manifestations. In particular, the cardiovascular manifestations are responsible for high morbidity and mortality.
Methods and results: A systematic literature search was performed of studies published in Medline until December 2010, using the key-words: COPD, bacterial colonization, COPD exacerbation, atherosclerosis, systemic inflammation, cardiovascular event and risk factors. In addition to the studies identified in the primary search, reference lists of included articles were analyzed for additional papers related to the topic.

The pathogenetic mechanisms underlying atherosclerosis – namely inflammation, oxidative stress and endothelial dysfunction – are in common with COPD. Moreover, they are increased in the presence of COPD, especially in patients who present airway bacterial colonization, increased rate of exacerbations and elevated levels of both airway and systemic inflammation.
Conclusion: COPD is associated with an increased burden of atherosclerotic disease. Systemic inflammation and oxidative stress play key roles in this association. COPD patients with airway bacterial colonization, as compared to patients without airway colonization, generally present more frequent exacerbations and higher levels of both airway and systemic inflammation. This COPD subgroup should be considered at particularly increased risk of developing cardiovascular complications and receive more attention concerning diagnosis, treatment, prevention and research.

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Introduction

Chronic obstructive pulmonary disease (COPD) affects over 5% of adult population in Western countries and accounts for approximately 750,000 hospitalizations every year in the United States,[1] with an economic burden of 24 billion dollars.[2] Moreover, its prevalence and mortality is projected to rise continuously, and the World Health Organization predicts that COPD will become by 2020 the third leading cause of death (currently fourth) and the fifth leading cause of disability (currently twelfth), worldwide.[3]

COPD is a chronic inflammatory disease of the lung characterized by the presence of poorly reversible and generally progressive airflow limitation.[4] In over 80% of cases, cigarette smoking is considered to be the causative factor.[5,6]

The clinical picture of COPD is frequently complicated by extrapulmonary manifestations,[7] such as skeletal muscle dysfunction and wasting,[8] osteoporosis[9] and atherosclerosis.[10] These manifestations are thought to be due to the spreading of the inflammatory response from the lung into the systemic circulation,[11–14] with possible involvement of various organs.

The clinical course of COPD is punctuated by recurrent episodes of acute-subacute increase in both airway and systemic inflammation (Fig. 1), as well as in respiratory symptoms, otherwise known as exacerbations.[15] Exacerbations have a major negative impact on the patient's quality of life, and contribute significantly to the accelerated decline in lung function typically observed in COPD.[16–19]

Exacerbations are caused mainly by bacteria and viruses,[20] but various predisposing factors appear to play a role, including airway bacterial colonization.[20,21]

Compared to patients whose airways are not colonized, COPD patients with airway bacterial colonization present more frequent exacerbations, and a higher level of airway inflammation both in the stable state and during exacerbations.[22–24] Moreover, in some studies bacterial colonization of the airways has been associated also with systemic inflammation both in the stable state[25] and during exacerbations.[26] In this context, an association between sputum purulence and increased serum C-reactive protein (CRP) levels during an exacerbation of COPD has also been described in another study.[27] Taken together, these observations suggest that there may be a relationship between airway bacterial colonization and systemic inflammatory responses.[26,28–30]

Although respiratory failure is a common endpoint in advanced COPD, patients die more frequently from cardiovascular events, such as coronary disease, arrhythmias, stroke, and sudden death, as well as from lung cancer, rather than from respiratory failure.[5] Accordingly, the risk for cardiovascular disease is markedly increased in patients with COPD,[31] and poor lung function has been shown in these patients to be a powerful predictor of cardiovascular risk, even after adjusting for established cardiovascular risk factors.[32] In particular, in the large Lung Health Study, Anthonisen and coworkers report that for every 10% decrease in forced expiratory volume in 1 s (FEV_1) there is an increase of 14% in all-cause mortality, of 28% in cardiovascular mortality, and of almost 20% in non-fatal coronary events.[33] It is worth noting that in this study adjustments were made for the most relevant confounders, such as age, sex, smoking, cholesterol, social class, and educational level.[33]

The mechanisms by which the pulmonary changes observed in COPD can lead to increased cardiovascular morbidity and mortality are still poorly understood. However, inflammatory pathways have recently emerged as

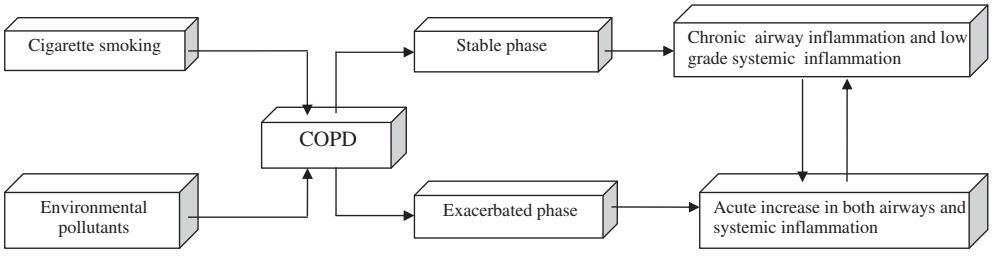

Figure 1 Cigarette smoking and/or environmental pollutants cause COPD in predisposed subjects. COPD in stable phase is characterized by chronic airway inflammation and low grade systemic inflammation. Acute exacerbations of COPD are responsible for an increase in both airway and systemic inflammation.