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EDITORIAL

# Can inhaled steroids mend a broken heart in chronic obstructive pulmonary disease?

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It has been recognised for several decades that individuals with reduced forced expiratory volume in one second ($FEV_1$) are at increased risk of cardiovascular events, including myocardial infarction, stroke and arrhythmias [1–3]. Since reduced $FEV_1$ and cardiovascular disease often share a common risk factor, cigarette smoking, many had ascribed the above relationship to the confounding effects of smoking. However, a closer examination of the epidemiological data reveals some salient but subtle features that suggest a far more complex reality. First, many of the large epidemiologic studies, which established reduced $FEV_1$ as a risk factor for cardiovascular events, had carefully controlled for the effects of cigarette smoking using sophisticated and well-accepted statistical methods and had excluded at baseline those individuals with overt cardiovascular disease [4]. Secondly, these studies demonstrated that even among life-time nonsmokers, reduced $FEV_1$ was a determinant of cardiovascular disease [3, 5, 6]. Thirdly, the relationship was dose-dependent, such that individuals with the most severe reduction in $FEV_1$ had the highest risk of cardiovascular events, while those with the least amount of impairment in $FEV_1$ had the lowest risk regardless of the smoking status [4]. Taken together, these data indicated that the relationship between reduced $FEV_1$ and cardiovascular disease could not be entirely explained by the effects of cigarette smoking; they implied other causative pathways.

Two decades of epidemiological research have also revealed that the contribution of reduced $FEV_1$ to cardiovascular events is nontrivial. In fact, it is quite large. In one population-based study, HOLE *et al.* [3] showed when the lowest quintile of $FEV_1$ (<73–75% of predicted) was compared with the highest quintile, the population-attributable risk for deaths related to ischemic heart disease was 26% in males and 24% in females, independent of the burden imposed by cigarette smoking. In other words, in this study, reduced $FEV_1$ may have been responsible for at least 24–26% of all deaths related to ischemic heart disease. Remarkably, the magnitude of the cardiovascular mortality burden attributed to reduced $FEV_1$ was similar to that imposed by hypercholesterolemia, which had a population attributable risk of ~21–25% [3].

Other studies have shown that in addition to baseline $FEV_1$, rapid decline in $FEV_1$, a hallmark of chronic obstructive pulmonary disease (COPD), is another risk factor for cardiovascular events. In the Malmo ''Men Born in 1914'' Study, for instance, the cardiovascular event rate among smokers in the high, middle and low thirds with regard to the decline in $FEV_1$ was 56.0, 41.0 and 22.7 events, respectively, per 1,000 person-yrs (p-value for trend=0.01) [7]. In the Baltimore Longitudinal Study of Aging Study, individuals who experienced the most rapid decline in $FEV_1$ over a 16-yr follow-up, were three to five times more likely to die from a cardiac cause of death than those who had the slowest decline in $FEV_1$, after adjustments for age, baseline $FEV_1$, smoking status, hypertension status, body mass index, and mean serum cholesterol level [8]. Even among lifetime nonsmokers, accelerated decline in $FEV_1$ was associated with a 5–10-fold increase in risk for cardiac death, which suggests that the relationship between changes in $FEV_1$ and cardiovascular events occurs independently of the effects of smoking.

In established COPD, the relationship between reduced $FEV_1$ and cardiovascular events is also evident. During the initial 5-yr follow-up of the Lung Health Study, which studied 5,887 individuals with mild-to-moderate COPD, cardiovascular event was the principal cause of death in 25% of the decedents and accounted for 42% of the first hospitalisations and 48% of the second hospitalisations [9]. The rate of hospitalisation for lower respiratory tract infection was only one-third of that for cardiovascular illnesses. For every 10% decrease in $FEV_1$, cardiovascular mortality increased by 28%, and nonfatal coronary events increased by almost 20%, after adjustments for relevant confounders such age, sex, smoking status and treatment assignment [9]. These and several other studies provide solid evidence that pulmonary disorders, such as COPD, contribute significantly to cardiovascular morbidity and mortality and therapies that can mitigate cardiovascular events in COPD may have important implications for the management of COPD patients.

In this issue of the *European Respiratory Journal*, HUIART *et al.* [10] report some promising data on the use of inhaled corticosteroids to possibly lower the incidence of myocardial infarction in COPD. They studied 371 cases and 1,864 control subjects in 1990–1997 and found that users of inhaled corticosteroids had a nonsignificant 18% reduction in the risk for acute myocardial infarction. Most of the beneficial signal came from a subgroup that used on average 50–200 ug per day of inhaled beclomethasone or equivalent. Remarkably, this subgroup experienced a 32% relative reduction in the risk for acute myocardial infarction ($p<0.05$). However, this study failed to find a dose–response relationship, as one would hope to see in a biological system [11]. The obvious strengths of this

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study are the large sample size, the population-based approach to patient sampling and the likely complete ascertainment of acute myocardial infarction events in the cohort. However, this study was not a randomised controlled trial and contains all the major shortcomings of observational studies [12], which invariably lead to the question, ''are the results valid or are they confounded?''. Additionally, the databases used by the authors did not contain $FEV_1$ data or smoking history. *In lieu* of this, the authors used receipt of anti-COPD medications to define COPD, making the case definition of COPD problematic. For these and other reasons, observational studies such as this one cannot be considered definitive and should not cause us to change our therapeutic approach in managing patients with COPD [12].

The real merit of this study is that it challenges us to consider the effects of inhaled corticosteroids beyond the traditional limits of the pulmonary system. Corticosteroids are potent but nonspecific anti-inflammatory agents. As such, when given as an aerosol, they broadly down-regulate the inflammatory process in the airways [13]. If the nidus of the systemic inflammation, which is commonly observed in patients with established COPD [14], is airway inflammation, it is possible that by down-regulating airway inflammation, systemic inflammation may also be mitigated by inhaled corticosteroids. Consistent with this notion, PINTO-PLATA *et al.* [15] reported that circulating C-reactive protein (CRP) levels, a measure for systemic inflammation, were ~20% lower among patients with COPD who used inhaled corticosteroids, compared with those who did not. Similarly, we found among 41 patients with COPD that withdrawal of inhaled corticosteroids increased serum CRP levels by ~71%, while 2 weeks on inhaled fluticasone reduced CRP levels by ~50% [16]. Inhaled fluticasone also significantly reduced serum interleukin-6 levels by 26%. If these initial observations can be corroborated by other studies, down-regulation of systemic inflammation may be one potential pathway by which inhaled corticosteroids can confer beneficial effects on the cardiovascular system. This is plausible because systemic inflammation is an important cofactor in the genesis of atherosclerosis and plaque rupture [17] and certain therapies that attenuate systemic inflammation improve cardiovascular outcomes [18, 19].

However, before accepting the notion that inhaled corticosteroids can ''mend a broken heart'', more animal and clinical studies are needed to better understand the mechanistic and epidemiologic link between steroid therapy and cardiovascular disease in chronic obstructive pulmonary disease. Observational studies such as this one by HUIART *et al.* [10] are best used to generate new hypotheses. To this end, the current study has further added to the call for more research in this and other new and exciting areas of research in chronic obstructive pulmonary disease.

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