

REVIEW SERIES

Chronic obstructive pulmonary disease • 5: Systemic effects of COPD

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Thorax 2002;57:1067-1070

The role of body cell mass wasting, muscle wasting, and changes in muscle metabolism in the pathogenesis of chronic obstructive pulmonary disease is reviewed.

Chronic obstructive pulmonary disease (COPD) is characterised by the progressive development of airflow limitation that is not fully reversible. The clinical syndrome of COPD encompasses different disease conditions varying from chronic obstructive bronchitis with obstruction of small airways, to emphysema characterised by enlargement of air spaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways. The association of an abnormal inflammatory response of the lungs to noxious particles or gases with airflow limitation in COPD indicates the critical role of the inflammatory process in the pathogenesis of this disease.¹ The chronic local inflammatory process in COPD differs markedly from that seen in asthma, but is still less well defined.² Unlike chronic asthma in which inhaled corticosteroids are the mainstay of treatment, recent studies found no evidence that long term treatment with high doses of inhaled corticosteroids reduces the progression of COPD, even when treatment was started before the disease became symptomatic, indicating that the inflammatory process in COPD does not respond to steroids.³⁻⁵ To unravel further the pathogenetic mechanisms which may contribute to the impaired health of these patients, there has been growing interest in the literature to approach COPD as a disease with systemic manifestations as in other chronic inflammatory diseases.

SYSTEMIC EFFECTS OF COPD

The growing recognition of the role of inflammation and oxidative stress in the pathogenesis of COPD has not only been assessed in the airways and lung compartment, but also in the peripheral blood. Some authors have hypothesised that, based on the increased number of neutrophils sequestered in the pulmonary microvasculature in smokers and patients with COPD, an increased oxidant burden may occur and that these effects could be detected in plasma as an increase in markers of oxidant stress accompanied by a reduction in antioxidative capacity. Rahman *et al*⁶ found a marked imbalance in redox status in smokers and during acute exacerbations of COPD, and further evidence of persistent increased oxidative stress in the plasma of patients with COPD was provided by their finding of

higher levels of lipid peroxidation products. The presence of systemic oxidative stress was further supported by Noguera *et al*⁷ who reported the upregulation of some neutrophil adhesion molecules such as CD11/CD18 in circulating neutrophils in patients with stable COPD. They also assessed the expression of guanine nucleotide binding proteins (G proteins) and found that, irrespective of the clinical condition of the patients with COPD, there was a significant loss of G α immunoreactivity in circulating neutrophils; the potential implications of this observation remain unclear. Increased activity of cytochrome oxidase (CytOx), the terminal enzyme of the mitochondrial respiratory chain, was reported by Sauleda *et al*⁸ in the lymphocytes of patients with COPD compared with healthy subjects, and this was found to be significantly related to disease severity as reflected by the degree of airflow limitation. The same authors had previously reported that the activity of CytOx in skeletal muscle of patients with COPD was higher than in healthy control subjects.⁹

Changes in a number of proinflammatory mediators such as tumour necrosis factor (TNF) α and interleukin (IL)-8 as well as increased levels of acute phase proteins have been reported, even in patients with stable COPD.^{8,9} Exacerbations of COPD seem to be particularly associated with increased bronchial and systemic inflammation.¹²⁻¹⁶ In general, the course of an inflammatory process will be determined by the balance between pro- and anti-inflammatory mediators. A recent study assessed systemic levels of the anti-inflammatory mediators soluble IL-1 receptor type II (sIL-1RII), the decoy receptor of IL-1, and of the soluble TNF receptors 55 and 75 (sTNF-55 and sTNF-R75) which inhibit the biological activity of TNF. It was found that, in patients with stable COPD, sTNF-R55 was significantly increased compared with controls and sTNF-R75 showed a tendency to be increased. No differences were seen in circulating sIL-1RII levels between patients with COPD in a stable condition and controls. However, treatment of exacerbations was shown to be associated with an increase in sIL-1RII levels which could play a role in the clinical improvement of these patients.¹⁷ The cause as well as the consequences of these inflammatory changes in the clinical course of the disease process of COPD needs further evaluation, however. The lack of a response to some intervention strategies such as nutritional therapy seems to be related to the level of this systemic inflammatory response.¹⁸

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BODY CELL MASS WASTING IN COPD

Besides assessment of changes in inflammatory mediators, the systemic effects of a disease such as COPD can also be studied by assessing the structural or biochemical alterations in non-pulmonary structures or organs related to primary disease characteristics. Wasting of body cell mass is an important systemic manifestation as a loss of more than 40% of actively metabolising tissue is incompatible with life. The body cell mass represents the actively metabolising and contracting tissue and can be clinically recognised by weight loss in general, and loss in fat free mass in particular. Several studies have provided clear evidence for involvement of TNF α in the pathogenesis of tissue depletion in patients with COPD. Increased plasma levels of TNF α and soluble TNF receptors were found in patients with COPD, particularly those suffering from weight loss.^{11 18–20} Some studies have shown a direct relationship between TNF α levels and resting metabolic rate, whereas others have reported an association between resting metabolic rate and raised levels of acute phase proteins.^{11 21} In one study hypermetabolic patients with an acute phase response had a significantly lower fat free mass than hypermetabolic patients without the acute phase reaction despite a comparable body mass index, indicating that systemic inflammation may cause hypermetabolism and induce a catabolic response.¹¹

A possible factor contributing to pulmonary cachexia is the recently established link between cytokines and leptin. Leptin, a protein synthesised by adipose tissue and encoded by the *ob* gene, plays an important role in energy balance. It is postulated that leptin represents the afferent hormonal signal to the brain including the hypothalamus in a feedback mechanism regulating fat mass. The effects of leptin on food intake are mediated by two limbs of the weight control system: the appetite stimulating peptide (neuropeptide Y) and the satisfaction stimulating melanocyte stimulating hormone. In patients with emphysema, in particular, a significant relationship between plasma concentrations of leptin and sTNF-R55 adjusted for fat mass and oral corticosteroid use was reported.²² Baseline plasma leptin concentrations were inversely related to baseline dietary intake and to the change in body weight after nutritional intervention. Temporary disturbances in energy balance related to increased leptin concentrations as well as to the systemic inflammatory response were also reported during acute exacerbations.²³ Besides its function in energy homeostasis, leptin plays an important role in T cell mediated immunity, angiogenesis, reproduction, and ventilatory control.^{24–27} Further data are needed to confirm the role of the interaction between cytokines and leptin in patients with COPD.

An imbalance in the continuous process of protein degradation and replacement may also contribute to the process of body cell mass wasting. Limited data are available to date on protein synthesis and breakdown in COPD. In non-depleted patients with COPD assessed under stable conditions a balanced increase in protein breakdown and synthesis has been reported.²⁸ Disturbances in this tightly regulated equilibrium have to be evaluated in future studies, especially during periods of acute exacerbation.

MUSCLE WASTING IN COPD

Several studies have shown a preferential loss of muscle mass in patients with COPD, especially in the lower extremities.²⁹ There is now abundant evidence from studies in incubated muscles and muscle extracts that the ATP dependent ubiquitin-proteasome pathway is responsible for most of the increased proteolysis in various types of muscle atrophy.^{30 31} Several adaptations indicating activation of the ubiquitin-proteasome pathway have been found and these appear to be common to many different forms of muscle atrophy. However, it still remains unclear how most muscle proteins are ubiquitinated and degraded. Furthermore, variations in the under-

lying mechanisms leading to muscle atrophy need to be explored, especially the rate or order of degradation of individual muscle proteins and differences in activation of ubiquitination enzymes by different catabolic stimuli.³¹

Direct effects of TNF α on differentiated skeletal muscle cells were reported by Li *et al*³² who showed that TNF α treatment of differentiated myotubes stimulated time-dependent and concentration-dependent reductions in total protein content and loss of adult myosin heavy chain content. These changes were evident at TNF concentrations similar to those measured in patients. The TNF signal was transduced in part by activation of NF- κ B and TNF α rapidly stimulates ubiquitin conjugation to muscle proteins.

Besides disturbances in the energy or the balance between anabolism and catabolism, muscle wasting may be the result of a decreased number of fibres resulting from changes in the regulation of skeletal muscle regeneration or activation of apoptotic pathways. Muscle regeneration, as part of the adaptive response of skeletal muscle, depends on the activation of satellite cells. It is a process in which quiescent progenitor cells are stimulated to proliferate and subsequently to differentiate, strictly regulated by the myogenic bHLH transcription factor family and a second class of transcription factors, the myocyte enhancer factor-2. Guttridge *et al*³³ recently reported that, in differentiating myocytes, TNF induced activation of NF- κ B inhibited skeletal muscle differentiation by suppressing MyoD mRNA at the post-transcriptional level. MyoD is expressed in proliferating undifferentiated myoblasts and is essential for repair of injured or atrophied tissue. In differentiated myotubes a combination of TNF and interferon (IFN) γ signalling was required for downregulation of MyoD and dysfunction of skeletal muscle fibres. It therefore seems that inflammatory mediators such as TNF α and IFN γ are likely to affect skeletal muscle regulation at two phases: (1) by inhibition of the formation of new myofibres and (2) by degeneration of newly formed myotubes and by the inability to repair damaged skeletal muscle.

Langen *et al*³⁴ evaluated the effects of the inflammatory cytokines TNF α and IL-1 β on myocytes and found that TNF induced NF- κ B activation interfered with the expression of muscle proteins in differentiating myoblasts; the activity of muscle creatine kinase and the amount of myosin heavy chain (MyHC) decreased significantly after 72 hours of exposure to TNF α . A causal link between NF- κ B activation and inhibition of myogenic differentiation could be clearly shown. Based on the present findings, it can be hypothesised that inflammatory cytokines may contribute to muscle wasting through the inhibition of myogenic differentiation via an NF- κ B dependent pathway, and direct inhibition of NF- κ B may prove beneficial in reducing the muscle wasting associated with cachexia. Programmed cell death or apoptosis may also contribute to a reduction in muscle cells. Further studies are needed to unravel the mechanism of muscle wasting in chronic inflammatory diseases such as COPD.

CHANGES IN MUSCLE METABOLISM IN COPD

In addition to and independent of the loss of muscle mass, intrinsic abnormalities in skeletal muscle metabolism are present in patients with COPD. A decrease in the proportion of slow-twitch type 1 fibres and a relative increase in fast-twitch type 2 fibres are reported in the peripheral skeletal muscle of patients with stable severe COPD, indicating a relative shift from oxidative to glycolytic capacity.³⁵ In line with these morphological changes, reduced values were reported for enzymes involved in the tricarboxylic acid (TCA) cycle (citrate synthase) and in beta-oxidation of fatty acids (hydroxyacyl CoA dehydrogenase).³⁶ Glycolytic metabolism is less energy efficient because it produces less ATP per mole of glucose than oxidative metabolism. The functional consequences of these changes are reflected in significant changes in skeletal muscle

energy metabolism of patients with COPD.^{37–38} Alterations in adenine nucleotide metabolism are reflected in reduced values of ATP/adenosine diphosphate (ADP), phosphocreatine (PCR)/creatinine (Cr) ratio, and detectable levels of inosine monophosphate (IMP). Recent data on cerebral bioenergetics in patients with stable COPD have shown that there is an increasing dependence on glycolysis for energy production within cerebral cells.³⁹

Several studies have shown early increases in blood lactate levels during submaximal exercise in patients with COPD.^{36–40} Premature lactic acidosis has been associated with reduced oxidative enzyme concentrations in the lower limb muscles.

Recent data also give evidence for intrinsic alterations in the amino acid profile of peripheral skeletal muscles of patients with COPD. It has been found that leucine metabolism is altered in patients with COPD and that these changes are associated with low free fat mass and high insulin concentrations.⁴¹ Other studies have also reported decreased levels of glutamate in peripheral muscle biopsy specimens from patients with COPD.^{38–41} Intracellular glutamate has an important role in preserving high energy phosphates in muscle through different metabolic mechanisms. Moreover, intracellular glutamate is an important precursor for antioxidant glutathione and glutamine synthesis in the muscle. It has been shown that muscle glutamate is highly associated with glutathione and that emphysema patients, in particular, suffer from decreased muscular levels of glutamate. Glutathione levels are also significantly lower in patients with emphysema.⁴² It has also been shown that early lactic acidosis during exercise in patients with COPD is associated with a reduction in muscle glutamate.⁴³

A recent study of amino acid metabolism of the muscles during exercise in patients with COPD found a significant reduction in most muscle amino acid levels after exercise whereas plasma levels of the amino acids were increased, suggesting enhanced amino acid release from the muscle during exercise in these patients.⁴⁴ The increase in plasma alanine and glutamine levels was even higher after exercise, suggesting enhanced nitrogen efflux. Further studies of amino acid metabolism of the skeletal muscle during exercise are therefore needed to elucidate the potential role of amino acids in skeletal muscle dysfunction and wasting of fat free mass in patients with COPD.

CONCLUSIONS

Muscle weakness is an important clinical problem in patients with COPD. Muscle wasting in these patients is a complex process which results from changes in the control of both intermediary metabolism and of cell cycle regulation. These processes are regulated by extrinsic and intrinsic factors of the muscles themselves. Inflammatory mediators have been found to be involved in the wasting process. Optimal therapeutic targeting depends on a clear understanding of the precise mechanisms of this complex process. These systemic effects are important future targets in the management of patients with COPD.

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Thorax 2002 57: 1067-1070

doi: 10.1136/thorax.57.12.1067

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