Systemic inflammation in COPD

Skeletal muscle weakness, reduced exercise tolerance, and COPD: is systemic inflammation the missing link?

D D Sin, S F P Man

Systemic inflammation may be the “missing link” between airway dysfunction and the extrapulmonary manifestations of COPD

There is a growing recognition that chronic obstructive pulmonary disease (COPD) is a condition that involves multiple organs and systems. In addition to emphysema and airway inflammation and remodelling, COPD is associated with various local and systemic complications including cachexia, weight loss, osteoporosis, muscle wasting, heart failure, atherosclerosis, dementia, depression, and cancer. Strikingly, these extrapulmonary manifestations of COPD account for the vast majority of morbidity and mortality in COPD patients. Treatments that modify these complications may improve survival in patients with COPD, whereas treatments that exclusively target the airways generally do not.

SKELETAL MUSCLE DYSFUNCTION

One of the important extrapulmonary manifestations of COPD is skeletal muscle dysfunction and wasting. With increasing severity of disease, patients with COPD lose muscle bulk, especially in their thighs and upper arms. Over time, these patients lose exercise endurance and complain of fatigue and immobility. Not surprisingly, skeletal muscle dysfunction contributes to reduced health status of patients with COPD and substantially increases the risk of mortality, independent of traditional markers of COPD mortality such as baseline lung function, age, and cigarette smoking. Encouragingly, early interventions with exercise programmes may restore some of the lost health status related to muscle dysfunction and increase patients’ exercise tolerance and stamina.

Despite the importance of skeletal muscle performance in COPD morbidity and mortality, the pathophysiological mechanisms responsible for the muscle failure remain largely a mystery. Clearly, with advancing disease, skeletal muscle mass decreases in COPD. Biopsy analyses from quadriceps and elsewhere reveal a significant reduction in type I fibres and a relative increase in type II fibres compared with normal individuals, which probably contributes to the increased fatigability and reduced muscle endurance observed in COPD patients. Microscopically, these skeletal muscles show accelerated apoptosis, increased oxidative stress and inflammatory changes, raising the possibility that local inflammatory and oxidative milieu may be responsible for the pathological and physiological changes in the skeletal muscles in patients with COPD.

SYSTEMIC INFLAMMATION

Three papers published in this issue of Thorax raise another intriguing possibility. There is now a large body of data that shows that systemic inflammation exists in stable COPD and that the intensity of the inflammatory process relates to the severity of the underlying disease. The systemic inflammatory process has been linked with adverse cardiovascular outcomes (including sudden deaths, arrhythmias, strokes, and myocardial infarction) and excess mortality, independent of confounding factors such as age and smoking. These three papers indicate that systemic inflammation in COPD is a risk factor for peripheral muscle weakness, diminished workload, and reduced exercise tolerance. Although the studies were performed by three different groups using vastly different cohorts and different methodologies, the results are strikingly similar and coherent.

In the study by Yende and colleagues, they found that serum CRP levels were inversely related to the distance achieved in the 6 minute walk test, independent of other factors such as age, sex, and smoking history. In their cohort, 60% of the COPD patients were taking inhaled corticosteroids at the time of assessment. They found that users of inhaled corticosteroids had serum CRP levels that were on average about 40% lower than those of corticosteroid non-users. Adjustments for potential confounders made no material impact on these results since the two groups were well balanced in terms of age, sex distribution, baseline FEV1, and smoking history. These data suggest that inhaled corticosteroids may down-regulate systemic inflammation in
IMPLICATIONS OF THESE STUDIES

Collectively, what do these studies teach us about systemic inflammation, muscle function, and exercise performance in patients with COPD? Firstly, systemic inflammation, as measured by either CRP or IL-6 levels, is associated with reduced FEV₁. In fig 1 we summarised the relationship between mean CRP levels and the mean FEV₁ reported in the three papers. A clear (inverse) linear relationship can be seen between FEV₁ and CRP, highlighting the likely importance of systemic inflammation in the progression of COPD. Secondly, systemic inflammation is associated with reduced muscle strength, exercise tolerance, and health status in COPD patients. Thirdly, inhaled corticosteroids, which downregulate airway inflammation, may also modulate systemic inflammation in COPD. This observation provides one plausible (but not yet proven) mechanism by which these medications improve health status and other outcomes in patients with COPD.²⁷

There are, however, several important limitations to these studies that must be taken into consideration. Firstly, although the studies were well performed using validated methodologies in well characterised cohorts, they were cross sectional in design so the temporality of the relationships is uncertain. For instance, while it is tempting to ascribe systemic inflammation to muscle dysfunction, it is possible that muscle dysfunction (and perhaps the local oxidative stress and the inflammatory load within muscles) can promote systemic inflammation. The sepsis model argues in favour of systemic inflammation causing skeletal muscle dysfunction rather than the other way around.²³ Moreover, there are excellent experimental models including those from transgenic mice which show that systemic inflammatory mediators and, in particular, tumour necrosis factor (TNF) can promote proteasomal degradation and catabolism of muscle fibres, probably through nuclear factor-κB mediated pathways.²⁴ Similarly, IL-6 inhibits the secretion of insulin-like growth factor 1 (IGF-1) and its biological activity. IGF-1 is an important modulator of muscle mass and function not only during the developmental period but across the entire life span.²⁵²⁶

Secondly, despite the compelling logic regarding the effects of systemic inflammation on muscle dysfunction/wasting and exercise tolerance in COPD, we cannot assume that anti-inflammatory medications will necessarily improve health outcomes in COPD. An important lesson was learned with chronic heart failure (CHF). Analogous to COPD, muscle wasting and dysfunction are common findings in advanced CHF.²⁷ The skeletal muscles of patients with CHF, similar to COPD patients, have increased expression of TNF, IL-6 and other inflammatory cytokines and, systemically, these cytokines are increased compared with healthy controls.²⁷ There are now at least three published randomised controlled trials of anti-TNF treatments (etanercept and infliximab) in CHF. Although these treatments reduce serum CRP, IL-6 and TNF levels, they confer no measurable benefits for the patients. Two studies were terminated prematurely because of futility,²⁸ and the one remaining study showed an increased risk of death and number of hospital admissions for heart failure in patients randomised to infliximab compared with placebo.²⁹ These data are a sobering reminder of the enormous complexity of the inflammatory cascades and networks involved in chronic diseases such as CHF and COPD.

Notwithstanding, the three papers in this issue of Thorax have made important contributions to our current understanding of COPD. Collectively, they have extended our concept of COPD beyond the pulmonary system, provided a solid clinical and epidemiological rationale for linking systemic inflammation with peripheral muscle dysfunction, and raised the possibility of using anti-inflammatory treatment to mitigate systemic inflammation in the hope of improving health outcomes in these patients. Systemic inflammation may well be the “missing link” between airway dysfunction and the extrapulmonary manifestations in COPD. However, we should be mindful of the enormous complexity and intricacies of the inflammatory pathways in COPD. Future research in this area will undoubtedly shed more light on this matter and also raise more questions.


Authors’ affiliations

D D Sin, S F P Man, James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, St Paul’s Hospital and The Department of Medicine (Division of Respiratory), University of British Columbia, Vancouver, BC, Canada

Correspondence to: Dr D D Sin, James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, St Paul’s Hospital, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada; dsin@mlh.ubc.ca

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ASSOCIATION BETWEEN SIBSHIP SIZE/BIRTH ORDER AND ALLERGIC DISEASE

In this issue of Thorax, Kinra et al provide an historical perspective on the associations between allergic disease and sibship size/birth order. Their population comprised 14 000 students, predominantly male and about 50% of those eligible, who were screened at Glasgow University between 1948 and 1968. The students had a mean age of 19 years and were born between 1918 and 1952; for the purposes of this analysis, they were divided into three equally spaced birth cohorts. Intriguingly, there was no increase in the prevalence of self-reported allergic disease across the time frame of the three cohorts, although it is difficult to judge how representative this finding might be. The authors found clearly decreasing trends in reported allergic disease in at least 30 studies and usefulness reviewed by Karmaus and Bottecza. As with most of the diseases reported above, these observations have generally been attributed to different rates and timings of early (unspecified) childhood infection. Indeed, they form the cornerstone of the “hygiene hypothesis” whereby it is proposed that the risks of atopic disease are reduced by early contact with infection,1 a proposal bolstered by the recent suggestion that children born to Alpine farmers are protected in a similar manner.

Further debate on the explanation for the association between sibship size/birth order and childhood allergic disease

O of the 10 plagues visited on the biblical Egyptians, the last was the most terrible; after the rain of frogs, the plague of boils, and the hailstorms came the indiscriminate slaughter of all firstborn animals including children. Infanticide of this degree is thankfully rare—but is it possible that the author(s) of Exodus were expressing a subtler truth?

ASSOCIATIONS BETWEEN BIRTH ORDER/SIBSHIPS AND DISEASE

Studies of birth order—or sibship size—as a risk factor have a long history and have examined a wide variety of diseases. Thus, for example, the rates of Hodgkin’s lymphoma in young adults, acute lymphoblastic leukaemia, and type 1 diabetes mellitus all appear to fall with increasing birth order. In each case the pattern has been assumed to reflect the relatively late age at which children of low birth order (or their mothers during pregnancy) acquire common infections. A similar (but opposite) reasoning has been applied to the observations that children of low birth order are at reduced risks of non-Hodgkin’s lymphoma,11 schizophrenia,12 gastric carcinoma and ulcer,13 acute myeloblastic leukaemia,14 and some congenital heart defects.15 Children of low birth order are also more likely to have infantile pyloric stenosis, to be taller,16 to be right handed17 and, if they are male, to be heterosexual,18 these are less easily attributed to patterns of early infection.

Nowhere, however, are the patterns of birth order/sibship clearer than with the childhood respiratory allergies. First reported by Butler and Golding in 1986,19 reductions in the risks of hay fever, eczema, atopy and, less consistently, asthma with increasing birth order or sibling numbers have been reported in at least 30 studies and usefulness reviewed by Karmaus and Bottecza. As with most of the diseases above, these observations have generally been attributed to different rates and timings of early (unspecified) childhood infection. Indeed, they form the cornerstone of the “hygiene hypothesis” whereby it is proposed that the risks of atopic disease are reduced by early contact with infection,1 a proposal bolstered by the more recent suggestion that children born to Alpine farmers are protected in a similar manner.

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