

Chapter 2

The Role of Systemic Inflammation in COPD

Kristina L. Bailey, Jadvinder Goraya, and Stephen L. Rennard

Abstract Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with significant extrapulmonary effects. Many of the extrapulmonary effects of COPD are thought to be mediated by systemic inflammation. Local inflammation has always been appreciated as part of the COPD disease process; however, it is becoming clear that the inflammatory response is also systemic. There are multiple theories about the mechanisms driving the systemic inflammation associated with COPD. However, there is no consensus on which theory is correct. The systemic inflammation likely contributes to systemic manifestations of COPD, including cardiovascular disease, lung cancer, weight loss, osteoporosis and diabetes.

Keywords COPD • Extrapulmonary effects • Disease severity • Local inflammation • Lung parenchyma • Cytokines • Systemic • Tumor necrosis alpha • Interleukin • C-reactive proteins

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with significant extrapulmonary effects that may contribute to disease severity in individual patients [1]. Many of the extrapulmonary effects of COPD are believed to be mediated by systemic inflammation. Local inflammation

K.L. Bailey (✉) • J. Goraya • S.L. Rennard
Department of Internal Medicine, Pulmonary, Critical Care, Sleep and Allergy Division,
University of Nebraska Medical Center, Omaha, NE, USA
e-mail: kbailey@unmc.edu; srennard@unmc.edu

of the airways and lung parenchyma has always been acknowledged as part of the COPD disease process; however, it is becoming clear that the inflammatory response is systemic [2].

Many studies demonstrate that there is an increase in inflammatory cytokines not only in the lung, but systemically. There is an increase in tumor necrosis factor alpha (TNF- α) [3] interleukin (IL)-6, and IL-8 [4]. Inflammatory markers such as C-reactive protein (CRP) are also elevated [5]. This chapter will review the origins, clinical consequences, pathogenesis, and the treatment of systemic inflammation in COPD.

Origins of Systemic Inflammation

There are multiple theories about the mechanisms driving the systemic inflammation associated with COPD. There is no consensus on which theory is correct, although it is likely that several mechanisms may contribute.

One proposed mechanism suggests that the inflammatory process originates in the airways and lung parenchyma, then “spills over” into the systemic circulation [6]. One may then assume that the systemic inflammation should directly correlate with pulmonary inflammation. This, however, has not been demonstrated. Specifically, there is no consistent relationship between sputum neutrophil numbers and systemic neutrophil numbers or systemic biomarkers of inflammation such as CRP [7, 8]. Likewise, pulmonary inflammatory cytokine concentrations such as TNF- α and IL-8 do not show a correlation with systemic concentrations [9, 10].

Another proposed mechanism is that systemic inflammation is caused by tobacco smoke. This is an attractive theory because tobacco smoke has been implicated as a cause of other systemic inflammatory diseases such as atherosclerosis and coronary artery disease [11]. Indeed, in passive smoke exposure, there is increased systemic oxidative stress and peripheral vascular endothelial dysfunction [12]. However, multiple studies demonstrate that ex-smokers have evidence of persistent inflammation [9]. This implies that tobacco smoking may initiate inflammation, but does not explain the sustained inflammation seen in COPD.

It is also possible that the pathophysiologic changes that occur in the lung with COPD may lead to systemic inflammation. Processes that have been implicated include hypoxia and hyperinflation. Hypoxia is a common problem in COPD. In patients with mild COPD who undergo hypoxic challenge, there is an increase in serum IL-6 levels [13]. There is also a correlation between serum TNF- α levels and degree of hypoxemia in COPD patients [14]. Likewise, in animal experiments, hypoxia leads to increased TNF- α , macrophage inflammatory protein (MIP)-1 β , and monocyte chemoattractant protein (MCP)-1 MrnA [15]. Hyperinflation is also a common finding in COPD that results from chronic airway obstruction. Dynamic hyperinflation can lead to increases in systemic TNF- α and IL-8 [16], IL-6, and IL-1 β [17]. The presence of dynamic hyperinflation predicts a higher mortality for COPD patients [18].

It has been suggested that the increases in systemic inflammation observed in conjunction with COPD are at least in part due to the normal aging process. COPD is a chronic disease, which progresses very slowly, and the majority of patients are older. Normal aging is associated with increases in low-grade systemic inflammation, including production of cytokines such as IL-6 and TNF- α [19]. There is also an increase in nitric oxide and reactive oxygen species [20]. Aging cannot account for all COPD-related systemic inflammation, as most studies examining COPD include age-matched controls and the systemic inflammation in COPD patients is still greater.

It has been suggested that COPD may trigger the production of systemic inflammatory mediators in other parts of the body such as skeletal muscle and the bone marrow. For instance, compared to healthy controls, patients with COPD have increases in systemic inflammation, including TNF- α production, after exercise [21]. It was initially thought that the source of this inflammation might be the skeletal muscle itself [22]. However, in a well-controlled study, it was shown that the muscular TNF- α in COPD subjects was actually less than that of control subjects [23]. Another possibility is that the bone marrow may be involved in the initiation of systemic inflammation. This is an attractive theory because the bone marrow is the site of production of inflammatory cells. Smoking or air pollution may indirectly stimulate the bone marrow, which results in an accelerated release of mature and immature cells [24].

In summary, there are many theories regarding the origin of systemic inflammation in COPD. The true origin of systemic inflammation is likely to be multifactorial and more research is necessary to identify the different contributory factors and their relative importance.

Consequences of Systemic Inflammation

The systemic inflammation associated with COPD can contribute to the development of other disease states. The systemic manifestations of COPD are widespread and can affect nearly every system in the body. Disease states that are commonly related to the systemic inflammation seen in COPD include: cardiovascular disease, lung cancer, weight loss, osteoporosis, and diabetes.

Cardiovascular Disease

Cardiovascular disease has long been associated with COPD. Smoking is a major risk factor for both diseases, so it is not surprising that many patients with COPD also have cardiovascular disease. In fact, the majority of patients with COPD die from cardiovascular disorders [25, 26]. Although COPD and cardiovascular disease share smoking as a risk factor, there is an increased risk of fatal myocardial infarction,

independent of smoking status, in COPD patients [27]. There is also an increased risk of cardiovascular disease in smokers who develop COPD than in smokers that do not develop COPD [27]. Likewise, those with more severe COPD are also more likely to have cardiovascular disease [28] even when corrected for smoking. These studies suggest that it is not smoking alone that leads to the increased risk of cardiovascular disease. Importantly, having both COPD and cardiovascular disease increases mortality and hospitalizations over either condition separately [29].

The mechanisms for the synergistic interaction between COPD and cardiovascular disease are not well defined. It has been suggested that the chronic low-grade systemic inflammation seen with both diseases may drive both processes.

Lung Cancer

Lung cancer is a common cause of death in patients with COPD. Patients with COPD are four times more likely to develop lung cancer than smokers who have not developed COPD [30]. Smoking cessation does not diminish the risk of developing lung cancer [31]. Even in individuals who have never smoked, there is an increased risk of lung cancer with decreasing lung function and COPD [32].

The mechanism(s) of how COPD increases the risk for lung cancer is not well defined. However, there is emerging evidence that chronic inflammation may play a significant role in the pathogenesis of lung cancer as a tumor promoter. Inflammatory mechanisms have been shown to induce a tumor-promoting effect in lung cancer in mice. In this model, tobacco smoke promotes lung tumorigenesis by triggering IKK β - and JNK1-dependent inflammation [33]. There are also links between NF- κ B and lung cancer, including resistance to chemotherapy and induction of pro-metastatic, pro-angiogenic, and anti-apoptotic genes [34]. Likewise, epidermal growth factor, which promotes epithelial proliferation, is present in higher levels in COPD patients [35].

Weight Loss/Muscle Wasting

Many studies have shown nutritional abnormalities in patients with COPD. These include changes in caloric intake, basal metabolic rate, and body composition [36, 37]. Unexplained weight loss occurs in about 50% of patients with severe COPD, but it also occurs in 10–15% of those with mild to moderate disease [38]. Unexplained weight loss is a poor prognostic indicator in COPD, and is independent of FEV1 or hypoxia [39]. Likewise, malnutrition predicts longer hospitalization and more readmissions after acute exacerbation of COPD [40].

The weight loss seen in COPD is not due to decreased caloric intake. In fact, caloric intake in patients with COPD is often normal or increased [41]. This increase in caloric intake is often not enough to offset the increased basal metabolic rate in COPD [42]. The weight loss seen in COPD, which is likely due to cachexia, does not respond as well to nutritional supplementation as simple malnutrition [43].

However, if body weight is regained, the overall prognosis is improved, despite lack of change in lung function [39].

Skeletal muscle atrophy is the major cause of weight loss in COPD, with fat mass contributing only a small part of the total weight loss [38]. The remaining muscle is often weak [44], contributing to the limited exercise capacity in COPD.

The mechanisms of weight loss and skeletal muscle atrophy are also likely linked to systemic inflammation. There is a correlation between metabolic derangement and increased levels of inflammatory mediators in COPD [45]. TNF- α production is increased in COPD patients with weight loss [46], TNF- α , as well as other inflammatory cytokines, activates NF κ B, which can upregulate inducible nitric oxide synthase (iNOS) and lead to degradation of myosin [47], ultimately resulting in decreased skeletal muscle mass.

Osteoporosis

The prevalence of osteoporosis is very high in patients with COPD. Over half of the patients recruited for the large TORCH (Towards a Revolution in COPD Health) trial had osteopenia or osteoporosis [48]. In patients with severe COPD, the prevalence of osteoporosis goes up to 75%. In this study the use of steroids alone could not explain the high prevalence of osteoporosis in patients with COPD [49].

Osteoporosis adds significant morbidity to COPD. With progressive loss of bone mass, the patient is at high risk for vertebral or hip fractures. Vertebral compression fractures can cause kyphosis, which can result in worsened pulmonary function. Hip fractures cause significant morbidity such as pain, decreased mobility, and even mortality [50].

Osteoporosis associated with COPD is multifactorial in its etiology. It is most commonly seen in individuals who are elderly, are on steroids, have a history of smoking, or have chronic illness [51]. Patients who have moderate-to-severe COPD have nearly all of these clinical features that predispose them to osteoporosis. However, COPD itself may be a risk factor for osteoporosis and this may be related to systemic inflammation. The mechanism through which systemic inflammation leads to increased osteoporosis is very poorly understood. It is known that increased production of pro-inflammatory cytokines such as IL-1, TNF- α , and IL-6 is associated with osteoclastic bone resorption in a number of inflammatory disease states including rheumatoid arthritis [52]. In addition, the inflammatory mediator, circulating MMP-9, has also been related to the presence of osteoporosis in patients with COPD and not to lung function [53].

Diabetes

Type II diabetes is also frequently seen in conjunction with COPD. There is nearly a twofold increase in prevalence of type II diabetes in patients with COPD, even in

those with mild disease [54]. In the Women's Health Study, asthma and COPD were independently associated with an increased risk of type II diabetes [55]. This indicates that chronic airway inflammation may contribute to diabetes pathogenesis. The reason for this association is not yet fully understood, but it likely involves systemic inflammation. It does appear that there is an increase in insulin resistance in patients with COPD compared with healthy subjects. In this study, insulin resistance was related to higher serum IL-6, and TNF- α soluble receptor, suggesting that insulin resistance is related to systemic inflammation [56]. In patients with Type II diabetes, more severe systemic inflammation (elevated levels of TNF- α , fibrinogen, ferritin, and CRP) may be associated with both inadequate glucose control and worsening lung function [57]. Another possible cause of Type II diabetes in patients with COPD could be the use of inhaled steroids. Inhaled corticosteroid use was associated with a 34% increase in the rate of diabetes. The risk was greatest with the highest inhaled corticosteroid doses, equivalent to fluticasone 1,000 μ g per day or more [58].

Pathophysiology of Systemic Inflammation

The systemic inflammation associated with COPD has many different mediators. They include circulating inflammatory cells, inflammatory mediators such as cytokines, oxidative stress, and growth factors.

Circulating Inflammatory Cells

An integral part of systemic inflammatory response is the activation of bone marrow, which results in the release of leukocytes into the circulation [6], including neutrophils, monocytes/macrophages, and lymphocytes. Patients with COPD have various abnormalities in these circulating leukocytes. The abnormalities seen may have effects on organs other than the lung and therefore contribute to the systemic inflammation observed in COPD patients.

Neutrophils

Circulating neutrophils are an important component of host defense in the lung. In patients with COPD, circulating neutrophils do not function normally, which contributes to the systemic inflammatory response. In COPD, neutrophils have an increased chemotactic response, increased ability to digest connective tissue, and increased expression of cell surface adhesion molecules [59].

Although increased numbers of neutrophils are seen in the airway of patients with COPD, this does not necessarily translate to increased numbers of circulating neutrophils compared to healthy nonsmokers. There is, however, an inverse correlation

between FEV_1 and neutrophil numbers in circulation [60]. An inflammatory stimulus can trigger increased production of neutrophils from the bone marrow but also result in increased numbers of neutrophils in the lung parenchyma [61].

One important pathogenic mechanism responsible for abnormal neutrophil function in patients with COPD is that their neutrophils produce more reactive oxygen species (ROS) than smokers with normal lung function, and healthy nonsmokers [59, 62]. Systemic oxidative stress can upregulate the expression of adhesion molecules, facilitating recruitment into the lung [63].

We have a clear understanding that neutrophils play an integral part in the inflammatory response generated in COPD. The lack of differences in neutrophil activation and function among smokers with COPD and nonsmoker healthy subjects suggests that smoke itself is not responsible for this effect. Rather, these abnormalities are characteristic of COPD itself.

Lymphocytes

Lymphocytes play a prominent role in the systemic inflammation seen in patients with COPD. Nonsmoking COPD patients had higher number of CD^{8+} lymphocytes than nonsmoking healthy controls [64]. Studies also demonstrate that a higher CD^{8+} lymphocyte count is associated with both low CD^4/CD^8 ratio and a higher degree of airflow obstruction and lower FEV_1 [64–67]. Whether this abnormality is mirrored in the systemic circulation is unclear. Changes in the circulating lymphocytes are difficult to interpret because they may reflect a recruitment of circulating lymphocytes into the lung.

Current thinking suggests that abnormal lymphocyte regulation has a role in the pathogenesis of COPD. Proposed mechanisms include abnormalities in the apoptosis of T-cells. There is an increase in apoptosis along with an increase in T-cell migration/recruitment and a decrease in airways clearance by defective macrophages [68]. Apoptosis is under the control of Fas proteins, tissue growth factor ($TGF\beta$), and tumor necrosis factor ($TNF\alpha$) [66, 67, 69]. Fas protein belongs to the TNF family and is upregulated upon T-cell activation. The Fas/FasL (ligand) system induces apoptosis and regulates elimination of activated lymphocytes [70]. Higher numbers of CD^{8+} T-cells exhibiting Fas expression have been reported in COPD smokers as compared to healthy smokers and nonsmokers [67]. Similarly, $TNF\alpha$ and $TGF\beta$ have been shown to induce apoptosis in CD^{8+} T-cells in COPD patients [71]. Combined, these studies shed light on possible dysregulation in mechanisms that control apoptosis and may bear some responsibility in the pathogenesis of COPD.

Monocytes/Macrophages

Macrophages play an important role in the inflammatory response responsible for the pathophysiology of COPD. Monocytes circulating in the peripheral blood are recruited into the lungs, where they mature into macrophages. This recruitment is

upregulated in COPD. Monocyte-selective chemokines produced in the lungs are the signal for the migration of monocytes. In particular, macrophage chemotactic protein (MCP-1), a monocyte selective chemokine belonging to the CC chemokine family, is increased in the sputum and BAL of patients with COPD [72]. MCP-1 binds to the chemokine receptor (CCR-2) on the monocytes and mediates recruitment into the airway epithelium and the lung parenchyma. Chemokines from the CXC subfamily have also been shown to act as monocyte chemoattractants via the CXC receptor (CXCR-2). Similar to MCP-1, the CXC chemokine, GRO- α , exists in higher concentration in the sputum and BAL of smokers with COPD compared to healthy smokers and nonsmokers [73]. Interestingly, CXCR-2 expression is not present on all monocytes. Traves et al. postulates that there is upregulation of the recycling of the CXCR-2 receptor only in the COPD population compared to non-smokers and healthy smokers, which could be the reason for increased migration of monocytes in COPD [73].

Under normal circumstances, macrophages have a tissue lifespan of many months. In former smokers, cigarette particulates persist in the alveolar macrophages over 2 years after smoking cessation, indicating that macrophages in smokers persist for abnormally long durations [74]. Expression of anti-apoptotic protein Bcl-X_L and p21^{CIP/WAF1} in smokers could be one mechanism for this prolonged survival [56, 75]. Impaired mucocilliary clearance or inadequate lymphatic drainage may also impair the ability to clear macrophages from the airways in COPD patients.

Inflammatory Mediators

Patients with COPD have elevated levels of circulating cytokines, chemokines, and growth factors in their peripheral circulation. The components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid conditions.

Cytokines

IL-6

IL-6 is increased in the systemic circulation of COPD patients. This is particularly true during acute exacerbations. The downstream effects of elevated levels of IL-6 are not yet clearly defined because of its pleiotrophic effects. It is clear that IL-6 levels track with markers of systemic inflammation. For instance, increased circulating IL-6 has been shown to induce the acute phase reactant CRP production from the liver [76]. Increased IL-6 levels have also been shown to be associated with many of the systemic comorbidities of COPD. Elevated IL-6 may play a role in the development of pulmonary hypertension [77] insulin resistance [56], and osteoporosis [78].

TNF- α

Elevated levels of TNF- α are seen in the sputum of patients with COPD, especially during exacerbations. Many cells make TNF- α , including epithelial cells, T-cells, and mast cells, but the major source is macrophages. Macrophages from patients with COPD produce more TNF- α in vitro than macrophages from normal controls [79]. Elevated TNF- α levels are associated with systemic effects of COPD such as weight loss. Because of this association, TNF- α blocking antibodies, such as infliximab, have been studied as a treatment for COPD. Unfortunately, they have not been able to show any differences in inflammatory markers [80], Chronic Respiratory Questionnaire score, FEV₁, or 6-min walk [81]. There is evidence, however, that etanercept, another TNF- α antagonist, decreases COPD hospitalizations [82].

IL-1 β

IL-1 β is also elevated in the sputum of patients with COPD [83]. IL-1 β activates macrophages to secrete inflammatory cytokines. IL-1 β correlates with disease severity and FEV₁ [83]. It has also been linked to cachexia.

Chemokines

The first chemokine to be discovered in COPD is CXCL-8. Elevated levels of CXCL-8 are found in the sputum, BAL fluid, and the circulation of patients with COPD versus normal smokers and nonsmoking controls. CXCL8 activates CSCL1 (GRO- α) and CXCR2. CXCL-8 and CXCR2 play an important role in neutrophil and monocyte recruitment in COPD.

Growth Factors

Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

GM-CSF is secreted predominantly by macrophages in response to inflammatory stimuli and plays a role in the differentiation and survival of neutrophils. There are increased levels of GM-CSF in the BAL fluid of patients with COPD particularly during exacerbations [84].

Transforming Growth Factor- β (TGF- β)

TGF- β expression is increased in the airway epithelial cells and macrophages of the small airways of patients with COPD [85]. It can induce proliferation of fibroblasts and airway smooth muscle cells. It also can lead to suppression of the regulatory T cells such as Th1, Th2, and Th17 cells [86].

Treatment

Because systemic inflammation can lead to many of the comorbidities associated with COPD, it is important to consider how to best treat systemic inflammation. Although research into how best to treat the systemic inflammation associated with COPD is in its infancy, we do have some information. Some of the therapies we have traditionally used to treat COPD may also have an effect on systemic inflammation. In addition, drugs used to treat the comorbidities of COPD may also may have unexpected positive effects on systemic inflammation.

Inhaled Steroids

A small study of inhaled steroids shows a reduction in CRP levels in COPD patients [87]. However, a much larger controlled trial of high-dose inhaled steroids in COPD patients (TORCH trial) shows no reduction in IL-6 and CRP levels and no reduction in mortality, although these results may have been affected by withdrawal bias [88]. One of the advantages of inhaled corticosteroids is that they are delivered locally to the lung to avoid the systemic side effects of oral steroids. Perhaps it is not surprising then that inhaled steroids have little or no effect on systemic inflammation. Despite this fact, they still have positive effects on the overall care of COPD patients, such as reduced exacerbation frequency, improved health status, and spirometric values [89].

Anticholinergics

It has been suggested that anticholinergics such as tiotropium may have a role in decreasing systemic inflammation. This is because airway epithelial cells and macrophages can release acetylcholine, and this may activate neutrophils and macrophages. Theoretically, by antagonizing this pathway, there is a potential to decrease inflammation. However, in practice, tiotropium has no effect on serum IL-6 and CRP in COPD patients, although it does decrease the number of exacerbations [90].

Exercise/Pulmonary Rehabilitation

Pulmonary rehabilitation improves functional capacity, perception of dyspnea, BODE index, and health care utilization [91]. Because pulmonary rehabilitation has a positive effect on the overall health of COPD patients, one would think it may do so through decreasing systemic inflammation. However, to date, this has not been shown. There is no difference in systemic inflammatory markers such as CRP and IL-6 [92] after pulmonary rehabilitation. In fact, in one study, there was an increase

in production of IL-6 and TNF- α in muscle cells after exercise training [93]. Although there have not been differences in systemic inflammatory markers with pulmonary rehabilitation alone, there may be benefits when combined with nutritional therapy [94]. In this study there was a decrease in CRP, IL-6, IL-8, and TNF α after 12 weeks of low intensity exercise and nutritional supplementation of 400 kcal/day.

Smoking Cessation

Smoking cessation is always recommended for patients with COPD. It not only helps slow the progression of COPD, but also has beneficial effects on comorbidities such as cardiovascular disease and lung cancer. Smoking cessation also leads to decreases in systemic inflammation as measured by CRP [95].

Statins

3-Hydroxy-3-methylglutaryl-coenzyme A (*HMG-CoA*) *reductase* inhibitors, also known as statins, were developed to reduce cholesterol. However, statins are now known to have pleiotropic effects, including anti-inflammatory and immunomodulatory effects that may be important in the treatment of systemic inflammation from COPD.

Statins have been shown to decrease mortality after COPD exacerbation, even in the absence of ischemic heart disease in retrospective studies [96]. This is especially relevant, given the number of COPD patients who also have ischemic heart disease. Statins also decrease the number of COPD exacerbations in retrospective studies [97]. The mechanism(s) through which statins impart their beneficial effects are not completely understood. However, it is likely that at least part of their action is through decreasing systemic inflammation. Statins decrease markers of systemic inflammation such as CRP [98] and chemokines, such as CCL2 and CXCL8 [99].

Statins also may have beneficial effects on the comorbidities of COPD that are mediated by systemic inflammation. Statins are associated with a decreased risk of developing lung cancer in COPD patients [100]. They may also have a beneficial effect on diabetes and osteoporosis [101].

Prospective, randomized, controlled studies are needed to evaluate whether statins have a beneficial effect on the systemic inflammation related to COPD.

Summary

In summary, COPD can no longer be considered a disease only of the lungs. It is associated with systemic effects that are related to systemic inflammation. A better understanding of the origins of systemic inflammation in COPD will allow for better therapy for COPD and improved outcomes.

References

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532–55.
2. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax*. 2004;59(7):574–80.
3. Tanni SE, Pelegrino NR, Angeleli AY, Correa C, Godoy I. Smoking status and tumor necrosis factor- α mediated systemic inflammation in COPD patients. *J Inflamm (Lond)*. 2010;9(7):29.
4. Pinto-Plata VM, Livnat G, Girish M, Cabral H, Masdin P, Linacre P, et al. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest*. 2007;131(1):37–43.
5. Karadag F, Kirdar S, Karul AB, Ceylan E. The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. *Eur J Int Med*. 2008;19(2):104–8.
6. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21(2):347–60.
7. Singh D, Edwards L, Tal-Singer R, Rennard S. Sputum neutrophils as a biomarker in COPD: findings from the ECLIPSE study. *Respir Res*. 2010;11:77.
8. Roy K, Smith J, Kolsum U, Borrill Z, Vestbo J, Singh D. COPD phenotype description using principal components analysis. *Respir Res*. 2009;10:41.
9. Vernooij JH, Kucukaycan M, Jacobs JA, Chavannes NH, Buurman WA, Dentener MA, et al. Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. *Am J Respir Crit Care Med*. 2002;166(9):1218–24.
10. Michel O, Dentener M, Corazza F, Buurman W, Rylander R. Healthy subjects express differences in clinical responses to inhaled lipopolysaccharide that are related with inflammation and with atopy. *J Allergy Clin Immunol*. 2001;107(5):797–804.
11. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685–95.
12. Dietrich M, Block G, Benowitz NL, Morrow JD, Hudes M, 3rd Jacob P, et al. Vitamin C supplementation decreases oxidative stress biomarker f2-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke. *Nutr Cancer*. 2003;45(2):176–84.
13. Sabit R, Thomas P, Shale DJ, Collins P, Linnane SJ. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. *Chest*. 2010;138(1):47–51.
14. Takabatake N, Nakamura H, Abe S, Inoue S, Hino T, Saito H, et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor- α system in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(4 Pt 1):1179–84.
15. Madjdpour C, Jewell UR, Kneller S, Ziegler U, Schwendener R, Booy C, et al. Decreased alveolar oxygen induces lung inflammation. *Am J Physiol Lung Cell Mol Physiol*. 2003;284(2): L360–7.
16. Pini L, Valsecchi A, Boni E, Guerini M, Tantucci C. Acute dynamic hyperinflation and systemic inflammation in stable COPD patients. *Am J Respir Crit Care Med*. 2010;181:A2907.
17. Vassilakopoulos T, Katsaounou P, Karatza MH, Kollintza A, Zakynthinos S, Roussos C. Strenuous resistive breathing induces plasma cytokines: role of antioxidants and monocytes. *Am J Respir Crit Care Med*. 2002;166(12 Pt 1):1572–8.
18. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(6):591–7.
19. Sharma G, Hanania NA, Shim YM. The aging immune system and its relationship to the development of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2009;6(7): 573–80.

20. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest*. 2009;135(1):173–80.
21. Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X, et al. Increased tumour necrosis factor- α plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J*. 2003;21(5):789–94.
22. Montes de Oca M, Torres SH, De Sanctis J, Mata A, Hernandez N, Talamo C. Skeletal muscle inflammation and nitric oxide in patients with COPD. *Eur Respir J*. 2005;26(3):390–7.
23. Barreiro E, Schols AM, Polkey MI, Galdiz JB, Gosker HR, Swallow EB, et al. Cytokine profile in quadriceps muscles of patients with severe COPD. *Thorax*. 2008;63(2):100–7.
24. Terashima T, Wiggs B, English D, Hogg JC, van Eeden SF. The effect of cigarette smoking on the bone marrow. *Am J Respir Crit Care Med*. 1997;155(3):1021–6.
25. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J*. 2003;22(5):809–14.
26. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J*. 2006;27(3):627–43.
27. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc*. 2005;2(1):8–11.
28. Black-Shinn JL, Kinney GL, Wise A, Regan E, Make BJ, Krants M, et al. Cardiovascular disease is associated with COPD severity and reduced functional capacity. *Am J Respir Crit Care Med*. 2010;181:A5918.
29. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J*. 2008;32(4):962–9.
30. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. *Ann Intern Med*. 1987;106(4):512–8.
31. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142(4):233–9.
32. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med*. 2007;176(3):285–90.
33. Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M. Tobacco smoke promotes lung tumorigenesis by triggering IKK β - and JNK1-dependent inflammation. *Cancer Cell*. 2010;17(1):89–97.
34. Dennis PA, Van Waes C, Gutkind JS, Kellar KJ, Vinson C, Mukhin AG, et al. The biology of tobacco and nicotine: bench to bedside. *Cancer Epidemiol Biomarkers Prev*. 2005;14(4):764–7.
35. de Boer WI, Hau CM, van Schadewijk A, Stolk J, van Krieken JH, Hiemstra PS. Expression of epidermal growth factors and their receptors in the bronchial epithelium of subjects with chronic obstructive pulmonary disease. *Am J Clin Pathol*. 2006;125(2):184–92.
36. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(3 Pt 1):745–52.
37. Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. *Clin Chest Med*. 2000;21(4):753–62.
38. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis*. 1993;147(5):1151–6.
39. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(6 Pt 1):1791–7.
40. Giron R, Matesanz C, Garcia-Rio F, de Santiago E, Mancha A, Rodriguez-Salvanes F, et al. Nutritional state during COPD exacerbation: clinical and prognostic implications. *Ann Nutr Metab*. 2009;54(1):52–8.

41. Baarends EM, Schols AM, Pannemans DL, Westerterp KR, Wouters EF. Total free living energy expenditure in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1997;155(2):549–54.
42. Schols AM, Fredrix EW, Soeters PB, Westerterp KR, Wouters EF. Resting energy expenditure in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr*. 1991;54(6):983–7.
43. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. *Chest*. 2000;117(3):672–8.
44. Gosker HR, Kubat B, Schaart G, van der Vusse GJ, Wouters EF, Schols AM. Myopathological features in skeletal muscle of patients with chronic obstructive pulmonary disease. *Eur Respir J*. 2003;22(2):280–5.
45. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax*. 1996;51(8):819–24.
46. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor- α levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1994;150(5 Pt 1):1453–5.
47. Agusti A, Morla M, Sauleda J, Saus C, Busquets X. NF- κ B activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax*. 2004;59(6):483–7.
48. Ferguson GT, Calverley PM, Anderson JA, Jenkins CR, Jones PW, Willits LR, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the towards a revolution in COPD health study. *Chest*. 2009;136(6):1456–65.
49. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med*. 2007;101(1):177–85.
50. Block JE, Stubbs H. Hip fracture-associated mortality reconsidered. *Calcif Tissue Int*. 1997;61(1):84.
51. Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. *JAMA*. 2007;298(20):2389–98.
52. Mundy GR. Osteoporosis and inflammation. *Nutr Rev*. 2007;65(12 Pt 2):S147–51.
53. Bolton CE, Stone MD, Edwards PH, Duckers JM, Evans WD, Shale DJ. Circulating matrix metalloproteinase-9 and osteoporosis in patients with chronic obstructive pulmonary disease. *Chron Respir Dis*. 2009;6(2):81–7.
54. Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, et al. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabet Care*. 2004;27(10):2478–84.
55. Song Y, Klevak A, Manson JE, Buring JE, Liu S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the women's health study. *Diabet Res Clin Pract*. 2010;90(3):365–71.
56. Bolton CE, Evans M, Ionescu AA, Edwards SM, Morris RH, Dunseath G, et al. Insulin resistance and inflammation - a further systemic complication of COPD. *COPD*. 2007;4(2):121–6.
57. Dennis RJ, Maldonado D, Rojas MX, Aschner P, Rondon M, Charry L, et al. Inadequate glucose control in type 2 diabetes is associated with impaired lung function and systemic inflammation: a cross-sectional study. *BMC Pulm Med*. 2010;10:38.
58. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med*. 2010;123(11):1001–6.
59. Noguera A, Batle S, Miralles C, Iglesias J, Busquets X, MacNee W, et al. Enhanced neutrophil response in chronic obstructive pulmonary disease. *Thorax*. 2001;56(6):432–7.
60. Sparrow D, Glynn RJ, Cohen M, Weiss ST. The relationship of the peripheral leukocyte count and cigarette smoking to pulmonary function among adult men. *Chest*. 1984;86(3):383–6.

61. van Eeden SF, Lawrence E, Sato Y, Kitagawa Y, Hogg JC. Neutrophils released from the bone marrow by granulocyte colony-stimulating factor sequester in lung microvessels but are slow to migrate. *Eur Respir J*. 2000;15(6):1079–86.
62. Noguera A, Busquets X, Sauleda J, Villaverde JM, MacNee W, Agusti AG. Expression of adhesion molecules and G proteins in circulating neutrophils in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;158(5 Pt 1):1664–8.
63. Agusti A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc*. 2007;4(7):522–5.
64. de Jong JW, van der Belt-Gritter B, Koeter GH, Postma DS. Peripheral blood lymphocyte cell subsets in subjects with chronic obstructive pulmonary disease: association with smoking, IgE and lung function. *Respir Med*. 1997;91(2):67–76.
65. Kim WD, Kim WS, Koh Y, Lee SD, Lim CM, Kim DS, et al. Abnormal peripheral blood T-lymphocyte subsets in a subgroup of patients with COPD. *Chest*. 2002;122(2):437–44.
66. Hodge SJ, Hodge GL, Reynolds PN, Scicchitano R, Holmes M. Increased production of TGF-beta and apoptosis of T lymphocytes isolated from peripheral blood in COPD. *Am J Physiol Lung Cell Mol Physiol*. 2003;285(2):L492–9.
67. Domagala-Kulawik J, Hoser G, Dabrowska M, Chazan R. Increased proportion of Fas positive CD⁸⁺ cells in peripheral blood of patients with COPD. *Respir Med*. 2007;101(6):1338–43.
68. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J*. 2003;22(4):672–88.
69. Sauleda J, Garcia-Palmer FJ, Gonzalez G, Palou A, Agusti AG. The activity of cytochrome oxidase is increased in circulating lymphocytes of patients with chronic obstructive pulmonary disease, asthma, and chronic arthritis. *Am J Respir Crit Care Med*. 2000;161(1):32–5.
70. Varadhachary AS, Salgame P. CD95 mediated T cell apoptosis and its relevance to immune deviation. *Oncogene*. 1998;17(25):3271–6.
71. Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. *N Engl J Med*. 2000;342(18):1350–8.
72. de Boer WI, Sont JK, van Schadewijk A, Stolk J, van Krieken JH, Hiemstra PS. Monocyte chemoattractant protein 1, interleukin 8, and chronic airways inflammation in COPD. *J Pathol*. 2000;190(5):619–26.
73. Traves SL, Smith SJ, Barnes PJ, Donnelly LE. Specific CXC but not CC chemokines cause elevated monocyte migration in COPD: a role for CXCR2. *J Leukoc Biol*. 2004;76(2):441–50.
74. Marques LJ, Teschler H, Guzman J, Costabel U. Smoker's lung transplanted to a nonsmoker. Long-term detection of smoker's macrophages. *Am J Respir Crit Care Med*. 1997;156(5):1700–2.
75. Tomita K, Caramori G, Lim S, Ito K, Hanazawa T, Oates T, et al. Increased p21(CIP1/WAF1) and B cell lymphoma leukemia-x(L) expression and reduced apoptosis in alveolar macrophages from smokers. *Am J Respir Crit Care Med*. 2002;166(5):724–31.
76. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax*. 2000;55(2):114–20.
77. Chaouat A, Savale L, Chouaid C, Tu L, Sztrymf B, Canuet M, et al. Role for interleukin-6 in COPD-related pulmonary hypertension. *Chest*. 2009;136(3):678–87.
78. Bon JM, Zhang Y, Duncan SR, Pilewski JM, Zaldonis D, Zeevi A, et al. Plasma inflammatory mediators associated with bone metabolism in COPD. *COPD*. 2010;7(3):186–91.
79. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. *Am J Respir Crit Care Med*. 1996;153(2):633–7.
80. Dentener MA, Creutzberg EC, Pennings HJ, Rijkers GT, Mercken E, Wouters EF. Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration*. 2008;76(3):275–82.
81. Rennard SI, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175(9):926–34.

82. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther.* 2008;21(1):234–8.
83. Sapely E, Ahmad A, Bayley D, Newbold P, Snell N, Rugman P, et al. Imbalances between interleukin-1 and tumor necrosis factor agonists and antagonists in stable COPD. *J Clin Immunol.* 2009;29(4):508–16.
84. Balbi B, Bason C, Balleari E, Fiasella F, Pesci A, Ghio R, et al. Increased bronchoalveolar granulocytes and granulocyte/macrophage colony-stimulating factor during exacerbations of chronic bronchitis. *Eur Respir J.* 1997;10(4):846–50.
85. de Boer WI, van Schadewijk A, Sont JK, Sharma HS, Stolk J, Hiemstra PS, et al. Transforming growth factor beta1 and recruitment of macrophages and mast cells in airways in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;158(6):1951–7.
86. Wan YY, Flavell RA. Regulatory T cells, transforming growth factor-beta, and immune suppression. *Proc Am Thorac Soc.* 2007;4(3):271–6.
87. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2004;170(7):760–5.
88. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J.* 2011;5(1):44–9.
89. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007;356(8):775–89.
90. Powrie DJ, Wilkinson TM, Donaldson GC, Jones P, Scrine K, Viel K, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. *Eur Respir J.* 2007;30(3):472–8.
91. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2006;18(4):CD003793.
92. Bolton CE, Broekhuizen R, Ionescu AA, Nixon LS, Wouters EF, Shale DJ, et al. Cellular protein breakdown and systemic inflammation are unaffected by pulmonary rehabilitation in COPD. *Thorax.* 2007;62(2):109–14.
93. Vogiatzis I, Stratakos G, Simoes DC, Terzis G, Georgiadou O, Roussos C, et al. Effects of rehabilitative exercise on peripheral muscle TNFalpha, IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax.* 2007;62(11):950–6.
94. Sugawara K, Takahashi H, Kasai C, Kiyokawa N, Watanabe T, Fujii S, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med.* 2010;104(12):1883–9.
95. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J.* 2005;26(17):1765–73.
96. Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J.* 2007;29(2):279–83.
97. Blamoun AI, Batty GN, DeBari VA, Rashid AO, Sheikh M, Khan MA. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. *Int J Clin Pract.* 2008;62(9):1373–8.
98. Melbye H, Halvorsen DS, Hartz I, Medbo A, Brox J, Eggen AE, et al. Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. *Respir Med.* 2007;101(12):2541–9.
99. Hothersall E, McSharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. *Thorax.* 2006;61(8):729–34.
100. Khurana V, Bejjanki HR, Caldito G, Owens MW. Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. *Chest.* 2007;131(5):1282–8.
101. Paraskevas KI, Tzovaras AA, Briana DD, Mikhailidis DP. Emerging indications for statins: a pluripotent family of agents with several potential applications. *Curr Pharm Des.* 2007;13(35):3622–36.

Chronic Obstructive Pulmonary Disease
Co-Morbidities and Systemic Consequences

Nici, L.; ZuWallack, R. (Eds.)

2012, XII, 288 p., Hardcover

ISBN: 978-1-60761-672-6

A product of Humana Press