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REVIEW

Systemic effects of chronic obstructive pulmonary disease

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is characterised by an inappropriate/excessive inflammatory response of the lungs to respiratory pollutants, mainly tobacco smoking.

Recently, besides the typical pulmonary pathology of COPD (*i.e.* chronic bronchitis and emphysema), several effects occurring outside the lungs have been described, the so-called systemic effects of COPD. These effects are clinically relevant because they modify and can help in the classification and management of the disease.

The present review discusses the following systemic effects of chronic obstructive pulmonary disease: 1) systemic inflammation; 2) nutritional abnormalities and weight loss; 3) skeletal muscle dysfunction; and 4) other potential systemic effects. For each of these, the potential mechanisms and clinical implications are discussed and areas requiring further research are highlighted.

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According to the definition of the European Respiratory Society (ERS), chronic obstructive pulmonary disease (COPD) is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs due to varying combinations of diseases of the airways and emphysema [1]. This definition, as well as those published by many other societies and organisations [2–4], focuses exclusively on the lungs. Thus, it is not surprising that, in the staging and prognosis of the disease, only pulmonary variables such as forced expiratory volume in one second (FEV_1) or arterial oxygen tension (P_{a,O_2}) have been considered and that current therapy targets almost exclusively the lungs [1–4].

This situation is beginning to change since various recent studies have provided evidence that COPD is often associated with significant extrapulmonary abnormalities, the so-called "systemic effects of COPD" (table 1). There is increasing realisation that these systemic effects are clinically relevant and may contribute to better understanding and management of the disease. Exercise limitation, a common complaint in COPD [1–4] and a very significant contributor to the poor quality of life of these patients [5, 6], has been traditionally explained by the increased work of breathing and dynamic hyperinflation that result from the airflow limitation characteristic of COPD [1–4]. However, several recent studies have clearly shown that skeletal muscle dysfunction (SMD) is often a very significant contributor to exercise limitation in these patients [7]. The identification of SMD as a major systemic effect of the disease (table 1) has increased interest in skeletal muscle physiology in COPD very significantly and has clearly contributed to a better definition of the role of exercise training [8] and rehabilitation programmes in the clinical management of these patients [9–13]. Other studies have demonstrated that weight loss, another systemic effect of COPD (table 1), is a negative prognostic factor in these patients, independent of other prognostic indices based on the degree of pulmonary dysfunction, such as FEV_1 or P_{a,O_2} [14, 15]. Furthermore, unlike changes in FEV_1 and/or P_{a,O_2}, weight loss in COPD is reversible with appropriate therapy, and, whenever this happens, the prognosis improves [14]. The identification of weight loss and SMD as systemic effects of COPD has drawn attention to the importance of nutritional support, often combined with exercise programmes, for the improvement of quality of life and prognosis in these patients [16]. Finally, several recent studies have clearly shown that COPD is associated not only with an abnormal inflammatory response of the lung parenchyma [4] but also with evidence of systemic inflammation, including systemic oxidative stress, activation of circulating inflammatory cells and increased levels of proinflammatory cytokines [17].

Table 1. – Systemic effects of chronic obstructive pulmonary disease

Systemic inflammation
Oxidative stress
Activated inflammatory cells (neutrophils/lymphocytes)
Increased plasma levels of cytokines and acute phase proteins
Nutritional abnormalities and weight loss
Increased resting energy expenditure
Abnormal body composition
Abnormal amino acid metabolism
Skeletal muscle dysfunction
Loss of muscle mass
Abnormal structure/function
Exercise limitation
Other potential systemic effects
Cardiovascular effects
Nervous system effects
Osteoskeletal effects

In the present article, current knowledge regarding the extrapulmonary effects of COPD is reviewed and the biological characteristics of the systemic effects identified to date (table 1) and their potential mechanisms and clinical consequences described. Wherever possible, the discussion is based upon available evidence; where evidence is lacking, the authors have provided their opinions as discussion points. Attempts have been made to identify areas that require further research and that could lead to a better understanding of the pathobiology of the systemic effects of COPD. Because of the potential pathogenic role of systemic inflammation in other systemic effects of COPD, this is discussed first.

Systemic inflammation

It is currently accepted that an excessive/inadequate inflammatory response of the lungs to a variety of noxious inhaled gases or particles (mostly cigarette smoke) is a key pathogenic mechanism in COPD [4]. Various studies have shown that the lung inflammatory response is characterised by: 1) increased numbers of neutrophils, macrophages and T-lymphocytes with a CD8+ predominance; 2) augmented concentrations of proinflammatory cytokines, such as leukotriene B_4, interleukin (IL)-8 and tumour necrosis factor (TNF)-α, among others; and 3) evidence of oxidative stress caused by the inhalation of oxidants (tobacco smoke) and/or the activated inflammatory cells mentioned above [4]. It is less often realised that similar inflammatory changes can also be detected in the systemic circulation of these patients, including evidence of oxidative stress, the presence of activated inflammatory cells and increased plasma levels of proinflammatory cytokines. This concept is key to understanding the systemic effects of COPD. It will therefore be reviewed in detail here.

Systemic oxidative stress

The term oxidative stress includes all those functional or structural alterations caused by reactive oxygen species (ROS) [18]. The direct measurement of ROS *in vivo* is difficult due to their very short half-life [18]. Thus, assessment of ROS levels relies on demonstration of their biological consequences or fingerprints. RAHMAN *et al.* [19] determined the Trolox-equivalent antioxidant capacity and levels of products of lipid peroxidation in plasma as indices, or fingerprints, of overall oxidative stress in nonsmokers, healthy smokers and COPD patients, during both clinically stable periods and exacerbations of the disease. They found that both indices were significantly increased by smoking and COPD, the latter being particularly significant during episodes of exacerbation [19]. These findings have been confirmed by other investigators using other markers of systemic oxidative stress. PRATICÒ *et al.* [21] found that urinary levels of isoprostane $F_{2\alpha}$-III, a stable prostaglandin isomer formed by ROS-dependent peroxidation of arachidonic acid, which is excreted in urine [20], were higher in patients with COPD than in healthy controls matched for age, sex and smoking habit. Again, differences were more pronounced during exacerbations of the disease [21]. These studies indicate that both smoking and COPD, particularly during exacerbations, are associated with significant systemic oxidative stress [19, 21].

Circulating inflammatory cells

Several studies have shown alterations in various circulating inflammatory cells, including neutrophils and lymphocytes, in COPD, although the former have been more extensively studied in these patients. BURNETT *et al.* [22] demonstrated that neutrophils harvested from patients with COPD showed enhanced chemotaxis and extracellular proteolysis. In another study, NOGUERA *et al.* [23] reported that circulating neutrophils from COPD patients produced more ROS, or "respiratory burst", than those from nonsmokers or healthy smokers, both under basal conditions and after stimulation *in vitro*. The same authors showed that the level of expression of several surface adhesion molecules, particularly Mac-1 (CD11b), in circulating neutrophils was higher in patients with stable COPD than in healthy controls [24]. Interestingly, this difference disappeared during exacerbations of the disease, suggesting neutrophil sequestration in the pulmonary circulation during exacerbations [24]. In more recent preliminary work, NOGUERA *et al.* [25] showed that the increased expression of CD11b in neutrophils harvested from COPD patients was maintained during the process of neutrophil apoptosis *in vitro* (compared to healthy controls). As discussed below, this abnormality may be of relevance to the normal process of neutrophil clearance by macrophages from inflamed tissues. Other abnormalities described in circulating neutrophils in COPD include the downregulation of one G-protein subunit (stimulatory G_α ($G_{\alpha s}$)) [24]. $G_{\alpha s}$ is involved in the intracellular signal transduction pathway linked to CD11b expression [24] and also in the control of intracellular vesicular trafficking [26], the latter being relevant for correct activation of reduced nicotinamide adenine dinucleotide phosphate oxidase, the enzyme eventually responsible for the respiratory

burst in neutrophils [23]. It is therefore likely that $G_{\alpha s}$ plays a role in the regulation of some of the abnormalities described in circulating neutrophils in COPD, namely the increased expression of surface adhesion molecules [24] and the augmented respiratory burst [23].

Circulating lymphocytes have been less well studied than circulating neutrophils in patients with COPD. However, there are some indications of abnormal lymphocyte function in these patients. SAULEDA *et al.* [27] showed that the activity of cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain, was increased in circulating lymphocytes harvested from patients with stable COPD, as compared to healthy nonsmoking controls. Healthy smokers were not included in the study, but this abnormality could also be detected in circulating lymphocytes from patients with other chronic inflammatory diseases, both pulmonary (bronchial asthma) and nonpulmonary (chronic arthritis), suggesting that it may be a nonspecific marker of lymphocyte activation in chronic inflammatory diseases [28]. Interestingly, these investigators also reported the same abnormality (increased cytochrome oxidase activity) in the skeletal muscle of COPD patients [28], the significance of which is discussed below (see Skeletal muscle dysfunction section).

A low CD4+/CD8+ ratio is a characteristic feature of the pulmonary inflammatory response in COPD [29–33]. Whether this abnormality is mirrored in the systemic circulation in these patients is unclear because the majority of studies addressing this issue compared peripheral T-cell subsets in smoking and nonsmoking subjects and did not include patients with COPD [34–36]. MILLER *et al.* [34] did not find any significant difference in the total number of T-lymphocytes and T-cell subsets in light or moderate smokers compared with nonsmokers, but reported that numbers of circulating CD8+ T-cells were increased and CD4+ cells decreased in heavy smokers; interestingly, these changes disappeared 6 weeks after smoking cessation. Similarly, COSTABEL *et al.* [35] did not find significant differences in the proportion of CD4+ and CD8+ lymphocytes in the systemic blood of young healthy smokers, as compared to healthy nonsmokers, despite obvious differences in bronchoalveolar lavage fluid. Finally, EKBERG-JANSSON *et al.* [36] reported changes in the number of "activated" T-cells (using CD57+ and CD28+ as markers of activation) in the peripheral blood of healthy smokers compared to nonsmokers. Overall, the results of these studies seem to indicate that cigarette smoking can cause alterations in the number of circulating immunoregulatory T-cells, probably reversible after quitting smoking [34]. Whether this is also the case for COPD is less clear. In order to separate the role of smoking from that of COPD, DE JONG *et al.* [37] investigated lymphocyte subsets in the peripheral blood of (smoking and nonsmoking) COPD patients and (smoking and nonsmoking) healthy control subjects. They could not find significant differences in lymphocyte subsets when either total groups or smoking subjects of both groups were compared. However, the percentage of CD8+ lymphocytes was significantly higher in nonsmoking COPD subjects than nonsmoking healthy controls [37]. Further, these authors showed that, within the group of nonsmoking COPD subjects, a higher CD4+/CD8+ ratio in peripheral blood was associated with better lung function [37]. Whether these findings represent a consequence of the disease, *i.e.* spillover of the pulmonary inflammatory process, or a potential pathogenic mechanism, which maybe related to susceptibility to COPD development in some smokers, is unknown. However, it should be borne in mind that the CD4+/CD8+ ratio is genetically controlled in humans [38] and it could be hypothesised that a genetically determined, low CD4+/CD8+ ratio may render a smoker more susceptible to developing COPD. Investigation into this issue would be relevant to a better understanding of the pathogenesis of the disease.

Increased plasma levels of proinflammatory cytokines

Numerous studies have reported increased levels of circulating cytokines and acute phase reactants in the peripheral circulation of patients with COPD [39–43]. Abnormalities include increased concentrations of TNF-α, its receptors (TNFR-55 and TNFR-75), IL-6, IL-8, C-reactive protein, lipopolysaccharide-binding protein, Fas and Fas ligand [39–43]. These abnormalities were seen in patients considered clinically stable, but were generally more pronounced during exacerbations of the disease [42]. It is interesting to note here that a very similar cytokine profile, including increased levels of IL-6, IL-1β and granulocyte-macrophage colony-stimulating factor (GM-CSF), has been described recently in healthy subjects during the South-East Asian haze of 1997 [44]. This observation suggests that the pulmonary inflammatory response to particulate air pollutants (particles with a 50% cut-off aerodynamic diameter of 10 μm) is also associated with a systemic inflammatory response [44], like that seen in patients with COPD [42]. Finally, other authors have shown that peripheral monocytes harvested from patients with COPD are capable of producing more TNF-α when stimulated *in vitro* than those obtained from healthy controls [45]. This was particularly evident in patients with COPD and low body weight, suggesting that excessive production of TNF-α by peripheral monocytes may play a role in the pathogenesis of weight loss in COPD (see Nutritional abnormalities and weight loss section) [45].

The mechanisms of systemic inflammation in COPD are unclear but several, not mutually exclusive, mechanisms could be operative. First, tobacco smoke alone can cause, in the absence of COPD, significant extrapulmonary diseases, *e.g.* coronary artery disease. Young smokers and even passive smokers may present with endothelial dysfunction of the systemic vessels [46, 47] and systemic oxidative stress [20]. Clearly, tobacco smoking has the potential to contribute to systemic inflammation in COPD. A second potential mechanism is that the pulmonary inflammatory process in the lung in COPD is the source of the systemic inflammation. Inflammatory lung cells release inflammatory cytokines, such as TNF-α, IL-6, IL-1β, macrophage inflammatory protein 1α and GM-CSF, and increase

oxidant production on interaction with atmospheric particles, necrotic cells and other inflammatory mediators [44]. These proinflammatory mediators may reach the systemic circulation and/or contribute to the activation of inflammatory cells during transit through the pulmonary circulation. A third possibility is that some of the abnormalities described in the peripheral circulation of patients with COPD (*e.g.* the increased surface expression of several neutrophil adhesion molecules (CD11b) and downregulation of G-protein subunits ($G_{\alpha s}$) [24]) may be a cause rather than a consequence of COPD. This possibility is based upon the following observations. Only a percentage of smokers eventually develop COPD [48], suggesting the participation of other factors, probably genetic, in the pathogenesis of the disease [49]. It is possible that the neutrophil abnormalities seen in COPD could be the expression of a genetic predisposition that render these cells more susceptible to the effects of smoking or other proinflammatory agents. These cells could then exhibit a more vigorous response to the same degree of stimulation, including greater expression of surface adhesion molecules, which would facilitate their recruitment to the site of inflammation [24], and an increased respiratory burst that would enhance their damaging potential [23]. However, because it is still not known whether these abnormalities can be seen in susceptible smokers before they develop COPD, the potential role of these three mechanisms warrants further investigation.

Nutritional abnormalities and weight loss

Various studies have described the presence of nutritional abnormalities in patients with COPD. These include alterations in caloric intake, basal metabolic rate, intermediate metabolism and body composition [50–53]. The most obvious clinical expression of these nutritional abnormalities is unexplained weight loss. This is particularly prevalent in patients with severe COPD and chronic respiratory failure, occurring in ~50% of these patients [51], but can be seen also in ~10–15% of patients with mild-to-moderate disease [51].

Loss of skeletal muscle mass is the main cause of weight loss in COPD, whereas loss of fat mass contributes to a lesser extent [51]. Importantly, however, alterations in body composition can occur in COPD in the absence of clinically significant weight loss [43, 50, 51]. The detection of these more subtle alterations requires the use of sophisticated technology, such as dual-energy X-ray absorption or bioelectrical impedance measurements [16, 54, 55]. Using this technology, ENGELEN *et al.* [56] were able to show significant differences in body composition (lean mass, fat mass and bone mineral content) between not only patients with COPD and healthy volunteers but also COPD patients with predominantly chronic bronchitis and COPD patients with predominantly emphysema, classified by the usual clinical criteria and high-resolution computed tomographic findings.

The terms "malnourishment" and "cachexia" are often used indiscriminately in discussion of the nutritional abnormalities in COPD; however, important differences exist between these terms. As shown in table 2, both terms share several biochemical characteristics, but their origin and, importantly, response to dietary supplementation are very different. Several observations suggest that patients with COPD may suffer from cachexia rather than malnourishment. For instance, the caloric intake of patients with COPD is normal or even greater than normal, not lower, as in malnourishment; their metabolic rate is usually increased, whereas it is decreased in malnourished patients [57, 58]; and their response to nutritional support is often poor [59, 60].

The causes of these nutritional abnormalities are unclear. As mentioned above, decreased caloric intake does not appear to be very prominent in these patients, except during episodes of exacerbation of their disease [61]. In contrast, most patients with COPD exhibit an increased basal metabolic rate and, because this increased metabolic requirement is not met by a parallel increase in caloric intake, weight loss ensues [61]. The cause of the increased basal metabolic rate is also unclear. Traditionally, it has been explained on the basis of an increased oxygen consumption ($V'O_2$) of the respiratory muscles due to the increased work of breathing that characterises the disease [62]. However, it has been recently shown that skeletal nonrespiratory muscle $V'O_2$ is higher at any given load in patients with COPD than in age-matched healthy controls [63], indicating that bioenergetic abnormalities are also present in nonrespiratory muscles, and that these abnormalities probably contribute to the increased metabolic rate in patients with COPD [8, 64–68].

Several mechanisms could conceivably contribute to the increased metabolic rate in COPD. First, drugs commonly used in the treatment of COPD (*e.g.* β_2-agonists) can increase metabolic rate [69]. Secondly, systemic inflammation could also play a significant role, as shown by the relationship between metabolic derangement and increased levels of inflammatory mediators in COPD [40]. Thirdly, tissue hypoxia may also make a contribution [70], since other diseases characterised by tissue hypoxia, such as congestive heart failure, also show increased metabolic rate [71]. Further, a direct relationship between the activity of

Table 2. – Comparison of malnourishment and cachexia

	Malnourishment	Cachexia
Fat triglyceride content	↓	↓
Skeletal muscle protein content	↓	↓
Origin	Decreased intake	?
Response to dietary supplementation	Good	Poor

↓: very reduced.

cytochrome oxidase, the mitochondrial enzyme that consumes oxygen, in skeletal muscle and the degree of arterial hypoxaemia present in COPD has been found [28]. Similar upregulation of cytochrome oxidase was also found in circulating lymphocytes harvested from patients with COPD [27], suggesting that this bioenergetic abnormality may affect tissues other than skeletal muscle.

Weight loss is an important prognostic factor in COPD patients, and their prognostic value is independent of that of other prognostic indicators, such as FEV1 or P_{a,O_2}, which assess the degree of pulmonary dysfunction [14, 15]. Therefore, weight loss constitutes a new systemic domain of COPD not considered by traditional measures of lung function. Further, SCHOLS *et al.* [14] showed that the prognosis improved in patients with COPD if body weight could be regained after appropriate therapy, despite the absence of changes in lung function. Therefore, these data indicate that the clinical assessment of patients with COPD should take into consideration, along with the severity of the lung disease [1, 2], the extrapulmonary systemic consequences of COPD, of which weight loss is of paramount importance [72]. In this context, CELLI *et al.* [72] showed that a composite score that included different domains of the disease (FEV1, body weight, exercise capacity, perception of symptoms, *etc.*) was able to predict utilisation of healthcare resources in patients with COPD much better than FEV1 alone. This approach may have significant health economics implications and could serve to evaluate the outcome of different therapeutic interventions in a more comprehensive way than the traditional methods, based mainly on FEV1.

Skeletal muscle dysfunction

COPD is characterised by a pathological rate of decline in lung function with age, and, as a result, patients with COPD often complain of dyspnoea and exercise intolerance [73]. The concept that exercise intolerance in COPD was due to dyspnoea, in turn caused by the increased work of breathing secondary to airflow obstruction, was first challenged by KILLIAN and coworkers [74, 75], who showed that many patients with COPD stop exercise because of leg fatigue rather than dyspnoea. This observation was probably the first indication that skeletal muscle was abnormal in COPD and strongly stimulated research in the field. Several publications have now confirmed that SMD is common in patients with COPD, and that it contributes significantly to limiting their exercise capacity and quality of life [7, 76]. Interestingly, the respiratory muscles, particularly the diaphragm, appear to behave quite differently from skeletal muscles in these patients, from both structural and functional points of view [7], probably due to the very different conditions under which both work in these patients, the skeletal muscles being generally underused whereas the diaphragm is constantly working against an increased load [77, 78]. Discussion of this topic, however, exceeds the scope of the present review and so is not discussed further.

Despite the fact that SMD is probably the systemic effect of COPD most extensively studied, its mechanisms are still poorly understood. It is important to realise that SMD in COPD is probably characterised by two different, but possibly related, phenomena: 1) net loss of muscle mass, an intrinsic muscular phenomenon; and 2) dysfunction or malfunction of the remaining muscle. Muscle malfunction may be secondary to either intrinsic muscle alterations (mitochondrial abnormalities and loss of contractile proteins) or alterations in the external milieu in which the muscle works (hypoxia, hypercapnia and acidosis), resulting from the abnormalities of pulmonary gas exchange that characterise COPD [79]. Although conceptually important, the separation of these two aspects of SMD is extremely difficult *in vivo* and both probably play some role in any given patient. With this caveat in mind, the text that follows discusses potential mechanisms of SMD in COPD (table 3).

Sedentarism

Due to shortness of breath during exercise, patients with COPD often adopt a sedentary lifestyle. Physical inactivity causes net loss of muscle mass, reduces the force generating capacity of muscle and decreases its resistance to fatigue [80]. Exercise training improves muscle function in COPD patients [8, 63, 81, 82], indicating that sedentarism is likely to be an important contributor to SMD. However, complete normalisation of muscle physiology is often not fully achieved after rehabilitation, and, more importantly, some of the biochemical abnormalities found in muscles are unlikely to be explained by physical inactivity. For instance, the increased activity of cytochrome oxidase observed in the skeletal muscle of patients with COPD (and discussed above in the context of the increased metabolic rate in COPD) cannot be explained by sedentarism, which is characterised by decreased, not increased, cytochrome oxidase activity [28]. Further, this same abnormality occurs in circulating lymphocytes [27], and, given that these cells are not influenced by inactivity and detraining, other explanations are required (see below). Finally, at variance with the normal training response, exercise in patients with COPD enhances the release of amino acids, particularly alanine and glutamine [52], from skeletal muscle, suggesting the presence of intrinsic muscle abnormalities of intermediate amino acid metabolism [53].

Table 3. – Potential mechanisms of skeletal muscle dysfunction in chronic obstructive pulmonary disease

Sedentarism
Nutritional abnormalities/cachexia
Tissue hypoxia
Systemic inflammation
Skeletal muscle apoptosis
Oxidative stress
Abnormal nitric oxide regulation
Tobacco
Individual susceptibility
Hormone alterations
Electrolyte alterations
Drugs

Tissue hypoxia

Several observations support a potential pathogenic role for tissue hypoxia in the development of SMD in COPD. First, chronic hypoxia suppresses protein synthesis in muscle cells, causes net loss of amino acids and reduces expression of myosin heavy chain isoforms [83, 84]. Secondly, healthy subjects at high altitude (hypobaric hypoxia) lose muscle mass [85, 86]. Thirdly, skeletal muscle from patients with COPD and chronic respiratory failure exhibits structural (decrease of type I fibres [87, 88]) and functional (upregulation of mitochondrial cytochrome oxidase [28]) alterations proportional to the severity of arterial hypoxaemia. If tissue hypoxia plays a pathogenic role, domiciliary oxygen therapy may have a beneficial effect upon SMD in COPD. This possibility should be addressed in further studies.

Systemic inflammation

Systemic inflammation is likely to be an important pathogenetic mechanism of SMD in COPD. As discussed above, COPD patients show increased plasma levels of a variety of proinflammatory cytokines, particularly TNF-α [39–41, 43, 89]. Also, circulating monocytes harvested from such patients produce more TNF-α *in vitro* than those from healthy controls [45], and several authors have now shown increased plasma concentrations of soluble TNF-α receptors [40, 41, 43]. TNF-α can affect muscle cells in a number of ways [90]. In differentiated myocites studied *in vitro*, TNF-α activates the transcription factor nuclear factor-κB and degrades myosin heavy chains through the ubiquitin/proteasome complex (U/P) [90]. Several studies have now shown that dysregulation of the U/P system contributes to the loss of muscular mass caused by sepsis or tumours in rats [91]. Whether this also occurs in COPD patients has not yet been investigated. Alternatively, TNF-α can induce the expression of a variety of genes, such as those encoding the inducible form of nitric oxide synthase (iNOS), TNF-α itself and many other proinflammatory cytokines, that would create a closed loop and contribute to the persistence and amplification of the inflammatory cascade [90]. Finally, TNF-α can induce apoptosis in several cell systems [92]. It has recently been shown that excessive apoptosis of skeletal muscle occurs in patients with COPD and weight loss [93]. Increased levels of circulating TNF-α and increased apoptosis of skeletal muscle cells have also been described recently in patients with chronic heart failure [94, 95], suggesting that this mechanism may be operating in other chronic diseases and not be unique to COPD [76]. Given that cytochrome c release from the mitochondria is an early event in apoptosis [96, 97] and that the activity of cytochrome oxidase is increased in COPD patients [28], mitochondrial abnormalities could play a mechanistic role in this context. This should be examined carefully, since a better understanding of the molecular pathways controlling this phenomenon may lead to the development of new therapeutic alternatives for these patients [98].

Oxidative stress

As discussed above, patients with COPD exhibit oxidative stress in their systemic circulation, particularly during exacerbations of their disease [19], that could also be relevant to the pathogenesis of SMD [99]. Oxidative stress causes muscle fatigue [100] and facilitates proteolysis [91, 101]. This might be particularly relevant since regulation of glutathione, the most important intracellular antioxidant [99], is abnormal in the skeletal muscle of patients with COPD [102]. Finally, oxidative stress is an important contributor to the normal process of ageing characterised by, among other things, loss of muscle mass [103, 104]. Whether or not a premature and/or accelerated ageing process occurs in COPD patients with SMD has not been explored to date, but this possibility is currently being investigated by the present authors.

Nitric oxide

Nitric oxide is a free radical synthesised from the amino acid L-arginine by the action of three nitric oxide synthases (NOS) [105], all of which are expressed in human muscle [106]. Two NOS isoforms, the so-called type I neuronal or brain NOS and type III or endothelial NOS, are expressed constitutively, whereas the third isoform, type II NOS or iNOS, is expressed in response to a variety of stimuli, including cytokines, oxidants and/or hypoxia [106]. The role of NO in the pathogenesis of SMD in COPD is unclear, but it could play a mechanistic role through several, not mutually exclusive, pathways. First, given that the number of capillaries in the skeletal muscle of patients with COPD is lower than normal [107], it is conceivable that endothelial NOS expression is also reduced. This could contribute to jeopardising control of the microcirculation and supply of oxygen to working muscle, eventually resulting in tissue hypoxia (see above). Secondly, systemic inflammation can upregulate the expression of iNOS in skeletal muscle [108]. Preliminary results suggest that this occurs in COPD patients who loose weight [109]. In turn, the increased NO production resulting from iNOS upregulation can cause protein nitrotyrosination and facilitate protein degradation through the U/P system [91] and/or enhance skeletal muscle apoptosis [110]. Results indicate that both do indeed occur in patients with COPD and low body weight [93, 109]. Finally, iNOS induction can also cause contractile failure [111], thus potentially limiting exercise tolerance in these patients.

Tobacco smoke

Although it is accepted that tobacco smoke is the main risk factor for COPD [73], much less attention has been paid to the potential effects of tobacco smoke upon skeletal muscle structure and function in these patients. However, tobacco smoke clearly reaches the systemic circulation, as shown by the increased prevalence of coronary artery disease and endothelial dysfunction in smokers [46, 47], and contains many substances

potentially harmful to skeletal muscle. For instance, nicotine alters the expression of important growth factors, such as TGF-β1, involved in the maintenance of muscular mass [112] and competes with acetylcholine for its receptor at the neuromuscular junction, thus having the potential to affect muscle contraction directly [113]. Therefore, it is possible that tobacco smoke may also contribute to SMD in COPD; this should be investigated.

Individual susceptibility

It is now accepted that chronic smoking is necessary but not sufficient to cause COPD since only a percentage of smokers develop COPD [73]. A similar, but not as widely recognised concept is the fact that not all patients with COPD lose muscle mass during the course of their disease [51]. Although this may be related to severity [51] or phenotype of disease [56], a genetic component similar to that suggested to explain the development of COPD in only a proportion of smokers [114, 115] cannot be excluded. The genes potentially involved in this process are unknown. Some potential candidate genes include those encoding for the angiotensin-converting enzyme (ACE), several transcription factors (myogenic basic helix-loop-helix gene D (MyoD) and myocyte-enhancer factor (MEF)-2) and proteins related to the process of histone acetylation/deacetylation (cyclic adenosine monophosphate responsive element-binding protein (CBP)/p300 and histone deacetylase (HDAC)5). The ACE gene is known to influence the muscular response to training in athletes [116] and the development of right ventricular hypertrophy in patients with COPD [117]. Further, a very recent report has shown that use of ACE inhibitors can reduce the normal decline in muscle mass that occurs during ageing and improve exercise capacity [118], thus raising the possibility of using these drugs therapeutically in patients with COPD and weight loss. MyoD and MEF-2, as well as CBP/p300 and HDAC5, have very recently been shown to play a fundamental role in the failure of muscle cells to regenerate after injury in patients with cancer cachexia [119, 120]. Whether they play any role in the pathogenesis of SMD in patients with COPD has not been explored. In summary, the potential role of a genetic background predisposing some COPD patients to the development of SMD is unclear but deserves further investigation. The new microarray technology [121, 122] is currently being used to investigate differential gene expression in the skeletal muscle of patients with COPD with and without weight loss [123].

Other mechanisms

There are other potential mechanisms that, alone or in combination, could contribute to SMD in patients with COPD. For instance, the regulation of several hormone pathways seems altered in patients with COPD, including findings of low testosterone and growth hormone levels [124, 125] and reduced plasma leptin concentration [126–128]. All of these are potentially important in the control of muscle mass and body weight and may therefore contribute to the abnormal amino acid metabolism described in the skeletal muscle of patients with COPD [52, 53]. Likewise, for a variety of reasons (diet, inactivity and drug therapy), abnormal plasma electrolyte values, such as low concentrations of potassium, phosphorus, calcium and magnesium, are not uncommon in patients with COPD and can also cause contractile dysfunction and muscle weakness [129–132]. A recent position paper issued jointly by the ERS and the American Thoracic Society indicates that administration of ionic supplements, when necessary, can improve muscle function in these patients [7]. Finally, many of the drugs used in the treatment of COPD can also interfere with skeletal muscle function. For instance, β_2-adrenergic drugs cause increased oxygen consumption [69], a condition that by itself can cause oxidative stress, and treatment with oral corticoids can cause skeletal muscle weakness in patients with COPD [133–136] and, more importantly, also seems to jeopardise their prognosis, as shown by a very recent population-based cohort study of 22,620 individuals carried out in Canada [137]. In this study, after adjusting for age, sex, comorbidity, treatment and previous emergency visits for COPD, treatment with oral steroids significantly increased all-cause mortality and the risk of repeated hospitalisation in patients with COPD [137]. Whether this observation is a marker of disease severity or truly reflects an undesired systemic effect is unclear due to the retrospective nature of the study. However, it agrees with previous observations supporting a negative effect of oral steroid treatment upon skeletal muscle in COPD patients [133–136].

SMD in COPD has two obvious consequences: 1) it contributes significantly to weight loss [51], a poor prognostic factor in these patients [14, 15]; and 2) it is one of the main causes of exercise limitation [7], having a profound impact on quality of life [5, 138]. Thus, appropriate treatment of SMD should be a priority in the clinical management of COPD [7]. Currently, this is based mostly upon rehabilitation programmes, nutritional support and, perhaps, oxygen therapy [9–11, 13, 43, 76, 139]. However, more specific and effective therapies need to be developed. In this context, the use of anabolic steroids is a potentially effective treatment whose use in SMD should be better delineated [14]. Since TNF-α might be a biological mediator of SMD in COPD, it could be speculated that the use of antibodies directed against TNF-α may be beneficial in these patients. These antibodies have been effective in the treatment of other chronic inflammatory diseases, such as rheumatoid arthritis, in which TNF-α plays a key pathogenic role [140–145]. This therapeutic approach should be explored.

In summary, the cellular mechanisms of SMD in COPD are not clearly understood, but probably result from the combination of several complex and interrelated factors (table 3). Many of these mechanisms may not be exclusive to COPD and may also play an important role in other chronic diseases, such as cardiac and renal failure, cancer and acquired immune deficiency syndrome [76]. Like patients with COPD, patients with chronic heart failure also lose skeletal

muscle mass during the course of their disease [76], and the skeletal muscle of patients with chronic heart failure exhibits similar histopathological abnormalities to those reported in COPD [76], including increased apoptosis [146]. Finally, the mechanisms cited to explain these abnormalities are very similar to those discussed above for COPD, and include inactivity, tissue hypoxia, oxidative stress and systemic inflammation [76]. Thus, it is very likely that SMD may not be unique to COPD but represent a final pathway common to several chronic diseases. If so, this would further strengthen the importance of investigating and eventually revealing the molecular mechanisms underlying it because, by doing so, new potential therapeutic avenues may be opened up for many chronic debilitating diseases, including COPD.

Other potential systemic effects of chronic obstructive pulmonary disease

Besides the currently accepted systemic effects described above, systemic inflammation, nutritional abnormalities and SMD, other organ systems might also be affected by the systemic influences of COPD.

Cardiovascular effects

Coronary artery disease is not rare in patients with COPD because both diseases share similar risk factors, such as cigarette smoking, increased age and inactivity. However, in the absence of coronary artery disease and overt cor pulmonale, it is presently unclear whether or not left ventricular function is normal in stable patients with COPD [147]. Since cardiac output appears to increase normally during exercise, even in severe COPD [147], the link between cardiac output and $V'O_2$ seems preserved. However, at peak exercise, cardiac output is ~50% of what a normal subject of the same age could achieve by reaching a higher $V'O_2$ [147]. Two potential explanations are possible for this finding. First, the regulation of cardiac output during exercise in lung disease may remain so tight that, despite the capacity for a higher cardiac output, it matches the level of exercise (and thus, $V'O_2$) achieved [147]. The second more intriguing possibility is that, despite the absence of overt heart failure, left ventricular function may be compromised in COPD and a higher cardiac output may not be achievable. Although this possibility is speculative, it may merit further study since similar mechanisms to those described for skeletal muscle may be operative in the myocardium [148–151].

The endothelium is no longer seen as a passive barrier but as a very active tissue with key physiological functions in the control of vascular tone and tissue perfusion [105]. In resected lung specimens studied *in vitro*, it has been shown that endothelial function is abnormal in COPD [152]. The use of Doppler echocardiographic technology has allowed the noninvasive study of endothelial function in other vascular territories *in vivo* [46, 47, 153]. It has been shown that in patients with COPD, the endothelial function of the renal circulation is also abnormal [154, 155]. Whether or not this abnormality may also occur in other systemic vascular territories is not known at present.

Nervous system effects

Various aspects of the nervous system may be abnormal in patients with COPD. For instance, the use of nuclear magnetic resonance spectroscopy has shown recently that the bioenergetic metabolism of the brain is altered in these patients [156]. Whether this represents a physiological adaptation to chronic hypoxia, as occurs at altitude [157], or whether it may be considered another systemic effect of COPD mediated by other unknown mechanisms is unclear.

Another potential systemic effect of COPD upon the central nervous system relates to the high prevalence of depression reported in these patients [158–160]. It is possible that this may simply represent a physiological response to chronic debilitating disease. However, it is equally plausible that it may bear some relationship to the systemic inflammation that occurs in COPD, since TNF-α and other cytokines and molecules, such as nitric oxide, have been implicated in the pathogenesis of depression in several experimental models [161–163]. Better delineation of these issues may open new therapeutic possibilities in COPD.

Finally, some recent data suggest that the autonomic nervous system may also be altered in patients with COPD [164]. TAKABATAKE *et al.* [164] showed indirect evidence of abnormal autonomic nervous system control in patients with COPD, particularly those with low body weight, and a related deregulation of the normal circadian rhythm of leptin. Given that leptin has important effects on neuroendocine function, appetite regulation, body weight control and thermogenesis in humans [164], and that previous studies have shown reduced plasma leptin concentrations in patients with COPD [126–128], these findings may well also be relevant to the pathogenesis of SMD and weight loss in COPD.

Osteoskeletal effects

The prevalence of osteoporosis is increased in patients with COPD [165, 166]. Osteoporosis can have multiple causes, singly or in combination, including malnutrition, sedentarism, smoking, steroid treatment and systemic inflammation [166–168]. Since most of them are already considered potential pathogenic factors of SMD in COPD, they could theoretically also contribute to osteoporosis, and, in this context, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD [56]. It is interesting to note that emphysema and osteoporosis are both characterised by net loss of lung or bone tissue mass and, pictorially, an osteoporotic bone looks quite similar to an emphysematous lung! It is therefore tempting to speculate that the two conditions might share common mechanisms to explain the accelerated loss of tissue mass or its defective repair. This intriguing

possibility merits further study because better understanding of the causes of the "excessive" osteoporosis of COPD may allow the design of new therapeutic alternatives that, eventually, may contribute to palliating its symptoms and reducing the associated healthcare costs [169].

Conclusions

The studies discussed in the present review clearly support the concept that chronic obstructive pulmonary disease can no longer be considered a disease affecting the lungs alone. The available evidence indicates that: 1) chronic obstructive pulmonary disease has an important systemic component; 2) clinical assessment of chronic obstructive pulmonary disease ought to take into consideration the systemic components of the disease; and the treatment of these extrapulmonary effects appears to be important in the clinical management of the disease. A better understanding of the systemic effects of chronic obstructive pulmonary disease may permit new therapeutic strategies that might result in a better health status and prognosis for these patients.

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