Systemic Manifestations of COPD

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COPD is characterized primarily by the presence of largely fixed airflow limitation, but there is increasing evidence and acceptance that COPD can no longer be defined as a disease restricted to the lungs. COPD has a much wider impact on health status, and FEV₁ is not just a lung function parameter for grading COPD severity but also a marker of premature death from any cause (Fig 1).¹ COPD is actually the fourth-leading cause of chronic morbidity and mortality worldwide. Mortality from COPD is expected to increase further and to rank at the third position in 2020, after coronary artery disease and stroke.²

According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines, a diagnosis of COPD can be established by a fixed ratio of postbronchodilator FEV₁ and FVC below 0.7 measured by spirometry.³ The spirometric severity is graded according to the percentage of FEV₁ predicted (GOLD stage I-IV). This functional definition, based on airflow limitation, has been used to characterize the disease until now, but a marker of premature death from any cause (Fig 1).¹ COPD is actually the fourth-leading cause of chronic morbidity and mortality worldwide. Mortality from COPD is expected to increase further and to rank at the third position in 2020, after coronary artery disease and stroke.²

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; CRP = C-reactive protein; GOLD = Global Initiative for Chronic Obstructive Lung Disease
cancer, increased arterial stiffness, and osteoporosis.5-10 Furthermore, the knowledge that specific classes of drugs such as selective phosphodiesterase 4 inhibitors positively affect the course of the disease only in specific COPD populations but not in others supports the theory that COPD is a heterogeneous disease that needs tailored therapeutic approaches.11

Patients with COPD exhibit comorbidities related to common risk factors and they are very frequently characterized by impaired physical activity. A common conceptual COPD approach places the diseased lung as the center and generates a widely accepted cause-effect relationship: physical inactivity and clinical consequences due to respiratory limitations favor the generation of comorbidities. Alternatively, the pulmonary manifestations of COPD might be one aspect of expression of a systemic inflammation with several other organic manifestations.12,13 According to this model, systemic inflammation (eg, triggered by physical inactivity or comorbidities) would favor the development of COPD as a syndrome in susceptible subjects. The relevance of this point of view is debatable because it has not been proven and raises a classic chicken and egg question: Is COPD the cause or the consequence of a not yet identified systemic illness?

LOCAL AND SYSTEMIC INFLAMMATION IN COPD

The airflow limitation in COPD results from airway inflammation due to an abnormal response of the lungs to noxious particles or gases.3 In Western countries, smoking is the main risk factor for the development of COPD, and 90% of patients are current or past smokers. Smoking is the most important risk factor not only for COPD but also for many other chronic diseases and certain cancers. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree, and pathologic changes characteristic of COPD are found in the proximal large airways, peripheral small airways, lung parenchyma, and pulmonary vasculature.14 The cellular pattern is quite heterogeneous, and macrophages, neutrophils, T lymphocytes (with a preponderance of the CD8+ subtype), B cells, and mast cells are involved.15

Apart from these local effects, smoking may significantly contribute to or cause systemic inflammation. A stimulation of the hematopoietic system with the release of polymorphonuclear leukocytes, the generation of systemic oxidative stress, an activation of coagulation factors, and a direct effect on the endothelial function of peripheral vessels have been attributed to smoking.16,17 These systemic effects of smoking could explain why patients with COPD often concomitantly display other chronic illnesses such as cardiovascular diseases, or metabolic disorders with or without other risk factors such as arterial hypertension, hyperlipidemia, and obesity.

Patients with COPD, in particular those whose disease is severe or who are experiencing exacerbations, show increased markers of systemic inflammation (Table 1).18-20 In stable COPD, plasma concentrations of C-reactive protein (CRP) are related to mortality in mild-to-moderate, but not in severe, disease stages.21,22 The level of CRP concentration is also related to health status and exercise capacity and seems to be a significant predictor of BMI.23 Independent of smoking status, increased levels of cytokines can be found locally in intercostal muscle biopsy specimens from patients with COPD, suggesting that the upregulation of proinflammatory cytokines might also be involved in respiratory muscle dysfunction.24 Whether this systemic inflammation is the result of a “spill-over” of local inflammation in the lungs, a systemic inflammatory effect that affects multiple organ systems, or is attributable to some comorbid conditions that affect the lungs, remains debatable.12,18,25 The origin of this systemic inflammation in COPD is still unknown and it is unclear whether there is a relationship between pulmonary and systemic inflammation.26

There is growing evidence that local and systemic oxidative stress, apart from systemic inflammation, is present in patients with COPD.37 However, oxidative stress, although related statistically to lung function impairment, might simply be an epiphenomenon because it represents an archetypical reaction to any form of inflammation.

Systemic inflammation is not only present in patients with COPD, but is also a common feature in various other chronic diseases. Elevated levels of inflammatory markers such as CRP and IL-6 were observed in patients with stable coronary artery disease, peripheral arterial disease, and diabetes, compared with individuals without disease.27,28 These conditions have to be taken into account when the causative role of COPD in systemic inflammation is investigated because these diseases often occur together. Systemic inflammation is potentially the common pathway leading to these chronic diseases and might explain the high prevalence of multiple chronic diseases in the same patient. Almost one-half of all people aged ≥ 65 years have at least three chronic medical conditions, and one-fifth have five or more.29 Aging itself is associated with a chronic low-grade inflammatory status and the theory that systemic inflammation is the common driver of chronic diseases would explain the high prevalence of chronic diseases with increasing age.30 This so-called “inflamm-aging” seems to be the consequence of lifelong antigenic exposure leading to genetic modifications. The individual capability of dealing with this inflammatory burden and developing
patients with COPD are at risk of other extrapulmonary disorders, such as peripheral skeletal muscle dysfunction, nutritional abnormalities, and osteoporosis. Large population studies further show that there is an increased prevalence of diabetes among COPD patients and that diabetes is independently associated with reduced lung function. As with all other comorbid conditions, it is not clear whether inflammation triggers metabolic deterioration or (more likely) whether metabolic signals trigger an inflammatory response. COPD is also moderately associated with chronic kidney disease, and moderate to severe COPD stages were independently associated with an increased risk of long-term mortality in patients with peripheral arterial disease and chronic kidney disease (Fig 3). Because not all of these comorbidities can be attributed to smoking alone, other reasons for this association have to be taken into account. The systemic inflammation itself may account for these extrapulmonary manifestations in COPD, but so far the evidence is circumstantial and the exact mechanisms responsible for these associations have not yet been totally elucidated.

The growing evidence that systemic inflammation is a key driver in COPD and is present in many other chronic diseases associated with COPD probably no longer justifies the concept that COPD is a disease restricted to the lungs. The majority of patients with COPD die from cardiovascular disorders or cancer, not respiratory disease. One can distance COPD from the traditional view, which was basically centered on the presence of chronic airflow obstruction, in that it has been proposed that COPD could be considered as part of a "chronic systemic inflammatory syndrome." This approach seems justified, given the associated comorbidities in patients with COPD. Apart from cardiovascular diseases and lung cancer, protective mechanisms seems to modulate individual susceptibility to common causes of morbidity and mortality in elderly people.
severity is clearly dependent on the presence of comorbidities. An overarching approach to diagnosis, assessment of severity, and management of COPD with its associated comorbidities has therefore been propagated recently. Any patient older than 40 years with a positive smoking history (10 pack years), symptoms, and a lung function compatible with COPD should be carefully evaluated for more general disorders associated with chronic systemic inflammation (ie, cardiovascular and metabolic diseases).

Pharmaceuticals are usually developed for individual diseases and targeted toward specific organs. Considering that the comorbidities in COPD range from cardiovascular and metabolic disorders to osteoporosis and depression, each of them requiring its specific therapy, the treatment of patients with COPD would result in polypharmacy and indeed does so in many elderly. Assuming that chronic inflammation is the common mechanism for most of these diseases, therapies directed toward chronic inflammation would theoretically be the “solution.” Taking the systemic inflammatory effects of smoking into account, smoking cessation itself is essential because it not only is the leading cause of COPD, but it also positively affects its associated comorbidities. Smoking cessation is associated with a decrease in the risk of myocardial events, reduces the risk of many types of cancers, and increases bone mineral density in postmenopausal women. Furthermore, stopping smoking has been shown to slow accelerated progression of renal failure in a small group with primary renal disease. Although cigarette smoking is accepted as a risk factor for diabetes, its cessation curiously leads to a higher short-term risk that is partially mediated by weight gain and systemic inflammation.

Implementation in Clinical Daily Routine

Comorbidities and systemic features present in patients with COPD not only have prognostic value but also result in implications for medical treatment. Until now, the pharmacologic treatment of patients with COPD has been centered mainly on the lungs, specifically the bronchi, and is primarily symptomatic. Considering the different aspects in the pathogenesis of COPD and the evidence that treatment of certain comorbidities positively affects the course of the disease itself, treatment modalities may become more complex. The treatment of COPD should no longer be centered only on controlling symptoms and reducing exacerbations, but should also be focused on comorbidities. This is particularly relevant for those comorbidities that are easier to prevent and treat than COPD, thus improving health status and prognosis. Pulmonary rehabilitation seems to address several aspects of this complex disease and might be the only approach to cover the broad spectrum of disease variety (see “Pulmonary Rehabilitation”).

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Pulmonary Rehabilitation

Physical activity is significantly reduced in patients with COPD and gradually declines with higher
About the disease itself, its time course and treatment options, as well as psychosocial support, including smoking cessation and nutritional interventions, are part of a successful rehabilitation program. By taking this holistic approach, pulmonary rehabilitation also addresses the comorbidities associated with COPD and seems to be the only broad therapeutic approach.

**Pharmacologic Interventions**

Until recently, there have been no specific pharmacologic treatments of COPD; the available therapies are “borrowed” from asthma and adapted to COPD, even though the underlying inflammatory pattern in asthma is very different.[^54^] Most of the large clinical trials have shown that the available drugs for COPD do not significantly modify the long-term decline in FEV₁, the hallmark of the disease.[^55,56^] Pharmacologic...
treatment of COPD is therefore still mainly used to decrease symptoms, reduce the rate of exacerbations, and improve exercise tolerance and general health status.

**Bronchodilators and Inhaled Corticosteroids**

Bronchodilators play a central role in the management of patients with COPD and are the mainstay of current pharmacologic treatment. The most commonly used inhaled bronchodilators are β₂-agonists and anticholinergics with variable duration of action. These drugs improve health-related quality of life and reduce exacerbations. Current guidelines recommend treating patients who have moderate to severe COPD with a long-acting bronchodilator. In patients with severe COPD and repeated exacerbations, additional inhaled corticosteroids should be evaluated. Inhaled corticosteroids can decrease local inflammation to some extent in steroid-naïve patients with moderate to severe COPD, but both fluticasone with or without salmeterol and tiotropium failed to reduce CRP or IL-6 levels in the serum of patients with COPD. This observation suggests that available drugs can suppress local lung-specific inflammation but they are not able to prevent systemic inflammation questioning the relevance of a spill-over of inflammatory mediators from the lung into the systemic circulation.

**Statins**

Another approach would be the treatment of systemic diseases associated with COPD. A few observational studies have shown that the treatment of comorbid diseases has some benefit on COPD itself (Table 2). The effect of statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) was analyzed retrospectively in COPD patients with and without concomitant heart disease. A reduced rate of hospitalization due to COPD and reduced total mortality was observed in both groups, whereas the risk of a myocardial infarction was reduced only in a high-risk cardiovascular cohort. The largest benefits occurred with the combination of statins and either ACE inhibitors or ARB. Statin use was also associated independently with improved short- and long-term survival in patients with COPD and peripheral arterial disease (Fig 4). These studies, however, have clear limitations in their methodology; they suggest that statins or ACE inhibitors/ARB might have dual cardiopulmonary properties and might be able to alter the prognosis of patients with COPD, but these findings need to be confirmed in prospective and carefully controlled trials before any conclusions about the management of COPD can be drawn.

It is well known that the effect of statins goes far beyond lowering cholesterol and thereby decreasing mortality from cardiovascular disease and stroke. Statins also show antiinflammatory, antioxidant, and immunomodulatory characteristics. They are able to reduce CRP levels independent of their effect on the low-density lipoprotein cholesterol level and their pleiotropic effect is attributed to the inhibition of the hydroxy-methylglutaryl coenzyme A reductase. Given the increasing evidence that COPD is a systemic inflammatory disease, these pleiotropic effects of statins could explain their positive effects on patients with COPD.
Patients with COPD are at increased risk of coronary artery disease, and β-blockers play a pivotal role in the management of cardiovascular diseases. There is a general reluctance to use these substances in patients with COPD because of an unfounded fear of inducing bronchospasm. A large Cochrane database review revealed that cardioselective β-blockers did not adversely affect the FEV₁ or induce respiratory symptoms compared with placebo, independent of the severity of the COPD. β-blockers also did not affect the FEV₁ response to β₂-agonists. Given the demonstrated efficacy of β-blockers in treating coronary artery disease and congestive heart failure, and the recent evidence that treatment with β-blockers may reduce the risk of exacerbations and improve survival in patients with COPD, the benefit of these medications outweighs the side effects and they should not be withheld from patients with COPD.

**Future Directions**

There is consistent evidence that the understanding of COPD has evolved from a disease limited to the airways to a complex and multicomponent syndrome characterized by pulmonary and systemic inflammation. Chronic diseases, including COPD, share common aspects, and chronic systemic inflammation seems to be one of the linking elements. The origin of this systemic inflammation is still unclear. Because smoking itself induces an inflammatory response and therefore interferes with the postulated systemic inflammatory syndrome in the pathogenesis of COPD, future efforts might be centered on non-smoking COPD phenotypes for a better assessment of the role of inflammation and the associated comorbidities. Because evidence indicates that newer anti-inflammatory pharmacotherapeutics (eg, selective phosphodiesterase 4 inhibitors) are effective in only certain clinical subgroups, the different phenotypes of COPD have to be further elucidated if treatment is to be optimized. Prospective interventional trials should aim to answer the question as to whether the successful treatment of the comorbidities associated with COPD also positively influences the course of the lung disease. Physicians treating patients with COPD have to become aware of this development and need to include the assessment and diagnosis of associated diseases beyond the lungs. Taking extrapulmonary comorbidities into account, the treatment of patients with COPD must become a multidisciplinary approach, and ultimately the development of guidelines directing clinical care must be reflective of these developments moving from an organ-specific to a more holistic approach.

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