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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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Contents

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

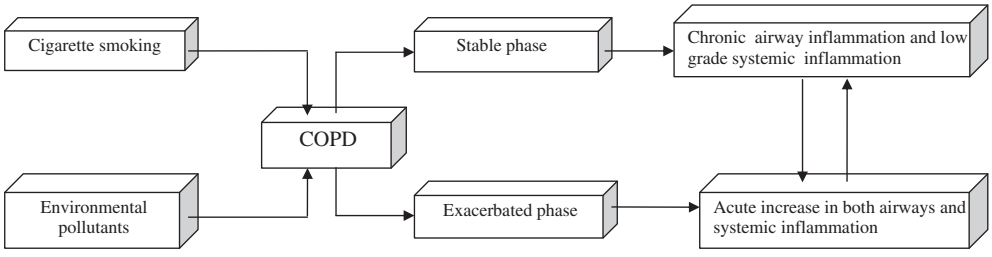

Figure 1 Cigarette smoking and/or environmental pollutants cause COPD in predisposed subjects. COPD in stable phase is characterized by chronic airway inflammation and low grade systemic inflammation. Acute exacerbations of COPD are responsible for an increase in both airway and systemic inflammation.

playing a pivotal role in the pathogenesis of atherosclerosis.[34] On the other hand, as outlined above, also COPD is now considered to be an inflammatory disease in which both pulmonary and systemic inflammation appear to have a role. Systemic inflammation could then constitute the link between COPD and respiratory symptoms, on the one hand, and atherosclerosis and increased cardiovascular risk, on the other.

The present review will begin with a brief outline of the current epidemiological and clinical evidence on the cardiovascular morbidity and mortality associated with COPD. After a summary of the inflammatory pathways involved in both COPD and atherosclerosis, it will then discuss the possible relationship between airway bacterial colonization, exacerbation frequency, and systemic inflammation in COPD. It will conclude with an overview of the prospects for future research.

Cardiovascular morbidity and mortality associated with COPD

The existence of an association between COPD and cardiovascular morbidity and mortality is supported by both epidemiological and prospective clinical studies.

In the Third National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, a cohort of 1861 subjects, aged 40—60 years, was followed and cardiovascular mortality assessed. Individuals in the lowest FEV_1 quintile had the highest risk of cardiovascular mortality (relative risk 3.36; 95% confidence interval 1.54—7.34), with a fivefold increase in the risk, in comparison to individuals in the highest FEV_1 quintile.[32] In the large Tucson Epidemiological Study of Airways Obstructive Disease,[35] a cardiovascular event was reported on the death certificate as the primary cause of death in as many as 42% of patients who presented COPD as a contributing cause. In the Lung Health Study,[33] examining the causes of death and hospitalization in 5887 patients with mild to moderate COPD over a period of five years, all-cause mortality resulted to be 2.5%, and, of this, 25% was due to cardiovascular events.

In a population-based cohort of 5648 patients with COPD, as compared to the general population, Huiart and colleagues found significantly higher rates of cardiovascular morbidity and mortality.[36] In the Towards a Revolution in COPD Health trial, involving more than 6000 COPD patients randomized to receive either a combination of salmeterol/fluticasone propionate, its monotherapy components, or placebo for 3 years, mortality was ascribed to respiratory complications, cardiovascular events, and cancer in 36%, 27%, and 22% of cases, respectively.[37] In population-based studies, several groups evaluated the relationship between FEV_1 and cardiovascular mortality, and reported results similar to those cited above.[38—40]

Cardiovascular risk appears also to be increased in subjects with chronic bronchitis. In a 13-year follow-up study involving 19,444 randomly selected eastern Finnish subjects of both gender, men with cough and phlegm were reported to have an elevated risk of dying from cardiovascular disease independently of the major cardiovascular risk factors.[41] In the Multifactor Primary Prevention Trial conducted in Sweden,[42] individuals with daily cough and sputum production presented an age-adjusted 42% increase in the risk of cardiovascular mortality compared to individuals without respiratory symptoms.

Inflammatory pathways in COPD

A chronic inflammatory response, with accumulation of neutrophils, macrophages, and cytotoxic T-lymphocytes, and release of a number of chemical mediators is a characteristic feature of COPD. The inflammatory process induces the activation of elastolytic enzymes and metalloproteinases that are responsible for the emphysematous and airway remodelling changes observed in COPD.[43]

COPD has also been associated to pulmonary and systemic oxidative stress, both in the stable state and during exacerbations.[44,45] In this regard, peripheral blood neutrophils harvested from patients with COPD, as compared to neutrophils from normal subjects, produce more reactive oxygen species (ROS).[46] This increased oxidative stress may be the result of either the large burden of activated inflammatory cells present in the lower airways, or of the reduced antioxidant capacity of the lung, or a combination of the two.[47]

In general, oxidative stress seems to play an important role in amplifying the inflammatory process, due to the activation of oxidant-sensitive transcriptional factors that lead to an increased transcription of pro-inflammatory genes.[47] In particular, in COPD the excessive ROS production, especially during exacerbations, has a detrimental effect on the cellular components and biomolecules (lipids, proteins, nucleic acids), and contributes to endothelial dysfunction.[48—50]

Among the various intracellular ROS, superoxide anion appears to be particularly important in that it inactivates nitric oxide by transforming it into peroxynitrite,[51] so abolishing its numerous anti-inflammatory actions such as inhibition of leukocyte adhesion to endothelium, inhibition of platelet aggregation, reduction in the tone and proliferation of smooth muscle cells, alteration of lipoprotein metabolism, and activation of the antioxidative superoxide dismutase enzyme system.[52,53]

Moreover, superoxide anion causes endothelial dysfunction, that further amplifies the inflammatory response.[51] In this regard, Barr et al. observed a significant relationship between some indexes of endothelial dysfunction on the one hand, and severity of airway obstruction, severity of emphysema, and some markers of systemic inflammation, e.g. CRP and leukocyte count, on the other.[54] In another study it has been reported that both endothelium-dependent and endothelium-independent vasodilatation is significantly impaired in patients with stable COPD.[55]

As anticipated above, increased systemic inflammation in association with airway bacterial colonization has been observed in patients with stable COPD. However, whether bacterial colonization is able to drive endothelial dysfunction is an important point that, unfortunately, has not yet been adequately addressed in the literature.

Conversely, it has been reported that endothelial dysfunction increases during an acute exacerbation of COPD, and improves as the exacerbation recedes.[56] The authors suggest that the exacerbation induced enhancement of systemic inflammation and, in particular, the increased

concentration of CRP may contribute to the observed increase in endothelial dysfunction during exacerbations.[56] Accordingly, CRP has been shown to present a number of actions that may significantly impair endothelial function.[57,58] Of note, CRP potently down-regulates endothelial nitric oxide synthase (eNOS) transcription and destabilizes eNOS mRNA, with consequent decreases in both basal and stimulated NO release.[59]

One of the consequences of endothelial dysfunction, namely arterial stiffness, that can be measured by aortic pulse wave velocity, results to be increased in patients with COPD, as compared to non-COPD subjects matched for a number of cardiovascular risk factors.[60] Arterial stiffness is furthermore higher in patients with severe to very severe COPD compared to those with mild to moderate disease.[61] Indeed, McAllister and coworkers found that both FEV_1 and computerized scan based emphysema severity are the most powerful predictors of arterial stiffness in COPD patients, suggesting the existence of common pathogenetic features between chronic obstruction of the lung and systemic vascular dysfunction.[61] Finally, both in patients with COPD and in healthy subjects, arterial stiffness has been shown to correlate with markers of systemic inflammation, such as interleukin (IL)-6 and CRP serum levels.[31,60,62]

Inflammatory pathways in atherosclerosis

Similarly to COPD, inflammation and oxidative stress play a central role in the pathogenesis of atherosclerosis at all stages of severity of the disease.[34,63] The cell types involved in the atherosclerotic process include vascular endothelial and smooth muscle cells, T-, B-, and NK T-lymphocytes, monocytes/macrophages, and dendritic cells.[64]

Injury and subsequent activation of vascular endothelium are considered to be the primer events in atherogenesis.[65] Once activated, vascular endothelium produces IL-1, IL-6 and other cytokines, and expresses several surface adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E- and P-selectin, making it possible for leukocytes to adhere to the damaged endothelial surface.[65,66] Conversely, under normal physiologic conditions, namely in the absence of external insults, the human endothelium does not usually permit adhesion of leukocytes, which are known to be the building blocks of the arterial plaque genesis.

The expression of adhesion molecules and chemokines by endothelial cells initially facilitates the recruitment of macrophages. These express on their surfaces the so-called scavenger receptors, which enable them to take up circulating lipids, and become foam cells.[65] Plaque formation is accomplished by the activation and proliferation of vascular smooth muscle cells, which migrate from the arterial media into the intima, and produce an extracellular matrix, whose accumulation in the plaque determines the formation of fibro-fatty lesions.[65,66]

Endothelial dysfunction, accumulation of inflammatory cells and lipids, and secretion of pro-inflammatory cytokines by macrophages and other cells characterize the early plaque, and constitute a chronic pro-atherogenic environment. In this context, CRP seems to contribute significantly to aggravation of arterial lesions in that, as indicated by some studies,[67,68] it interacts with endothelial cells, stimulating them to produce IL-6 and endothelin-1. Moreover, CRP up-regulates the production of adhesion molecules, monocyte chemotactic protein-1, and other inflammatory cytokines, activates the complement system, promotes the uptake of low-density lipoprotein (LDL) cholesterol by macrophages and fosters the leukocyte adhesion to the vascular endothelium, so amplifying the inflammatory cascade.[67,68]

Thus, CRP should be considered not only as a marker of inflammation, but also as a pathogenetic factor in atherosclerosis. Bearing this in mind, it is not surprising that CRP serum level has been reported in a number of studies as a strong, independent predictor of cardiovascular morbidity and mortality.[68] For example, in the Framingham Study, CRP levels of <1, $1-3$, and >3 mg/L corresponded to low, moderate, and high-risk patient-groups for cardiovascular events, respectively.[69]

Myeloperoxidase is an enzyme secreted from activated neutrophils, monocytes, and macrophages, which has emerged as a potential contributing factor in the induction and/or propagation of atherosclerosis.[70] It generates a number of ROS and diffusible radical species, that are capable of both initiating lipid peroxidation[71] and promoting an array of post-translational modifications of target proteins.[72,73] Myeloperoxidase has also been implicated in the *in vivo* enzymatic oxidation of low-density lipoproteins, which potentiates the lipoprotein uptake from macrophages, with increased cholesterol deposition and foam cell formation.[71]

Cigarette smoking represents one of the most relevant risk factors for atherosclerosis, as well as for COPD. In fact, it has been demonstrated that smokers are at significantly higher risk of developing severe early atherosclerosis. However, the pro-atherogenic effect of cigarette smoke shortly reverses after cessation of smoking, and in quitters the risk rapidly reaches that of nonsmokers, unless, as shown by Kiechl and colleagues, they present clinical or serological evidence of chronic airway infection.[74] With this regard a number of infectious agents have been implicated in the atherogenesis. Sero-epidemiological studies have suggested that several microorganisms, such as *Chlamydia pneumonia*, *Helicobacter pylori*, *cytomegalovirus*, *herpes simplex virus*1, and *hepatitis A virus* could all be considered as risk factors for atherosclerosis.[75–79] Moreover, prospective studies have indicated an increased risk for cardiovascular events in patients with serological evidence of prior infection, particularly in cases of multiple infections.[80]

Also some animal studies suggest a role for infection in atherogenesis. Indeed, observations in mice indicate that repeated, short-lasting infectious insults could cause endothelial dysfunction and arterial damage, thus contributing to atherosclerosis progression.[81,82]

Since direct evidence relating a specific infectious agent to atherogenesis is lacking at the moment, the current view is that probably no single pathogen or single infectious episode accounts for a multifactorial disease such as atherosclerosis.[75]

In this regard, it has recently been suggested that it is the "infectious burden",[83,84] rather than any specific pathogen, that determines the infection-related propensity to develop atherosclerosis. In this context, individuals exposed to numerous infections throughout the life span would be the most likely to develop atherosclerosis. Of

note, the infectious burden seems to be related to the serum CRP level.[85,86]

A number of mechanisms, in conjunction with other cardiovascular risk factors, have been advocated to explain the role of infections in atherosclerosis.[76]

In vitro and *in vivo* epidemiological data suggest that infectious agents have the potential to produce a pro-inflammatory, pro-coagulant and pro-atherogenetic environment in the vessel wall.[87]

Moreover, infections could contribute to atherogenesis through their effects on lipid metabolism. Indeed, during both acute and chronic infections a marked decrease may occur in the levels of high-density lipoproteins, which possess several important anti-atherogenic properties.

Another mechanism by which infections could exert a pro-atherogenic action may be the induction of molecular mimicry-based autoimmunity responses.[88] For example, heat shock proteins, which are a family of highly across-species-conserved proteins, may be overexpressed due to infectious agents, and act as "cryptic antigens".[75,89] The immune response evoked by a pathogen might, therefore, be addressed to a self antigen, represented by arterial heat shock proteins, so inducing an autoimmune reaction that may aggravate the atherosclerotic process.[75]

Airway bacterial colonization, exacerbation frequency, and systemic inflammation in COPD

The average frequency of COPD exacerbations is 1–2 annually, with a progressive increase as the severity of disease increases.[20] As indicated from clinical studies, the exacerbation frequency has a significant influence on the natural history of COPD, with a major negative impact on the patient's well-being, hospital admission, and decline in lung function.[16,17,19] A subpopulation of COPD patients has recently been identified that is particularly prone to develop exacerbations, and seems to represent a distinct phenotype of the disease characterized by frequent exacerbations.[90]

Several lines of evidence indicate bacteria as the aetiological agents in up to 50% of COPD exacerbations.[20] Until recently, a bacterial exacerbation was considered as the result of an increased concentration (bacterial load) of the same bacteria that chronically colonize the lower airways of patients with stable COPD.[20,91] Other observations, however, suggest that an additional role in the pathogenesis of COPD exacerbation may be played by acquisition of a new bacterial strain.[91,92]

In bronchoscopy studies, the prevalence of airway colonization has been found to be about 25% and 50% in stable and exacerbated COPD, respectively.[93]

It is generally assumed that airway bacterial colonization in COPD during a phase of stability of the disease is probably the result of a balance in which impaired host defences are able to limit the number of bacteria but not eradicate them,[25] with cigarette smoking and severe airway obstruction representing two additional risk factors for colonization.[94]

The bacteria that most frequently colonize the lower airways of COPD patients (Table 1) include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*,[21,23] whereas gram-negative Enterobacteriaceae, *Staphylococcus aureus*, *Haemophilu sparainfluenzae*, and *Haemophilus haemolyticus* are less frequently found.[95]

Table 1 Microbial pathogens isolated in COPD.

Bacteria
Haemophilus influenzae
Streptococcus pneumoniae
Moraxella catarrhalis
Pseudomonas aeruginosa
Enterobacteriaceae
Haemophilus haemolitycus
Haemophilus parainfluenzae
Staphylococcus aureus
Neisseria spp
Atypical bacteria
Chlamydophila pneumoniae
Mycoplasma pneumoniae

In the respiratory tract, the first-line antimicrobial defence is represented by the barrier function of epithelia, the mucociliary system, some antimicrobial peptides, such as lisozyme, and the surfactant proteins, which are all constitutively expressed.[96,97] The second- and third-line defence is provided by the innate and adaptive immune response, respectively, both of which depend on the recognition of pathogens by means of particular "pattern-recognition receptors".[97] Among these, the Toll-like receptors (TLR) are the best characterized, and seem to play a key role in the host protection against microbes, by activating multiple signalling pathways.[17] The expression of TLR-2 and TLR-4 on alveolar macrophages has been found to be significantly reduced in stable COPD patients and healthy smokers,[98] suggesting some depression of the innate immune response in these subjects.

A number of studies have shown that airway inflammation in COPD, both in the stable state and during exacerbations, is related to airway colonization.[24,99,100] Indeed, sputum levels of cytokines and chemokines, such as tumor necrosis factor α, IL-8, and leukotriene B4, as well as sputum levels of neutrophil products, such as myeloperoxidase and neutrophil elastase, are increased in COPD patients with airway colonization, as compared to patients whose airways are not colonized.[20,100,101] Similar results have been obtained from bronchoalveolar lavage studies.[22]

While the association between airway bacterial colonization and airway inflammation is well established, the relationship between bacterial colonization of the airways and systemic inflammatory response in COPD in the stable state has not been adequately explored and merits further investigation.

It has, however, been observed that COPD exacerbations are associated with a significant increase in both airway and systemic inflammation,[27,29] and that the degree of systemic inflammation during exacerbations parallels the degree of lower airway inflammation.[29]

In comparison to non-bacterial exacerbations, COPD exacerbations sustained by bacteria, especially if they are due to acquisition of a new bacterial strain, are associated with an increased level of both airway and systemic inflammation.[25,101]

COPD patients with frequent exacerbations present, during the stable state of the disease, increased total cell and neutrophil counts, as well as increased IL-6, IL-8, and tumor necrosis factor-α levels in the induced sputum, in comparison to patients with less frequent exacerbations.[24] Moreover, it has been demonstrated that frequent exacerbators show a reduced response to therapy, which may result in persistently higher systemic inflammatory markers. This could, at least in part, explain both the shorter interval until the next exacerbation, as well as the accelerated decline in lung function observed in these patients.[15]

There is now evidence that COPD exacerbations do not always recover to baseline in regard to symptoms and lung function.[102] It may be that, as airway inflammatory markers are increased during exacerbations, airway inflammation perpetuates, leading to a progressive decline in lung function.

Conclusive remarks and future research prospects

As discussed above, both COPD and atherosclerosis are chronic, progressive, frequently coexisting disorders, that share several risk factors and recognize common pathogenetic pathways. Inflammation and oxidative stress seem to play a fundamental role in both diseases.

The increased prevalence of cardiovascular complications in non-respiratory chronic inflammatory diseases, such as rheumatoid arthritis,[103] suggests that also in COPD inflammation could represent the pathophysiological mechanism underlying the high cardiovascular morbidity and mortality observed.

In this regard, it is now recognized that in COPD systemic as well as airway inflammation, both in the stable state and during exacerbations, are increased in patients with frequent exacerbations, as compared to patients with fewer exacerbations. On the other hand, it is also acknowledged that frequent exacerbations are more likely to occur in patients with airway bacterial colonization.

Similarly to COPD, the inflammation of atherosclerosis is characterized by a chronic course, with intermittent periods of acute exacerbations. The greater systemic inflammation present in the stable state of COPD subjects with airway colonization could contribute to the inflammatory process underlying atherosclerosis. In addition, the peaks of inflammatory activity accompanying COPD exacerbations, especially if caused by infectious agents, could precipitate acute exacerbations of the atherosclerotic process, with increased risk of plaque rupture and thrombotic occlusion.

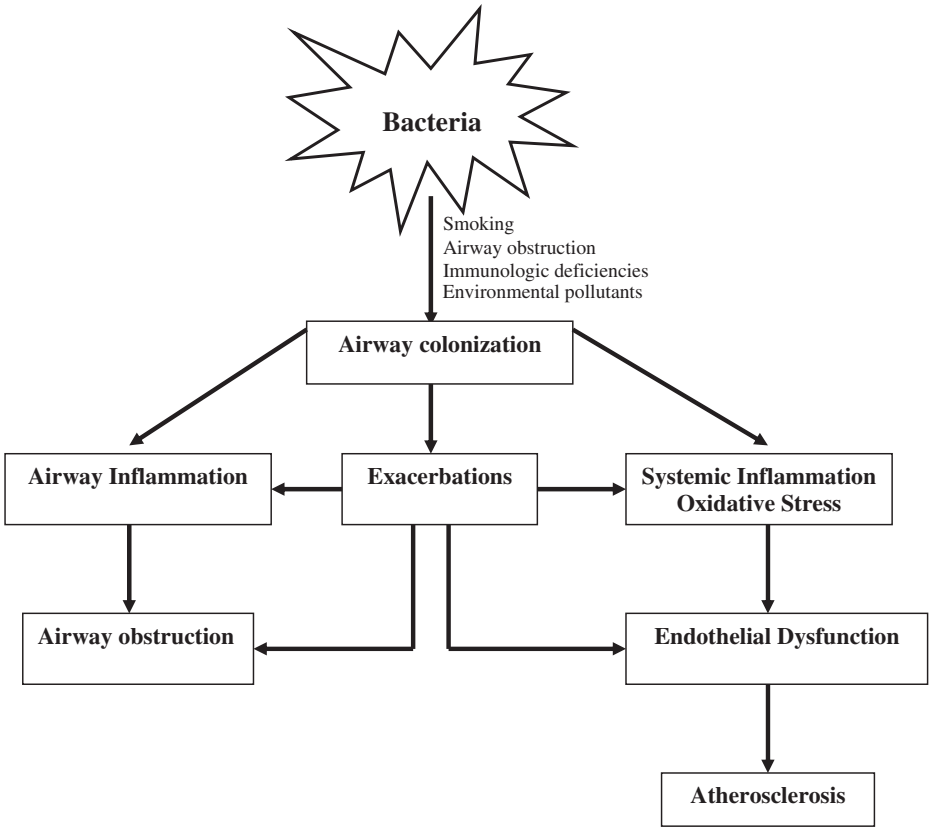

Figure 2 Schematic representation of the mechanisms by which airway colonization may contribute to atherosclerosis development and course in subjects with COPD. The model depicted illustrates that: a) in COPD airway obstruction, cigarette smoking, environmental pollutants and genetic factors predispose to airway bacterial colonization which lead to an increase in both airway and systemic inflammation; b) airway bacterial colonization increases the risk for COPD exacerbations; c) COPD exacerbations further increase airway inflammation and worsen airway obstruction, contributing to progression of the disease; d) COPD exacerbations to a greater extent increase also the systemic inflammatory response and oxidative stress; these, in turn, cause endothelial dysfunction, progression and destabilization of atherosclerotic lesions.

In conclusion, COPD is associated with an increased burden of atherosclerotic disease, and compelling evidence suggests that systemic inflammation and oxidative stress may play key roles in this association. Given that COPD patients with airway bacterial colonization generally experience more frequent episodes of disease exacerbation and present higher levels of both airway and systemic inflammation compared to those without airway colonization, this group should be considered at particularly increased risk of developing cardiovascular complications (Fig. 2).

Also considering that up to 35%—45% of the total cost absorbed by patients with COPD is spent in management of acute exacerbations,[104] preventive treatments specifically addressed to patients with frequent exacerbations are urgently needed. In this context, it would be particularly desirable to design treatments capable of abolishing or, at least, reducing airway bacterial colonization.

Conflict of interest statement

None declared.

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