

Systemic Effects of Chronic Obstructive Pulmonary Disease

What We Know and What We Don't Know (but Should)

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Chronic obstructive pulmonary disease (COPD) is associated with pulmonary and systemic inflammation. The latter is likely to contribute significantly to the pathobiology of numerous extrapulmonary effects of the disease—the so-called systemic effects of COPD. The clinical relevance of these systemic effects has been recently recognized; however, many important questions about its pathophysiology remain unanswered. This article reviews what is known about it and, more importantly, highlights what is not (but should be) known in order to stimulate research in this area, in the hope that a better understanding of this field may lead to better treatment options for patients with COPD.

Keywords: chronic bronchitis; chronic obstructive pulmonary disease; emphysema; inflammation

Chronic obstructive pulmonary disease (COPD) has been traditionally understood as a disease of the lungs characterized by chronic airflow obstruction, which, in turn, is due to the presence of specific structural abnormalities of both the airways (bronchitis and bronchiolitis) and the pulmonary parenchyma (emphysema) (1). Much more recently, a number of studies have indicated that these structural abnormalities were associated with an inflammatory reaction of the airways, alveoli, and pulmonary vessels (2). This inflammatory reaction seems to occur in all smokers but, for reasons that are still not clear, it appears to be greatly enhanced in those smokers who develop COPD (3). Furthermore, this abnormal inflammatory reaction can also be detected in the systemic circulation (4). It is likely that this systemic inflammation contributes significantly to the pathobiology of numerous extrapulmonary effects of the disease—the so-called systemic effects of COPD (5, 6). The clinical relevance of these systemic effects has been recognized in the more recent international guidelines for COPD diagnosis and treatment (7). In fact, it is likely that important clinical outcomes, including mortality or health status, eventually result from the interplay between the intrapulmonary and extrapulmonary effects that occur in COPD (Figure 1).

Despite the significant advancement in our understanding of COPD that has occurred over the past decade or so, many important questions about the pathophysiology of the disease remain unanswered. One particular area of interest is systemic inflammation in relation to the extrapulmonary effects that can occur in these patients. The goal of this article is to review the current understanding of this topic, to identify relevant gaps of knowledge

in this field, and to stimulate research in this area with the hope that a better understanding of these mechanisms may lead to better treatment options for patients with COPD (Table 1).

COPD IS ASSOCIATED WITH SYSTEMIC INFLAMMATION

Many different studies performed over the past decade have clearly established that COPD is associated with low-grade systemic inflammation (reviewed in References 5, 8). Gan and co-workers have recently reviewed them all in the form of a meta-analysis (4). That analysis confirmed that patients with stable COPD present increased numbers of leukocytes (some of them with an activated phenotype) (9, 10) and increased levels of acute phase response proteins (C-reactive protein [CRP] and fibrinogen) and cytokines (IL-6) and tumor necrosis factor (TNF)- α (4). The intensity of this systemic inflammation increases during exacerbations of COPD (11–14). Interestingly, other chronic conditions, such as chronic heart failure, obesity, or diabetes, and even the normal process of aging, also appear to be associated with a similar low-grade systemic inflammatory process (15–17).

THE ORIGIN OF SYSTEMIC INFLAMMATION IN COPD IS UNCLEAR

Given that COPD is associated with an abnormal inflammatory response of the lung parenchyma to inhaled pollutant and gases (mostly through cigarette smoking) (7), the most obvious explanation for the presence of systemic inflammation in these patients was that, somehow, this pulmonary inflammation was “spilling over” into the systemic circulation (5). However, several observations do not support this explanation. For instance, Vernooy and colleagues measured the levels of soluble TNF- α (and its receptors) and IL-8 in induced sputum and in plasma of 18 patients with COPD (mean FEV₁, 56% predicted) and could not find any relationship between values in sputum and values in blood (18). More recently, Hurst and colleagues were also unable to find such relationships (19). Overall, therefore, the hypothesis that systemic inflammation in COPD was originating in a form of “spillover” of the pulmonary compartment is not proven.

Other potential origins of systemic inflammation in COPD include smoking, lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction, and the bone marrow. It is well known that, in the absence of COPD, smoking is one important risk factor of cardiovascular disease (albeit, as discussed subsequently here, the presence of COPD increases significantly the risk of cardiovascular disease in smokers) (20). Furthermore, smoking does so through the induction of low-grade systemic inflammation and endothelial dysfunction, even in passive smokers (21). Thus, it is clear that smoking, *per se*, can cause systemic inflammation. However, Vernooy and colleagues found that former smokers also had evidence of systemic inflammation (18), indicating that smoking cannot be the only factor inducing systemic inflammation in

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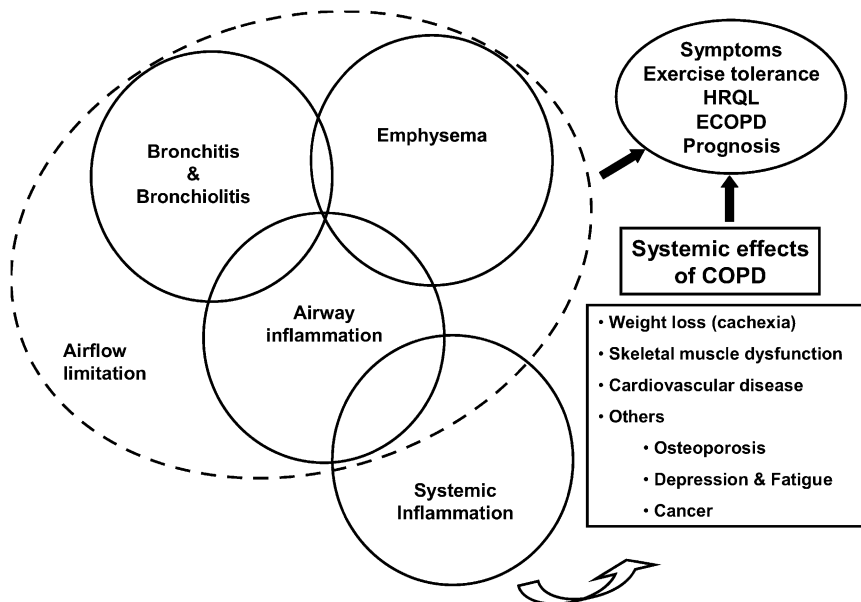


Figure 1. Chronic obstructive pulmonary disease (COPD) can be considered to have several domains, both inside and outside the lungs, that contribute to the physiologic (airflow obstruction) and clinical characteristics of patients. ECOPD = exacerbation of COPD; HRQL = health-related quality of life. Modified from Reference 6.

COPD. The persistence of inflammation after smoking cessation also occurs in the lungs of patients with COPD (3, 22), and has actually raised the possibility that the pathogenesis of COPD may include an autoimmune component (23). If so, this finding may also contribute to explaining systemic inflammation in these patients.

The chronic airflow obstruction that characterizes COPD often leads to increased work of breathing and lung hyperinflation (24). It has been shown that the latter can, in turn, stimulate the production of cytokines from the lungs (25–27). This action is, therefore, another potential mechanism contributing to systemic inflammation in COPD. Importantly, however, if this were the case, systemic inflammation in COPD should be responsive to bronchodilator therapy. In this context, it is worth noting the observation by Casanova and colleagues that lung hyperinflation influences prognosis in COPD very significantly (28).

Other potential sites of origin of systemic inflammation in COPD are the skeletal muscle and the bone marrow. Rabinovitch and colleagues have shown that, contrary to healthy subjects, systemic inflammation increases after muscular exercise in patients with COPD (29). The bone marrow is the production site of inflammatory cells, the release of which is known to be stimulated by smoking and air pollution (30–32). However, whether the bone marrow has specific abnormalities in COPD has not been systematically studied. A very recent investigation by Palange and colleagues, however, showed that circulating hemopoietic progenitors (CD34⁺ cells) were significantly reduced in 18 patients with COPD (mean FEV₁, 48% predicted) as compared with 12 control subjects, and CD34⁺ cell counts correlated with exercise capacity and severity of airflow obstruction (33).

Finally, when considering the origin of systemic inflammation in COPD, two other considerations need to be taken into account. First, the normal aging process is also associated with low-grade systemic inflammation (16, 34, 35), and COPD is an age-related disease (17). Furthermore, smoking has been shown to enhance telomeric loss (a marker of cell aging) (36), and evidence for cell senescence has been recently identified in the lung parenchyma of patients with emphysema (37, 38). All in all, therefore, a better understanding of the mechanisms of lung aging, and their relationship with the pathogenesis of COPD, may be very valuable in this setting. Second, even in subjects with lung function values within the normal range (FEV₁ values above 80% predicted), an inverse linear relationship exists between CRP concentrations and FEV₁ (39). This relationship occurs even in never-smoker subjects, indicating that systemic inflammation may be linked to early perturbations of pulmonary function (39). Whether systemic inflammation precedes or follows changes in lung function requires longitudinal studies.

TABLE 1. SYSTEMIC INFLAMMATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FACTS AND UNKNOWNNS

	Description
Facts	<p>Low-grade systemic inflammation occurs in patients with clinically stable COPD (and in many other chronic diseases, including the physiologic process of aging).</p> <p>In COPD, systemic inflammation persists after quitting smoking and increases during exacerbations of the disease.</p> <p>Steroid therapy (both inhaled and oral) decreases systemic inflammatory markers in patients with stable COPD.</p> <p>The origin of systemic inflammation in COPD is likely to be multifactorial. The identification of the different factors potentially contributing to it and their relative importance needs to be established.</p>
Unknowns	<p>Why systemic (and pulmonary) inflammation persists after quitting smoking is a key question that is so far unanswered.</p> <p>It is likely (but currently unproven) that systemic inflammation contributes to the pathophysiology of many systemic effects of COPD, including skeletal muscle dysfunction, cardiovascular disease, and osteoporosis.</p> <p>The impact on relevant clinical outcomes, such as mortality or health status, of a pharmacologically induced reduction of systemic inflammation in COPD is unproven.</p>

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

SYSTEMIC INFLAMMATION: LIKELY TO HAVE MAJOR CLINICAL IMPACT

Systemic inflammation has been implicated in the pathogenesis of the majority (if not all) of the systemic effects of COPD described to date, including weight loss, skeletal muscle dysfunction, cardiovascular disease, depression, and osteoporosis (5, 20, 40–42).

Unexplained weight loss occurs in about 50% of patients with severe COPD, but it can also be seen in about 10 to 15% of patients with mild to moderate disease (43). It is mostly due to loss of skeletal muscle mass (44) and, whenever it occurs, it highlights poor prognosis (45, 46). Interestingly, its prognostic value is independent of other, more traditional indices, such as FEV₁ or PaO₂ (45). Therefore, weight loss identifies a new systemic domain of COPD that needs to be taken into consideration in the clinical management of patients with COPD. The BODE (body mass index; airflow obstruction; dyspnea; exercise capacity) index, recently proposed by Celli and colleagues as a multidomain approach to better predict prognosis in patients with COPD, is a step forward in this direction (47). Weight loss in COPD is mostly due to skeletal muscle atrophy (5). Furthermore, the remaining muscle mass is often dysfunctional (48). This combination contributes significantly to reduce the exercise capacity (and thus, the health status) of patients with COPD (48). The mechanisms underlying skeletal muscle abnormalities in COPD are not precisely defined, but they are probably multiple and interdependent. Systemic inflammation is a likely contributor. For instance, cytokines, particularly TNF- α , activate the transcription factor nuclear factor (NF)- κ B, up-regulate the inducible form of the nitric oxide synthase, and facilitate the degradation of myosin heavy chains through the ubiquitin-proteasome complex (49). They can also promote apoptosis in skeletal muscle cells, as recently shown to occur in patients with COPD and low body weight (50).

Tobacco smoking is a well-recognized risk factor for both COPD and cardiovascular diseases. It has been recently recognized, however, that the presence of COPD increases the risk of cardiovascular disease among smokers even further (20). The mechanisms for this synergy are still under investigation, but the low-grade, persistent, systemic inflammation that characterizes COPD is likely to contribute significantly to the pathobiology of these cardiovascular abnormalities (20).

Other less well recognized systemic effects of COPD include a surprisingly high prevalence of depression (51) and osteoporosis (52, 53). It is possible that the low-grade, persistent, systemic inflammation described above may also contribute to these disorders (53, 54).

SYSTEMIC INFLAMMATION IN COPD IS TREATABLE

Sin and coworkers showed that, first, the withdrawal of inhaled corticosteroids in patients with COPD increased the plasma levels of CRP, a well-established marker of systemic inflammation (55), by about 30%. Second, they showed that 2 weeks of treatment with inhaled fluticasone (or oral prednisolone) reduced them by about 50% (55). If low-grade, chronic systemic inflammation is relevant in the pathogenesis of many of the systemic effects of COPD described above, then it is likely that the biological effects described by Sin and colleagues may well be clinically relevant. In fact, a retrospective study has suggested that the risk of acute myocardial infarction in patients with COPD was reduced by 32% in those receiving low doses of inhaled steroids (56). The recently published study TORCH (Towards a Revolution in COPD Health) has explored the potential beneficial effect on survival of the combination of salmeterol and fluticasone propionate (vs. placebo) in patients with moderate and severe COPD (57). Strictly speaking, the p value ($p = 0.052$) did not reach the predetermined level of statistical significance ($p < 0.05$). However, this was only after adjusting for the potential effect of the interim analysis performed, and, in absolute terms, there was a 17.5% reduction in the risk of death of in patients receiving the combination of salmeterol and fluticasone propionate. Unfortunately, no measurement of systemic inflammation

was obtained in these subjects, so the interpretation of these results is still open (57).

Other therapies may also be valuable for the treatment of systemic inflammation in COPD. Some of them are well-established therapeutic alternatives (long-term oxygen therapy, rehabilitation) whose effects on this particular domain of the disease have not been systematically studied. Others include novel therapies that are being tested or should be tested in the near future for their potential effects on systemic (and pulmonary) inflammation in these patients. These novel therapies include the use of phosphodiesterase 4 inhibitors (58, 59), angiotensin-converting enzyme inhibitors, and statins (60, 61).

CONCLUSIONS

COPD is a multicomponent disease characterized by pulmonary and systemic inflammation. The origin of the latter is unclear and probably multifactorial. It is likely to be a major contributor to the pathobiology of many (if not all) of the extrapulmonary effects of COPD, including skeletal muscle atrophy and dysfunction and cardiovascular disease. Available evidence suggests that systemic inflammation in COPD can be reduced by steroid therapy (both oral and inhaled). The potential effects of this observation on clinically relevant outcomes in these patients (e.g., mortality, health status) remain to be demonstrated, but open a new avenue to improve the therapy and care of patients with this devastating disease.

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