COPD and comorbidities

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Chronic obstructive pulmonary disease (COPD) is a common condition affecting 4-9% of the adult population and ranks among the five most prevalent causes of death worldwide[1,2]. COPD is characterized by poorly reversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases, particularly cigarette smoke[3].

It is now recognized that COPD has both local and systemic effects. The exact mechanism of these systemic effects is not known, but is believed to be related to enhanced systemic inflammation and oxidative stress[4]. The origin of systemic inflammation in COPD is unclear but it is likely to be multi-factorial. Potential mechanisms include smoking, "spilling-over" of the pulmonary inflammatory response into the systemic circulation, activation of inflammatory cells during their transit through an inflamed milieu in the lungs, lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction, and/or abnormal bone marrow response[4].

Cigarette smoke does not only cause airway and lung inflammation but also systemic inflammation, systemic oxidative stress and endothelial dysfunction. These effects of smoking may contribute substantially to the development of cardiovascular diseases, metabolic disorders and some cancers induced by smoking in combination with or without other risk factors such as hyperlipidemia, obesity, sedentary life and increased blood pressure. Despite the fact that tobacco smoking is a well recognized risk factor for both COPD and cardiovascular diseases, it has been recently recognized that the latter are more prevalent among smokers who have developed COPD[5].

COPD is also associated with several comorbidities. Traditionally, comorbidity is defined as a disease coexisting with the primary disease of interest. In COPD this definition is slightly problematic since certain coexisting illnesses may be a consequence or may present a causal association with COPD. The most common comorbidities described in association with COPD are hypertension, diabetes, heart failure, ischaemic heart disease, cancer, osteoporosis, depression and anemia. COPD comorbidities should be considered when estimating the social and economic burden of the disease. These comorbid diseases clearly affect health outcomes in COPD[6]. In fact, COPD patients are thought to mainly die of non-respiratory disorders such as cancer or cardiovascular diseases although it is difficult to determine the underlying cause of death among patients with multiple diseases, especially when a common risk factor such as tobacco use is involved. In a

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recent study, it was shown that in COPD patients treated with long-term oxygen therapy, comorbidities were one of the predictors of all-cause and respiratory mortality[7]. Moreover, comorbidities are associated with a higher risk of hospitalization and are one of the strongest predictors of increased cost in COPD[8]. Clinical practice guidelines seem to ignore the fact that most patients with COPD quite often have additional comorbidities. The increased recognition of the role of comorbidities in COPD has made all-cause mortality a paramount end-point for the evaluation of novel therapies. The two recently published large COPD trials, TORCH (TOwards a Revolution in COPD Health) and UPLIFT (Understanding the Potential Long-term Impacts on Function with Tiotropium) are examples of how COPD studies have changed because of comorbidities.

A recent evaluation of the USA National Hospital Discharge Survey analyzed more than 47 million hospital discharges for COPD that occurred in the USA from 1979 to 2001 in adults >25 years of age. The prevalence and in-hospital mortality were greater in hospital discharges with COPD mentioned as a primary or secondary diagnosis versus those that did not mention COPD. Specifically, a higher rate of in-hospital mortality for pneumonia, hypertension, heart failure and thoracic malignancies was associated with a hospital diagnosis of COPD[9].

COPD is an independent risk factor for cardiovascular disease. Strong epidemiological evidence points to reduced FEV_1 as a marker for cardiovascular mortality. In a longitudinal population-based study including patients from the NHANES I it was shown that patients with poor lung function had the highest risk of cardiovascular mortality[10]. This association of decreased lung function and increased cardiovascular mortality is further supported by other studies such as the Copenhagen City Heart Study[11]. The underlying mechanisms linking COPD to atherosclerosis, ischemic heart disease and stroke are not fully elucidated. Persistent systemic low-grade inflammation is believed to be one of the central events leading to plaque formation[12]. Under normal conditions the human endothelium does not support leukocyte adhesion, which is the building block of plaque genesis. However, in an inflammatory state such as COPD, the endothelium overexpresses surface adhesion molecules that allow circulating white blood cells to adhere to damaged endothelial surfaces and accordingly trigger inflammatory reactions[13]. Exaggerated subclinical atherosclerosis has been found in smokers with airflow obstruction compared to control smokers and control non-smokers without airflow obstruction[14]. Impaired vascular reactivity is an important factor in the pathogenesis of cardiovascular disease and endothelial function seems to be significantly impaired in patients with stable COPD[15]. It has been shown that arterial wall stiffness which relates to cardiovascular risk is increased in patients with COPD compared to smoking control subjects and healthy subjects[16]. These findings suggest that COPD may result in endothelial dysfunction which may be a mechanism for the enhanced cardiovascular risk in COPD. Moreover, in another study systemic arterial wall stiffness was associated with emphysema as assessed by CT scanning[17]. Moreover, in a recent study in a Greek cohort of COPD patients without cardiovascular comorbidities, the presence of emphysema in high-resolution CT scans was related to increased systemic oxidative stress and fibrinogen[18]. These findings indicate that mechanisms involved in airway wall destruction and emphysema may also produce increased cardiovascular risk in patients with COPD.

Mortality due to COPD continues to rise, whereas mortality related to cardiovascular disease appears to decline. This is partly due to the widespread use of preventive therapies that have been shown to reduce cardiovascular mortality. Accordingly, a question arises whether appropriate use of such therapies could have a similar impact on COPD mortality. Statin therapy may provide a new therapeutic option in COPD. Statins, which are mainly used as lipid-lowering agents for treatment of metabolic syndrome, have been shown to exert both local lung and systemic anti-inflammatory and antioxidant effects[19]. Statin treatment was associated with a slower rate of decline in FEV_1 in elderly subjects[20]. This was supported by further retrospective studies using large databases that have shown an effect of statins on mortality of COPD patients[21]. Randomized control clinical trials are clearly warranted to assess whether these findings can be confirmed prospectively, thus providing a new treatment for these patients.

Similarly, drugs used to treat respiratory diseases could have beneficial effects in cardiovascular diseases. An intriguing finding raised from a post hoc analysis of the European Respiratory Society study on COPD (EUROSCOP) was that long-term inhaled corticosteroids (ICS) although not effective in reducing the long-term rate of decline in FEV_1, they lowered the incidence of ischemic cardiac events in patients with mild COPD[22]. This finding was further supported by other retrospective database studies[23] clearly showing that ICS may reduce systemic inflammation in patients with COPD.

There is a clear link between COPD and lung cancer

independently of active smoking. There is growing evidence that chronic inflammation may play a salient role in the pathogenesis of lung cancer. At the molecular level, activation of nuclear factor (NF)-kB transcription factor may have major relevance for both cancer and COPD. There are studies suggesting that NF-kB activation in the airways of COPD patients causes chronic inflammation and increases the risk of lung tumour development[24,25]. An analysis of 22-year follow-up data from 5402 participants from the first National Health and Nutrition Examination Survey (NHANES I) including a total of 113 cases of lung cancer revealed an inverse correlation between lung cancer risk and the degree of airflow obstruction[26].

COPD is also associated with osteoporosis in up to 70% of patients, and is related to several underlying mechanisms, including malnutrition, sedentary life, smoking, steroid treatment and systemic inflammation. The prevalence of osteoporosis is increased in more severe disease, and both osteoporosis and osteopenia are invariably present in patients with low body-mass index and fat-free mass[27]. Moreover, COPD has been recently recognized as an independent risk factor for the identification of osteoporosis in men[28].

Anemia has been shown to be an independent risk factor for reduced functional capacity and increased mortality in COPD[29,30]. In a retrospective analysis of hemoglobin levels in a cohort of 683 COPD patients anemia was present in 70% of patients and polycythemia in 6%[31].

Depression represents another frequent comorbidity in COPD patients, especially due to the fact that they often face major physical impairment and chronic dyspnea. Patients with severe disease are in even greater risk of developing depression[32]. The treatment of depression in COPD patients is important, as it further diminishes the functional performance of individual patients and is associated with impaired quality of life[33].

Massive evidence suggests that clinical features of COPD and airflow limitation are poorly correlated, so that a more comprehensive approach is needed. It is clear that prognostic tools that better capture comorbidities demonstrate superior performance that does FEV_1 alone. The BODE index (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) is a multidimensional instrument that was found to predict prognosis of COPD patients better than FEV_1. In fact, the BODE index was more effective in predicting COPD all-cause and respiratory mortality than FEV_1 alone[34]. This indicates that it is important to evaluate globally each individual patient when assessing COPD prognosis, beyond the "gold-standard" FEV_1 measurement. This global assessment definitely includes comorbidities, since they may well interfere in the vicious circle of dyspnea and impaired exercise capacity of COPD patients[35].

The causal relationship of COPD and several comorbidities is not clear. Do comorbidities make patients more susceptible to the consequences of COPD, does COPD increase their susceptibility to these comorbidities, or is it a combination of both? Definitely, more work is needed to establish the potential mechanisms and causal pathways that link comorbidities and COPD.

REFERENCES

1. Pena VS, Miravitlles M, Gabriel R, et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest 2000; 118:981–989.
2. Life in the 21st century: a vision for all. Geneva, Switzerland: World Health Organization, 1998.
3. Rabe KF, Hurd S, Anzueto A. et al. Global strategy for the diagnosis, management and prevention of COPD: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-555.
4. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370:797-99.
5. 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;107:1514–19.
6. Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006;27:627-643.
7. Marti S, Munioz X, Rios J, Morell F, Ferrer J. Body weight and comorbidity predict mortality in COPD patients treated with oxygen therapy. Eur Respir J 2006;27:689-696.
8. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32:962-969.
9. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest 2005;128:2005–2011.
10. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a populationbased study and a systematic review of the literature. Chest 2005; 127:1952–1959.
11. Truelsen T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. Int J Epidemiol 2001;30:145–151.
12. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999;340:115–126.
13. Verma S, Li SH, Badiwala MV, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation 2002;105:1890–1896.

14. Iwamoto H, Yokoyama A, Kitahara Y, et al. Airflow limitation in smokers is associated with subclinical atherosclerosis. Am J Respir Crit Care Med 2009;179:35-40.
15. Eickhoff P, Valipour A, Kiss D, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;178:1211-1218.
16. Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax 2007;
17. Mc Allister DA, Maclay JD, Mills NL, et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;176:1208-1214.
18. Papaioannou AI, Mazioti A, Kiropoulos T, et al. Systemic and airway inflammation and the presence of emphysema in patients with COPD. Respir Med 2010;104:275-282
19. Johnson BA, Iacono AT, Zeevi A, et al. Statin use is associated with improved function and survival of lung allografts. Am J Respir Crit Care Med 2003;167:1271-1278.
20. Alexeeff SE, Litonjua AA, Sparrow D, et al. Statin use reduces decline in lung function: VA Normative Aging Study. Am J Respir Crit Care Med 2007;176:742-747
21. Soyseth V, Brekke PH, Smith P, et al. Statin use is associated with reduced mortality in COPD. Eur Respir J 2007;29:279-283.
22. Lofdahl CG, Postma DS, Pride NB, et al. Possible protection by inhaled budesonide against ischaemic cardiac events in mild COPD. Eur Respir J 2007;29:1115-1119.
23. Huiart L, Ernst P, Ranouil X, et al. Low-dose inhaled corticosteroids and the risk of acute myocardial infarction in COPD. Eur Respir J 2005;25:634-639.
24. Wright JG, Christman JW. The role of nuclear factor kappa B in the pathogenesis of pulmonary diseases: implications for therapy. Am J Respir Med 2003;2:211–219.
25. Mukhopadhyay T, Roth JA, Maxwell SA. Altered expression of the p50 subunit of the NF-kappa B transcription factor complex in non-small cell lung carcinoma. Oncogene 1995; 11:999–1003.
26. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data from the First National Health and Nutrition Examination Survey follow-up. Arch Intern Med 2003;163:1475–1480.
27. Bolton CE, Ionescu AA, Shiels KM, et al. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:1286-1293.
28. Shepherd AJ, Cass AR, Carlson CA, Ray L. Development and internal validation of the male osteoporosis risk estimation score. Ann Fam Med 2007;5:540-546.
29. Similowski T, Agusti A, MacNee W, et al. The potential impact of anaemia of chronic disease in COPD. Eur Respir J 2006;27:390-396.
30. John M, Hoering S, Doehner W, et al. Anemia and inflammation in COPD. Chest 2005;127:825-829.
31. Cote C, Zilberberg MD, Mody SH, et al. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 2007;29:923-929.
32. van Manen JG, Bindels PJ, Dekker FW, et al. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. Thorax 2002;57:412-416.
33. Norwood R. Prevalence and impact of depression in chronic obstructive pulmonary disease patients. Curr Opin Pulm Med 2006;12:113-117.
34. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350:1005–1012.
35. Papaioannou AI, Loukides S, Gourgoulianis KI, Kostikas K. Global assessment of the COPD patient: Time to look beyond FEV1? Respir Med 2009; 103:650-660.