Systemic Effects of Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) affects various structural and functional domains in the lungs. It also has significant extrapulmonary effects, the so-called systemic effects of COPD. Weight loss, nutritional abnormalities, and skeletal muscle dysfunction are well-recognized systemic effects of COPD. Other less well-known but potentially important systemic effects include an increased risk of cardiovascular disease and several neurologic and skeletal defects. The mechanisms underlying these systemic effects are unclear, but they are probably interrelated and multifactorial, including inactivity, systemic inflammation, tissue hypoxia and oxidative stress among others. These systemic effects add to the respiratory morbidity produced by the underlying pulmonary disease and should be considered in the clinical assessment as well as the treatment of affected patients.

Keywords: extrapulmonary effects; multicomponent disease; oxidative stress; tissue hypoxia

Chronic obstructive pulmonary disease (COPD) affects various domains of lung structure and function, leading to airflow limitation (1). Besides these pulmonary abnormalities, COPD is also associated with significant effects in distant organs outside the lungs, the so-called systemic effects of COPD (2, 3). This article reviews the types, mechanisms, and clinical implications of these systemic effects. Understanding that COPD is more than a lung disease may open up new opportunities for the clinical management of this devastating condition.

TYPES AND MECHANISMS

Table 1 lists the systemic effects of COPD that have been best described to date. Although the mechanisms underlying these systemic effects are unclear, probably multiple, and likely interrelated, systemic inflammation, tissue hypoxia, oxidative stress, and sedentarism are the most relevant (Table 2).

Nutritional Abnormalities and Weight Loss

Nutritional abnormalities, including alterations in caloric intake, basal metabolic rate, intermediate metabolism, and body composition, are common in COPD (4). Unexplained weight loss occurs in about 50% of patients with severe COPD and chronic respiratory failure, but it can also be seen in about 10 to 15% of patients with mild to moderate disease (5). Loss of skeletal muscle mass is the main cause of weight loss in COPD, with loss of fat mass contributing to a lesser extent (4). Importantly, however, alterations in body composition can occur in COPD in the absence of clinically significant weight loss (4).

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It is unlikely that these abnormalities are due to decreased caloric intake, which does not appear to be prominent in these patients except during episodes of exacerbation of the disease. In contrast, most patients with COPD have an increased basal metabolic rate, which often results in weight loss (4). This increased metabolic rate can, in turn, be due to several different mechanisms, including the increased work of breathing that characterizes the disease (4), drugs that are commonly used in the treatment of COPD (such as β_2 agonists) (6), systemic inflammation (*see below*, Skeletal Muscle Dysfunction) (7), and/or tissue hypoxia (8).

Skeletal Muscle Dysfunction

Skeletal muscle dysfunction is common in patients with COPD (9). It is characterized by specific anatomic changes (e.g., fiber-type composition and atrophy) and functional changes (e.g., strength, endurance, and enzyme activities) and contributes significantly to limited exercise capacity and reduced quality of life (9). The respiratory muscles, in particular the diaphragm, appear to behave quite differently from skeletal muscles in patients with COPD, from both the structural and functional points of view (2, 9). The difference is probably due to the different conditions under which both work in these patients. The skeletal muscles are generally underused, whereas the diaphragm is constantly working against an increased load (10, 11).

The mechanisms of skeletal muscle dysfunction are unclear. Sedentarism, tissue hypoxia, and systemic inflammation are likely to be relevant pathogenic factors. The last of these has been the subject of intense research because cytokines, such as tumor necrosis factor (TNF)-α, and oxidative and nitrosative stress can contribute to protein inactivation and degradation, resulting in dysfunction, atrophy, and apoptosis (12–14). We now know that patients with COPD show increased levels of several circulating cytokines and acute-phase reactants including interleukins 6 and 8, TNF-α, TNF receptors 55 and 75, C-reactive protein, lipopolysaccharide-binding protein, Fas, and Fas ligand (3), as well as evidence of systemic oxidative stress (15, 16). In fact, circulating inflammatory cells appear to be "activated" in patients with COPD. Thus, peripheral blood neutrophils harvested from patients with COPD show enhanced chemotaxis and extracellular proteolysis (17), produce more reactive oxygen species (18), and have enhanced expression of several surface adhesion molecules, particularly Mac-1 (CD11b) (19). Interestingly, Mac-1 upregulation persists during the process of neutrophil apoptosis *in vitro* (20). This may interfere with the normal process of neutrophil clearance from inflamed tissues by macrophages.

Other circulating inflammatory cells are also abnormal in COPD. Sauleda and colleagues reported higher activity of cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain, in circulating lymphocytes in COPD and also in patients with asthma and chronic arthritis (21). Therefore, elevated cytochrome oxidase activity suggests that it may be a nonspecific marker of lymphocyte activation in chronic inflammatory diseases (20).

The origin of this systemic inflammation in COPD is unclear. Apart from smoking itself (22), inflamed pulmonary parenchy-

TABLE 1. SYSTEMIC EFFECTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Nutritional abnormalities and weight loss
• Increased resting energy expenditure
• Abnormal body composition
• Abnormal amino acid metabolism
Skeletal muscle dysfunction
• Loss of muscle mass
• Abnormal structure/function
Other potential systemic effects
• Cardiovascular effects
• Nervous system effects
• Skeletal effects
• Bone marrow effects

Adapted from Agustí and coworkers (2).

TABLE 2. POTENTIAL MECHANISMS OF THE SYSTEMIC EFFECTS DESCRIBED IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Related to COPD itself
• Spillover of pulmonary inflammation/activation of inflammatory cells in the lungs
• Tissue hypoxia (reoxygenation? pH? Pa_{CO_2}?)
• Sedentarism/inactivity due to dyspnea on exertion
Related to the cause(s) of COPD
• Smoking
• Genetic characteristics of the host
Other, as yet unidentified

mal cells are a likely source of proinflammatory mediators that may reach the systemic circulation and/or contribute to the activation of inflammatory cells during their transit through the pulmonary circulation. For instance, de Godoy and associates showed that peripheral blood monocytes harvested from patients with COPD with low body weight produce more TNF-α when stimulated *in vitro* than those obtained from healthy control subjects (23). Finally, exercise can also contribute to systemic inflammation and oxidative stress in patients with COPD (24).

Cardiovascular Effects

COPD increases the risk of cardiovascular disease by two- to threefold (25). Several studies have shown that the endothelial function in COPD is abnormal in both pulmonary (26) and systemic (renal) circulations (27, 28). The mechanisms underlying these abnormalities are also unclear. Of course, tobacco smoking is a shared risk factor for both COPD and cardiovascular disease. Yet, it is possible that other factors may increase the cardiovascular risk of patients with COPD even further. In this respect, many authors agree that the persistent, low-grade, systemic inflammation that occurs in COPD (*see above*) may contribute significantly to the pathobiology of these cardiovascular abnormalities in COPD (25). If so, this may have important therapeutic implications in the management of these patients (*see below*) because antiinflammatory therapy would be beneficial not only for the chronic inflammatory process of their lungs but also for the prevention of cardiovascular disease.

Other Systemic Effects

It is possible that COPD, through the common mechanisms discussed above (namely sedentarism, tissue hypoxia, oxidative stress, and systemic inflammation), may cause other harmful effects in other, extrapulmonary organs. This possibility will have to be explored carefully in future because these mechanisms (or organs) may eventually become relevant therapeutic targets.

Among these other potentially relevant systemic effects of COPD, alterations of the nervous system, bone marrow, and skeletal system appear particularly likely. Various aspects of the nervous system may be abnormal in patients with COPD. The energy metabolism of the brain is altered in these patients (29). Depression is highly prevalent in COPD (30), and it is possible that it bears some relationship to the systemic inflammation that occurs in the disease (31). The autonomic nervous system may also be altered in patients with COPD, particularly those with low body weight (32). The presence of mild chronic anemia has not been formally investigated in COPD, but it has been demonstrated to occur in other chronic conditions, such as chronic heart failure (33). If relevant in COPD, this may contribute to the limited exercise capacity (and muscle function) of these individuals. Finally, the prevalence of osteoporosis is increased in patients with COPD (34, 35). Because proinflammatory cytokines can alter bone metabolism significantly, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD (36).

CLINICAL RELEVANCE AND THERAPEUTIC OPTIONS

The systemic effects reviewed above are likely to have a profound clinical impact on the management of COPD. First, weight loss and skeletal muscle dysfunction clearly limit the exercise capacity of these patients and, therefore, have a direct negative effect on their quality of life. Second, weight loss is a prognostic factor in patients with COPD that, importantly, is independent of other prognostic indicators, such as FEV_1 or Pa_{O_2}, that assess the degree of pulmonary dysfunction (37, 38). In this regard, Schols and colleagues showed that prognosis improved in patients with COPD if body weight could be regained, despite the absence of changes in lung function (37). Thus, weight loss identifies a new systemic domain of COPD not considered by the traditional measures of lung function (39).

These observations indicate, therefore, that in addition to the severity of lung disease, the clinical assessment of patients with COPD should take into consideration the extrapulmonary consequences of COPD, with weight loss being a critical indicator. This new approach underlies the creation of the BODE Index (body mass index [B], the degree of airflow obstruction [O] and functional dyspnea [D], and exercise capacity [E] as assessed by the 6-minute walking test), which has been shown to be better than FEV_1 at predicting the risk of all-cause death and the risk of death from respiratory causes among patients with COPD (39). This multidimensional approach has now been formally recognized in the new COPD guidelines by the American Thoracic Society and the European Respiratory Society (1).

Because the pathogenesis of these systemic effects of COPD is still not well understood, we lack specific therapies for them. However, some recommendations can be made from what is known at present, and some predictions can be anticipated. First, because sedentarism (due to shortness of breath) and tissue hypoxia can play a relevant pathogenic role, it is clear that the minimization of these two consequences of COPD may have a beneficial effect on these systemic effects. In this regard, optimal drug therapy in combination with physical rehabilitation and domiciliary oxygen therapy (when needed) seems advisable (1, 39). Second, because systemic inflammation is likely to play a significant pathogenic role in many of the systemic effects described so far, particularly regarding skeletal muscle dysfunction and cardiovascular disease, appropriate systemic antiinflammatory therapy may also prove helpful. In this context, two reports are worth noting. The first (40), by Sin and coworkers, showed that withdrawal of inhaled corticosteroids increased systemic inflamma-

tion, and that 2 weeks of treatment with inhaled fluticasone reduced it by more than 50%. These effects were maintained after an additional 8 weeks of inhaled fluticasone. If low-grade, chronic, systemic inflammation is relevant in the pathogenesis of cardiovascular disease both in general and in COPD in particular, then these effects may well be clinically relevant.

The second study, by Huiart and coworkers (41), showed a 32% reduction in the risk of acute myocardial infarction in patients with COPD receiving low doses of inhaled steroids. These potentially beneficial antiinflammatory effects of inhaled steroids may not occur with oral steroid therapy, which is known to be associated with well-described, undesirable systemic effects (hypertension, glucose intolerance, and muscle atrophy, to name a few). Finally, although nutritional supplementation may seem a logical option in undernourished patients, a metaanalysis does not support its usefulness (42). It is possible, however, that the combination of more specific nutritional support with effective antiinflammatory therapy (and regular exercise training) may provide different results in future.

The role of more specific therapeutic alternatives needs to be further explored. For instance, it is possible that the use of antibodies directed against TNF-α may be beneficial in these patients, as has already been shown in other chronic inflammatory diseases (43). Inhibitors of the angiotensin-converting enzyme prevent weight loss in patients with chronic heart failure (44), but their usefulness in COPD has not been investigated. The potential role of inducible nitric oxide synthase inhibitors may also merit investigation (45). Finally, it is interesting to note that in the National Emphysema Treatment Trial, the patients who benefited the most (in survival) were those with poor exercise capacity after rehabilitation (46). Because these patients are likely to have skeletal muscle dysfunction, this observation suggests that skeletal muscle dysfunction (and perhaps other systemic effects of COPD) can be ameliorated by removing diseased lung parenchyma. The mechanisms underlying the improvement are unclear but may be related to the removal of a potential site of systemic inflammation and/or to the improvement in oxygen transport that occurs after surgery. These and other possibilities require additional investigation.

CONCLUSION

COPD is associated with numerous and significant systemic effects that impact a wide range of extrapulmonary tissues and organ systems. The clinical management of the disease should address these effects to ensure that significant improvement in both the health status and prognosis of patients with COPD is observed.

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References

1. Celli BR, MacNee W, Agustí AG, Anzueto A, Berg B, Buist AS, Calverley PMA, Chavannes N, Dillard T, Fahy B, *et al.* Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
2. Agustí AGN, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21: 347–360.
3. Gan WQ, Man SFP, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004;59:574–580.
4. Schols AM. Nutrition in chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2000;6:110–115.
5. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FCM, Wouters EFM. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr* 1998;52:396–401.
6. Amoroso P, Wilson SR, Moxham J, Ponte J. Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. *Thorax* 1993;48: 882–885.
7. Pouw EM, Schols AM, Deutz NEP, Wouters EFM. Plasma and muscle amino acid levels in relation to resting energy expenditure and inflammation in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:797–801.
8. Sridhar MK. Why do patients with emphysema lose weight? *Lancet* 1999;345:1190–1191.
9. American Thoracic Society, European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease: a statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159:S1–S40.
10. Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med* 1997;337:1799–1806.
11. Sauleda J, Gea J, Orozco-Levi M, Corominas J, Minguella J, Aguar C, Broquetas J, Agustí AGN. Structure and function relationships of the respiratory muscles. *Eur Respir J* 1998;11:906–911.
12. Li Y-P, Schwartz RJ, Waddell ID, Holloway BR, Reid MB. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-κB activation in response to tumor necrosis factor α. *FASEB J* 1998; 12:871–880.
13. Agustí A, Morlá M, Sauleda J, Saus C, Busquets X. NF-κB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax* 2004;59:483–487.
14. Agustí AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E, Batle S, Busquets X. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166: 485–489.
15. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996; 154:1055–1060.
16. Praticò D, Basili S, Vieri M, Cordova C, Violi F, Fitzgerald GA. Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane $F_{2\alpha}$-III, an index of oxidant stress. *Am J Respir Crit Care Med* 1998;158:1709–1714.
17. Burnett D, Hill SL, Chamba A, Stockley RA. Neutrophils from subjects with chronic obstructive lung disease show enhanced chemotaxis and extracellular proteolysis. *Lancet* 1987;2:1043–1046.
18. Noguera A, Batle S, Miralles C, Iglesias J, Busquets X, MacNee W, Agustí AGN. Enhanced neutrophil response in chronic obstructive pulmonary disease. *Thorax* 2001;56:432–437.
19. Noguera A, Busquets X, Sauleda J, Villaverde JM, MacNee W, Agustí AGN, Santos C. Expression of adhesion molecules and G proteins in circulating neutrophils in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;158:1664–1668.
20. Noguera A, Sala E, Pons AR, Iglesias J, MacNee W, Agustí AGN. Expression of adhesion molecules during apoptosis of circulating neutrophils in COPD. *Chest* 2004;125:1837–1842.
21. Sauleda J, Garcia-Palmer FJ, Gonzalez G, Palou A, Agustí 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;161:32–35.
22. Celermajer DS, Adams MR, Clarkso P, Robinson J, McCredie R, Donald A, Deanfield JE. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. *N Engl J Med* 1996; 334:150–154.
23. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers MR. Elevated TNF-α production by peripheral blood monocytes of weight-losing COPD Patients. *Am J Respir Crit Care Med* 1996;153:633–637.
24. Rabinovich RA, Figueras M, Ardite E, Carbó N, Troosters T, Filella X, Barberà JA, Fernandez-Checa JC, Argilés JM, Roca J. Increased tumour necrosis factor-α plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J* 2003;21:789–794.
25. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514–1519.
26. Dinh-Xuan AT, Higenbottam TW, Clelland CA, Pepke-Zaba J, Cremona G, Butt Y, Large SR, Wells FC, Wallwork J. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991;324:1539–1547.

27. Howes TQ, Deane CR, Levin GE, Baudouin SV, Moxham J. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. *Am J Respir Crit Care Med* 1995;151:378–383.
28. Baudouin SV, Bott J, Ward A, Deane C, Moxham J. Short term effect of oxygen on renal haemodynamics in patients with hypoxaemic chronic obstructive airways disease. *Thorax* 1992;47:550–554.
29. Mathur R, Cox IJ, Oatridge A, Shephard DT, Shaw RJ, Taylor-Robinson SD. Cerebral bioenergetics in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1994–1999.
30. Wagena EJ, Huibers MJH, van Schayck CP. Antidepressants in the treatment of patients with COPD: possible associations between smoking cigarettes, COPD and depression. *Thorax* 2001;56:587–588.
31. Holden RJ, Pakula IS, Mooney PA. An immunological model connecting the pathogenesis of stress, depression and carcinoma. *Med Hypotheses* 1998;51:309–314.
32. Takabatake N, Nakamura H, Minamihaba O, Inage M, Inoue S, Kagaya S, Yamaki M, Tomoike H. A novel pathophysiologic phenomenon in cachexic patients with chronic obstructive pulmonary disease: the relationship between the circadian rhythm of circulating leptin and the very low-frequency component of heart rate variability. *Am J Respir Crit Care Med* 2001;163:1314–1319.
33. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002;39:1780–1786.
34. Incalzi RA, Caradonna P, Ranieri P, Basso S, Fuso L, Pagano F, Ciappi G, Pistelli R. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med* 2000;94:1079–1084.
35. Gross NJ. Extrapulmonary effects of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2001;7:84–92.
36. Engelen MPKJ, Schols AM, Lamers RJS, Wouters EFM. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. *Clin Nutr* 1999;18:275–280.
37. Schols AM, Slangen J, Volovics L, Wouters EFM. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–1797.
38. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856–1861.
39. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
40. Sin DD, Lacy P, Ernest York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:760–765.
41. Huiart L, Ernst P, Ranouil X, Suissa S. Low-dose inhaled corticosteroids and the risk of acute myocardial infarction in COPD. *Eur Respir J* 2005; 25:634–639.
42. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. *Chest* 2000;117:672–678.
43. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–1593.
44. Anker SD, Negassa A, Coats AJS, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077–1083.
45. Agustí A, Morlá M, Sauleda J, Saus C, Busquets X. NF-κB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax* 2004;59:483–487.
46. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.