The holistic perspective of chronic obstructive pulmonary disease: doubt some more

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Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating disease characterized by a distinctive inflammatory response of the airways that persists even when smoking has stopped [Willemse *et al.* 2005; Van Der Vaart *et al.* 2004]. With an increasingly recognized number of medical conditions often associated with COPD, the attention of the medical community has been recently shifted to the systemic dimension of the disease. The review article by Nicola Sinden and Robert Stockley in this issue of the Journal [Sinden and Stockley, 2010] offers a comprehensive and thought-provoking update on the topics of COPD comorbidities, their contribution to COPD morbidity and mortality and their integrated management in the context of a systemic syndrome.

The common link between COPD and its comorbidities appears to be systemic inflammation as suggested by the observation of raised circulating levels of tumor necrosis factor (TNF)- α [Takabatake *et al.* 2000] and C-reactive protein (CRP) [Kony *et al.* 2004] in the systemic circulation of COPD patients. Moreover, the level of systemic inflammation increases in parallel with the severity of COPD [Franciosi *et al.* 2006]. However, severity of COPD is also a function of intensity and duration of smoking (the so called ‘pack/years’), which is also significantly associated with systemic inflammation. Therefore, normalization for smoking use is strongly recommended for the correct interpretation of these findings. The reason for the reported low-grade systemic inflammation in COPD is not clear and the

so-called phenomenon of ‘overspill’ of inflammatory mediators generated in the airways entering the systemic circulation is, to date, a hypothesis. Alternatively, the origins of circulating inflammatory markers in smoking-related diseases can be also traced to the endothelium, which becomes metabolically activated upon smoke exposure [Cacciola *et al.* 2007].

If systemic inflammation is strong and prevalent in frank inflammatory disorders, such as rheumatoid arthritis, in COPD the evidence for notable systemic inflammation lacks consistency. The frequently quoted meta-analysis by Gan and colleagues [Gan *et al.* 2004] on this subject matter merely shows a mean difference of 0.6 mg/L for CRP in COPD patients compared to controls. Although statistically significant, it is hard to believe that this is clinically relevant. Moreover, low-grade systemic inflammation could be also resulting from the exposure to cigarette smoke and/or air pollutants.

In contrast to the substantial increases in blood CRP observed in relation to infection, relapse of inflammatory diseases or tissue injury, minor elevations in CRP levels have been recognised as a possible marker of the systemic component of several medical disorders [Ridker, 2001]. This has been aided by the development of assays to measure CRP levels with far greater sensitivity than previous methods (described as high-sensitivity or hs-CRP assays) and has led to a flood of literature investigating CRP levels in healthy and diseased individuals [Ridker, 2004]. Thus, as for

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COPD, in recent years there has been an increasing tendency to associate chronic degenerative (e.g. osteoporosis), inflammatory (e.g. rheumatoid arthritis, systemic lupus erythematosus, vasculitis) and metabolic (e.g. diabetes, obesity, metabolic syndrome) disorders with raised circulating levels of CRP [Pepys and Hirschfield, 2003].

The escalating interest in CRP stems from its role as an important predictive marker for determining risk of cardiovascular mortality and morbidity. This may be particularly relevant for diseases with a systemic inflammatory component and elevated CRP levels including COPD. However, in establishing a connection between COPD, CRP levels and raised cardiovascular mortality and morbidity, it is imperative to consider the prominent role of cigarette smoking.

First of all, cigarette smoking *per se* can induce systemic inflammation and lead to raised CRP. Smoking is known to activate endothelium by a direct toxic effect and consequently trigger generation of circulating inflammatory markers. Moreover, there is evidence that mean CRP levels are significantly higher in smokers than in never-smokers with convincing dose-dependent correlation between CRP and smoking habits [Wannamethee *et al.* 2005; Lowe *et al.* 2001]. One study demonstrated that CRP levels correlated with pack-years of smoking and predict all-cause mortality in patients with mild-to-moderate COPD in the short term, although this prediction becomes weaker with time [Man *et al.* 2006]. However, in patients with moderate-to-very severe COPD, no relationship could be identified between CRP levels and likelihood of survival [De Torres *et al.* 2008].

Most decisively, it should not be ignored that cigarette smoking is the single most important risk factor for cardiovascular mortality and morbidity [Yusuf *et al.* 2004] and that quitting produces a substantial reduction in mortality after myocardial infarction [Wilson *et al.* 2000]. It is, however, surprising that most studies that have examined CRP status in former smokers suggest that levels remain elevated for up to 10 years after smoking cessation, which reflects the fact that the underlying tissue damage caused by smoking takes some time to recover [Yanbaeva *et al.* 2007]. Consequently, measurement of CRP levels in smoking-related conditions may not be that efficient in predicting cardiovascular mortality and morbidity after all. Despite the numerous studies

that describe the use of serum CRP levels as a predictive marker for determining risk of cardiovascular disease (CVD), this observation is in agreement with more recent meta-analyses that appear to downplay the significance of CRP as a prognostic marker [Lowe and Pepys, 2006].

That said, the systemic components of COPD are more likely to be due to the complex phenotypic expression dictated by a common underlying aetiological factor with clear systemic effects: cigarette smoke. It is well known that cigarette smoking harms nearly every system of the human body, thus causing a broad range of diseases, including each and every one of those listed in close association with COPD [Boyle *et al.* 2004]. On the other hand, less importance can be attached to the role of low-grade systemic inflammation. For example, it is unclear from the recent cross-sectional evidence whether the low-grade systemic inflammation reported in COPD has a causal role in COPD-associated comorbidities. Moreover, many frequently associated COPD comorbidities (e.g. CVD, lung cancer, diabetes, rheumatoid arthritis) are known to occur long before the onset of COPD and to be significantly associated with cigarette smoking. In essence, these comorbidities are co-existing with COPD because of the systemic damaging effects of cigarette smoke.

The notion that chronic low-grade systemic inflammation is an integral component of COPD, raises the attractive possibility that anti-inflammatory treatment for the respiratory tract may show benefits to comorbidities in other organ systems and vice versa. The second part of the review article by Sinden and Stockley [2010] is devoted to this debate. Unfortunately, a close scrutiny of the current evidence fails to provide a convincing role for current standard pharmacological treatments for COPD in controlling its associated comorbidities and in reducing the overall risk of cardiovascular mortality. In the TORCH study [Calverley *et al.* 2007], involving more than 6000 patients with COPD, combination therapy of inhaled corticosteroids (ICS) and long-acting β -agonists (LABAs) was reported to marginally (but not significantly) reduce the mortality risk from non-pulmonary causes. Likewise, in the UPLIFT trial [Tashkin *et al.* 2008], a placebo-controlled double-blind study involving 5993 patients with COPD randomized to either add-on tiotropium 18 μ g (a long-acting anticholinergic) or placebo for 4 years, a very modest reduction in mortality

was observed in the tiotropium than the placebo group (14.9% *versus* 16.5%), but the difference was not statistically significant.

Conversely, standard pharmacological treatments for non-pulmonary comorbidities of COPD (in particular those for CVD) have an important role in improving the prognosis of patients with COPD. For example, a number of observational studies suggest that patients with COPD taking statins have lower mortality from COPD exacerbations and lower cardiovascular mortality compared to those not taking statins [Mortensen *et al.* 2009; Soyseth *et al.* 2007]. International guidelines are clear in defining the unequivocal morbidity and mortality benefits of β -blockade in patients with CVD [Dickstein *et al.* 2008], but they are less clear in defining whether, β -blockers should be avoided in patients with COPD. The Euro Heart Failure Survey has convincingly shown that pulmonary disease is the most powerful independent predictor of β -blocker underutilization (odds ratio 0.35) [Komajda *et al.* 2003]. Thus, a broader use of selective β -blockade in patients with COPD and co-existent CVD it is likely to save many lives.

Perhaps, the most effective strategy for an integrated management in the context of a smoking-related systemic syndrome is smoking cessation. Permanent abstinence is known to reduce the risk of morbidity and mortality from COPD and several of its associated comorbidities including lung cancer and CVD [Anthonisen *et al.* 2005; Lightwood and Glantz, 1997; US Department of Health and Human Services, 1990]. Unfortunately, the powerful addictive qualities of nicotine create a huge hurdle, even for those having a sincere desire to quit with approximately 80% of smokers who attempt to quit on their own relapsing within the first month of abstinence [Hughes *et al.* 2004]. Multiple attempts and nicotine-dependence treatment are required to achieve enduring abstinence [Fiore *et al.* 2008].

Conclusion

Although chronic low-grade systemic inflammation is an integral component of COPD, its contribution to the non-pulmonary comorbidities of COPD is unclear. Given that the current evidence comes from a cross-sectional report, a conclusive proof that systemic inflammation is contributing to greater risk of non-pulmonary comorbidities of COPD will not be reached until evidence from large long-term prospective

study normalized for intensity and duration of smoking is obtained.

The recognition of COPD as a complex, multi-component disease with preventable morbidities and mortality, implicates a wider involvement of primary care physicians, internists and geriatricians. They have all the necessary skills to play an important role in the management of systemic and complex diseases requiring an holistic approach, and COPD with its associated non-pulmonary comorbidities is no exception. Through effective application of smoking cessation initiatives and appropriate pharmacotherapy, primary care physicians, internists and geriatricians can make a substantial contribution to achieving improvements in the quality of life of COPD patients, as well as having an impact on the course of the disease and survival outcomes.

Current standard pharmacological treatments for COPD (i.e. bronchodilators and corticosteroids) are largely ineffective not only in controlling the disease and reversing its progression, but also in reducing the overall risk of CVD. Although novel biologic and pharmacologic therapies for COPD that can concurrently target associated comorbidities are presently in clinical development [Morjaria *et al.* 2010], finding more effective ways of helping people to stop smoking will remain the most immediate goals of disease management for some time [Casella *et al.* 2010].

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