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. 1, 2 Treatments that modify these complications may improve survival in patients with COPD, whereas treatments that exclusively target the airways generally do not. 3, 7

SKELETAL MUSCLE DYSFUNCTION

One of the important extrapulmonary manifestations of COPD is skeletal muscle dysfunction and wasting. 1 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 dyspnoea with only a minimal degree of exertion. 8 These symptoms curtail their ability to exercise and compromise their cardiac fitness, which further limits their exercise tolerance, creating a vicious downward spiral that can eventually lead to generalised debility and immobility. 9 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. 10, 11 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. 7

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. 12 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. 13 Microscopically, these skeletal muscles show accelerated apoptosis, increased oxidative stress and inflammatory changes. 14 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. 15–17 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. 18 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. 19 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,22 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.23

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 proteosomal degradation and catabolism of muscle fibres, probably through nuclear factor-kB 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.25 26

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, systematically, these cytokines are increased compared with healthy controls.22 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 Respiriology), 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

Conflict of interest: The authors have received honoraria for speaking engagements from GlaxoSmithKline (GSK) and AstraZeneca and for consultative services from GSK. They have also received research funding from GSK.

REFERENCES
5 Antonisen NR, Carnett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health

Figure 1 Relationship between mean C-reactive protein (CRP) levels and mean forced expiratory volume in 1 second (FEV1) in the three studies.15–17 R2 of the line is 0.95. *FEV1 and CRP values were imputed based on the distribution of patients in GOLD III and IV classes and their reported CRP levels in the study.
Childhood allergies, birth order and family size

P Cullinan

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

O

f 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 slaying of children. Infanticide of this degree is of course of very great importance in the general population. Am J Med 2004;117:270–3.


Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123–30.


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 usefully reviewed by Karmas and Botzan. 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 atop disease are reduced by early contact with infection, a proposal bolstered by the more recent suggestion that children born to Alpine farmers are protected in a similar manner.
Skeletal muscle weakness, reduced exercise tolerance, and COPD: is systemic inflammation the missing link?

D D Sin and S F P Man

Thorax 2006 61: 1-3
doi: 10.1136/thx.2005.044941

Updated information and services can be found at:
http://thorax.bmj.com/content/61/1/1.1

These include:

References
This article cites 29 articles, 12 of which you can access for free at:
http://thorax.bmj.com/content/61/1/1.1#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Epidemiologic studies (1829)
- Inflammation (1020)
- Health education (1223)
- Smoking (1037)
- Tobacco use (1039)
- Long term care (6)
- Ischaemic heart disease (122)
- Osteoporosis (36)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/