Chronic Obstructive Pulmonary Disease and Cardiovascular Risk

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Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death in Spain with a population mortality rate of 33 per 100 000 inhabitants that increases to 176 per 100 000 in the population over 75 years of age. COPD is also one of the main causes of morbidity and now ranks among the most costly diseases that health care systems treat in developed countries. The future does not look good, either. Even if current smoking rates are corrected, we can expect the number of deaths due to COPD to double over the next 20 years. In fact, even though mortality due to cardiovascular and cerebrovascular diseases has been shown to be declining, COPD-related deaths increased by 71% between 1966 and 1995.[1-9]

Against this background, we should ask ourselves what COPD patients die from. Unfortunately, that question is not easy to answer given the limited reliability of death records, in which the contribution of COPD is underestimated.[10] While waiting for reports from the TORCH[11] study, which for the first time will analyze such questions carefully, we can speculate that vascular diseases are the main causes of death in COPD patients. A study by Soriano et al[12] based on records in the United Kingdom demonstrated that death came from processes in the respiratory system for 33.8% of patients with COPD, from cancer for 16.1%, and from cardiovascular disease for 24.4%.

COPD is a heterogeneous disorder causing lesions that lead to a variety of changes in the airways or lung parenchyma. For decades the main lines of research have focused on such changes, which are responsible for chronic airflow obstruction. However, clinical manifestations and, possibly, pathogenesis may not depend only on inflammatory and structural changes that take place in the lung. To support this theory, it has been suggested that certain lesions that can be seen in COPD are reflected in hematogenic parameters.[13] Moreover, it is possible to identify systemic manifestations that contribute to modifying disease phenotype, particularly at advanced stages of COPD.[14,15] Although no one disputes the existence of a "systemic component of COPD," there are many questions about its precise role in the course of the disease. Likewise, we know little about the differential mechanisms of pulmonary and systemic inflammatory responses that we can see in smokers who do or do not develop COPD. Nor do we understand how systemic and local pulmonary disorders interact, or how these conditions might contribute to comorbidity.

Atherosclerotic cardiovascular disease continues to be the main cause of death in the Western world and COPD is a significant risk factor for the presentation of acute complications of atherosclerotic processes.[16-18] Even slight airflow reductions are associated with greater risk of ischemic heart disease, stroke, and sudden cardiac death regardless of other risk factors. Even the presence of decreased lung function has been suggested to be a stronger predictor of overall mortality and death related to cardiovascular disease than are other more "popular" risk factors such as serum cholesterol levels.

Inflammation of the arterial wall is now accepted as one of the pathogenic mechanisms implicated in the development, progression, and destabilization of atherogenic processes and, in fact, arteriosclerosis is presently considered an inflammatory disease.[19] One question we have about this new conception of arteriosclerosis concerns the extent to which the systemic component of COPD might participate in the pathogenesis of vascular diseases.

Numerous studies have described elevated levels of a variety of inflammatory mediators in the circulating blood of patients with COPD. Nevertheless, attention has only recently been focused on 2 factors which may be important in the course of disease—fibrinogen and, particularly, C-reactive protein (CRP).[20] CRP, an acute phase reactant produced in the liver in response to interleukin 6, is a cardiovascular disease risk factor both

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in patients with known coronary heart disease and in apparently healthy individuals.[21,22] It is a more powerful predictor than low density lipoprotein cholesterol levels and it has added prognostic information to the Framingham risk score.[23] Nevertheless, recent studies suggest that CRP is not merely a nonspecific marker of inflammation but rather an authentic cardiovascular risk factor that is directly implicated in triggering and destabilizing coronary atherosclerosis, meaning that acute cardiovascular events take place and existing coronary disease progresses rapidly.[24-26] CRP exercises proinflammatory and proatherogenic effects on endothelial cells, upregulating the expression of adhesion molecules (such as intercellular adhesion molecule 1 and vascular adhesion molecule 1) and chemotactic molecules (monocyte chemotactic protein 1, for example). CRP also induces secretion of interleukin 6 and endothelin 1 in endothelium and inhibits the expression and bioavailability of endothelial nitric oxide synthase. It stimulates the release of proinflammatory cytokines like interleukin 1b and tumor necrosis factor α by monocytes, during an important phase in the formation of foam cells—by mediating the opsonization of low density lipoprotein cholesterol for macrophages. Furthermore, it has recently been suggested that the proinflammatory activity of CRP might be mediated at least partially by activation of the signal transduction pathway of the transcription factor nuclear factor κB, and this function has also been linked to the differentiation and survival of endothelial progenitor cells. The proatherogenic effects of CRP are not limited to the endothelium. The proliferation and migration of smooth muscle cells is also increased by the upregulation of angiotensin type 1 receptor expression. The production of free oxygen radicals is also enhanced by CRP, as is endothelial and monocytic response to lipopolysaccharides in the wall of gram-negative bacteria.[27,28]

In a recent study of 6629 subjects, Sin and Man[29] described a relationship between COPD and cardiovascular diseases by way of systemic inflammatory processes in these patients. Unlike other studies of reduced numbers of subjects, this study was of a large series and the authors were able to demonstrate the presence of systemic inflammation even in patients with mild to moderate obstruction (forced expiratory volume in the first second between 50% and 80% of predicted values). Such findings may explain why even slight airflow reductions increase risk of cardiovascular disease morbidity and mortality 2- to 3-fold. Thus, the importance of CRP as a risk factor was underlined, given that the likelihood of cardiac injury doubled when CRP levels were elevated. Plasma fibrinogen can also favor the development of atherosclerosis and its complications by increasing blood viscosity and acting as a cofactor in platelet aggregation.[30] Given that inhaled or oral corticosteroids are effective for reducing plasma CRP concentrations in patients with COPD,[31] these new findings are extremely interesting as they help justify current use of anti-inflammatory drugs and/or open the way for new applications based on observations other than lung function parameters or symptoms alone.

During exacerbations inflammatory phenomena may become accentuated. Chronic infection by gram-negative bacteria or *Chlamydia pneumoniae* may contribute to the inflammatory component of atherosclerosis.[32] These findings, along with the fact that during COPD exacerbations it is possible to demonstrate elevated plasma concentrations of the vasoconstrictor peptide endothelin 1, allow us to speculate about the existence of deteriorated vascular function during these episodes.[33] Moreover, the presence of an increased systemic inflammatory component, greater oxidative stress, and increased plasma fibrinogen concentrations[34] during COPD exacerbations may contribute to the pathogenesis of endothelial dysfunction and, therefore, the development of cardiac and cerebrovascular complications.

To conclude, there are now important indications that COPD is in itself a significant vascular risk factor. Delving deeper into the role of COPD would increase our understanding of the pathogenesis of the disease and its natural history. If the hypothesized relationship is confirmed, not only will we have improved our knowledge of COPD but we will also have started toward new therapeutic approaches that may attenuate the risk of complications and reduce mortality by targeting either the inflammatory component or oxidative stress or both.

REFERENCES

1. Barberà JA, Peces-Barba G, Agustí AGN, et al. Guía clínica para el diagnóstico y el tratamiento de la enfermedad pulmonar obstructiva crónica. Arch Bronconeumol. 2001;37:297-316.
2. Jaén Díaz JI, Castro Mesa C, Gontán García-Salamanca MJ, López de Castro F. Prevalencia y factores de riesgo de EPOC en fumadores y ex fumadores. Arch Bronconeumol. 2003;39:554-8.
3. Conferencia de Consenso sobre EPOC. Arch Bronconeumol. 2003;39 Supl 3:1-47.
4. Izquierdo JL. The burden of COPD in Spain: results from the confronting survey. Respir Med. 2003;97:S61-S9.
5. Escarrabill J. Costes sanitarios de la enfermedad pulmonar obstructiva crónica (EPOC). Arch Bronconeumol. 2003;39:435-6.
6. Izquierdo JL, de Miguel J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. Journal of COPD. 2004;1:215-23.
7. Izquierdo Alonso JL, Jiménez de Castro D. Presente y futuro en el tratamiento de la EPOC. Arch Bronconeumol. 2001;37:34-81.
8. Izquierdo Alonso JL. EPOC y asma. Arch Bronconeumol. 2001;37:1-2.
9. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. Am J Respir Crit Care Med. 2001;163:1256-76.
10. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. Eur Respir J. 2003;22:809-14.
11. The TORCH study group. The TORCH (Towards a Revolution in COPD Health) survival study protocol. Eur Respir J. 2004;24: 206-10.
12. Soriano JB, Vestbo J, Pride NB. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J. 2003;21:559-60.

13. Kim WD, Eidelman D, Izquierdo JL, et al. Centrilobular and panlobular emphysema in smokers. Two distinct morphological and functional entities. Am Rev Respir Dis. 1991;144:1385-90.
14. Gan WQ, Man SF, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59:574-80.
15. Wouters EFM, Creutzberg EC, Schools AM. Systemic effects in COPD. Chest. 2002;121:127S-30S.
16. Schunemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000;118: 656-64.
17. Bang KM, Gergen PJ, Kramer R, et al. The effect of pulmonary impairment on all-cause mortality in a national cohort. Chest. 1993;103:536-40.
18. Hole DJ, Watt GC, Davey-Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ. 1996;313:711-5.
19. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340:115-26.
20. Engstrom G, Lind P, Hedblad B, et al. Lung function and cardiovascular risk: relationship with inflammation-sensitive plasma proteins. Circulation. 2002;106:2555-60.
21. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973-9.
22. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated metaanalyses. BMJ. 2000;321:199-204.
23. Koenig W, Lowel H, Baumert J, et al. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation. 2004;109:1349-53.
24. Arroyo-Espliguero R, Avanzas P, Cosín-Sales J, et al. C-reactive protein elevation and disease activity in patients with coronary heart disease. Eur Heart J. 2004;25:401-8.
25. Arroyo-Espliguero R, Avanzas P, Kaski JC. Enfermedad cardiovascular ateroesclerótica: la utilidad de la proteína C reactiva en la identificación de la placa vulnerable y del paciente vulnerable. Rev Esp Cardiol. 2004;57:375-8.
26. Zouridakis E, Avanzas P, Arroyo-Espliguero R, et al. Markers of inflammation and rapid coronary artery disease progression in patients with stable angina pectoris. Circulation. 2004;110:1747-53.
27. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135-43.
28. Verma S, Li S, Badiwala M, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation. 2002;105:1890-6.
29. Sin DD, Man SF. 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;107:1514-9.
30. Dahl M, Tybjaerg-Hansen A, Vestbo J, et al. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Crit Care Med. 2001;164:1008-11.
31. Sin DD, Lacy P, York E, et al. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170:760-5.
32. Arroyo-Espliguero R, Avanzas P, Jeffery S, et al. CD 14 and toll-like receptor 4: a link between infection and acute coronary events? Heart. 2004;90:983-8.
33. Roland M, Bhowmik A, Sapsford RJ, et al. Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. Thorax. 2001;56:30-5.
34. Wedzicha JA, Seemungal TA, MacCallum PK, et al. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb Haemost. 2000;84:210-5.