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Co-morbid disease in COPD – more than a coincidence

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death worldwide. Its prevalence and mortality are increasing disproportionately among the elderly, women, persons of lower socioeconomic status, and the populations of developing countries (Anthonisen 1988; Borson et al 1998; Andreassen and Vestbo 2003). There is increasing recognition that COPD is a complex disorder, with many associated co-morbidities. The term "co-morbid" has traditionally been interpreted as "a medical condition existing simultaneously but independently with another condition in a patient." However, this does not seem to fit the more recent research on patients with COPD as co-morbid conditions occur more frequently in these patients that would be expected by chance. Such conditions include cardiovascular disease (CVD) (Calverley and Scott 2006), depression (Borson et al 1998), diabetes (Schmidt et al 1999), lung cancer (Omori et al 2006), and osteoporosis (Vogelmeier and Bals 2007). Some of these conditions may be worsened by COPD or complicated by COPD. For instance raised airway glucose concentrations in the airways that may occur in diabetes have been shown to precede an increase of respiratory pathogens (Baker et al 2006) and cardiovascular disease (CVD) is a very common cause of death in patients with COPD (Calverley and Scott 2006).

The paper by Anecchino and colleagues (2007) in this issue adds to the literature on the prevalence of co-morbidities in patients with COPD reporting on a study of the prevalence of COPD and 3 treated co-morbidities: CVD, depression and osteoporosis in Italy. This is an important study as it utilizes data from a large cohort of approximately 123,000 possible COPD patients. Of note is the high proportion (98%) of these patients who had been prescribed at least one "nonrespiratory" drug.

We need however to be cautious in interpreting this data for a number of reasons. Patients in this study were defined as having COPD and the co-morbid conditions by drug treatment rather than having a specific diagnosis. This means the patients studied may have had other respiratory diseases such as asthma and that patients with untreated CVD, depression and osteoporosis are excluded. Unfortunately, the authors chose to report on just three specific co-morbidities, cardiovascular, diabetes and depression. It is hoped that the authors will go on to include other important co-morbidities such as osteoporosis.

There appear to be a number of mechanisms by which co-morbid conditions arise in patients with COPD other than by chance. The first of these is sharing of common risk factors. These include poor socioeconomic status, smoking and age which are clearly risk factor for a large range of conditions. Indeed half of all people aged 65 years or older have been reported to have at least three chronic medical conditions, and a fifth have five or more (Boyd et al 2005). Another mechanism is the increasingly well described systemic effects of COPD (Fabbri and Rabe 2007). This systemic inflammation is now thought to impact on extra-pulmonary organs such the heart and blood vessels as well as the metabolic system. In addition, the effects of COPD increases the risks of other conditions with breathlessness, inactivity, and exacerbations resulting in depression, anxiety, and inactivity with resulting osteoporosis risk and muscle loss. Finally, COPD treatment may in itself increase the risk of other conditions particularly those related to oral steroid usage.

So what are the implications for management? Clearly, patients need a comprehensive assessment identifying and addressing co-morbidities. This should ideally be provided in a comprehensive way rather than a patient with COPD having fragmented care from a broad range of health professionals. This would include addressing common risk factors ie, age, smoking, and poor self-management of the primary chronic disease. Treatments need to be assessed that may address the systemic effects of COPD such the PDE-4 inhibitors and statins (Fabbri and Rabe 2007). Improving specific COPD outcome will improve some of its secondary effects such as depression and immobility. Finally, attempts should be made to minimise iatrogenic effects of COPD treatment particularly oral steroid therapy is clearly important.

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Do chronic obstructive pulmonary disease (COPD) patients that snore have an increased risk of obstructive sleep apnea?

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Obstructive sleep apnea (OSA) affects around 4% of middle-aged men (Young et al 1993). With this high prevalence of OSA and the rising worldwide increase in morbidity and mortality in chronic obstructive pulmonary disease (COPD) (WHO 2000), it is not surprising that research attentions have focused on the overlap between these two highly prevalent conditions with the aim of determining their relationship. A number of studies have investigated the association between OSA and COPD. In patients with COPD, studies have shown that as the depth of sleep increases so there is a reduction in minute ventilation with an increase in upper airway resistance (Ballard et al 1995) with up to 20% patients with severe COPD exhibiting co-existent OSA (Brander et al 1992). Although the Sleep Heart Health Study (Sanders et al 2003) found that OSA prevalence was not increased in mild COPD, undiagnosed airways obstruction can be present in $\geq$10 percent of patients with OSA (Lin and Huang 1992). These observations may simply reflect that the clinical relevance of the overlap between COPD and OSA only become apparent when one or both of these conditions are severe.

In this issue, Krieger and colleagues (2007) report on the respiratory disturbances that occur during sleep in COPD patients with mild airways obstruction. These researchers highlight that the differences in the literature pertaining to the incidence of nocturnal respiratory disturbance in COPD may be a consequence of inadequate techniques previously used to measure these events. Krieger and colleagues (2007) hypothesized that using more detailed measurements, such as measuring the arousal on the electroencephalogram in response to inspiratory flow limitation, or so called respiratory-effort related arousals (RERAs), in addition to standard respiratory measurements, COPD patients with daytime normoxia would have a greater severity of respiratory disturbance during sleep compared with non-COPD patients. However, in contrast to the original hypothesis, the authors showed that in a selected group of well-nourished (mean body mass index [BMI] 31 kg/m^2) COPD patients with mild airways obstruction (mean forced expiratory volume in one second [FEV_1]/forced vital capacity [FVC] 63%), who were referred to a sleep centre to investigate snoring, the severity of respiratory disturbance and nocturnal hypoxemia were similar to patients without airways obstruction. In fact, the COPD patients overall had a tendency to have lower respiratory disturbances during sleep.

Are these data novel and useful? Although not wholly novel, these data identify a number of useful clinical messages. In the group of patients studied, RERA measurements adds little to the standard respiratory measurements of flow and thoraco-abdominal movement, the apnea-hypopnea index (AHI), and so for the majority of cases it is acceptable to use AHI, which is technically less cumbersome to perform.

In addition, COPD patients with mild airways obstruction referred to sleep centers for further investigation of snoring have a similar severity of sleep-disordered breathing as compared with aged and BMI matched controls without COPD. These centres, therefore, can manage these COPD patients in a similar manner to other patients. Finally, the observation by Krieger and colleagues (2007) that the severity of airways obstruction, as evidence by FEV_1/FVC ratio, was inversely related to BMI, but AHI directly related to the severity of airways obstruction is an interesting result. Furthermore, these investigators showed that BMI is less predictive of the variance in AHI in COPD than those without COPD. These findings need some further discussion as body composition demographics in patients with COPD and OSA can be distinctly different. Indeed, it is established that there is a direct relationship between BMI and severity of OSA in patients without COPD such that a change in BMI is associated with change in AHI (Noseda et al 2006). In contrast, although body composition correlates with severe disease in COPD, there is an indirect relationship between body composition and disease severity such that a low BMI predicts poor outcome in COPD (Schols et al 2005). This adds to the complexity of the clinical problem and the results of the current study suggest that the correlations between severity of airways obstruction, BMI and severity of OSA do not necessarily extend to patients with COPD. In patients with COPD, one could predict that as airways obstruction increases so BMI would fall and thus AHI would decrease. However, this has still to be proven as the current study only investigated COPD patient with mild airways obstruction and preserved BMI. Despite AHI having 65% dependence on BMI, AHI had 85% dependence on airways obstruction, suggesting there could be greater relative importance of airways obstruction than body composition in COPD patients. More research comparing nocturnal respiratory disturbances in mild COPD and severe COPD is required, with attention directed on the effect of body composition, severity of OSA and severity of airways obstruction.

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