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REVIEW

Systemic manifestations and comorbidities of COPD

P.J. Barnes* and B.R. Celli#

ABSTRACT: **Increasing evidence indicates that chronic obstructive pulmonary disease (COPD) is a complex disease involving more than airflow obstruction. Airflow obstruction has profound effects on cardiac function and gas exchange with systemic consequences. In addition, as COPD results from inflammation and/or alterations in repair mechanisms, the ''spill-over'' of inflammatory mediators into the circulation may result in important systemic manifestations of the disease, such as skeletal muscle wasting and cachexia. Systemic inflammation may also initiate or worsen comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes. Comorbid diseases potentiate the morbidity of COPD, leading to increased hospitalisations, mortality and healthcare costs. Comorbidities complicate the management of COPD and need to be evaluated carefully. Current therapies for comorbid diseases, such as statins and peroxisome proliferator-activated receptor-agonists, may provide unexpected benefits for COPD patients. Treatment of COPD inflammation may concomitantly treat systemic inflammation and associated comorbidities. However, new broad-spectrum anti-inflammatory treatments, such as phosphodiesterase 4 inhibitors, have significant side-effects so it may be necessary to develop inhaled drugs in the future. Another approach is the reversal of corticosteroid resistance, for example with effective antioxidants. More research is needed on COPD comorbidities and their treatment.**

KEYWORDS: **Cardiac failure, depression, diabetes, ischaemic heart disease, lung cancer, osteoporosis**

Chronic obstructive pulmonary disease (COPD) is primarily characterised by the presence of airflow limitation resulting from airways inflammation and remodelling often associated with parenchymal destruction and the development of emphysema. However, in many patients the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-related quality of life and increased mortality. The best-recognised manifestations include the presence of concomitant cardiovascular compromise, malnutrition involving primarily the loss and dysfunction of skeletal muscles, osteoporosis, anaemia, increased gastroesophageal reflux and clinical depression and anxiety (table 1). Importantly, the presence of airflow limitation greatly increases the likelihood that patients may develop lung cancer over time. In addition, patients with COPD are older and frequently present with important comorbidities that also require medical attention. There is no doubt that comorbidities increase the risk of hospitalisation and mortality in COPD patients, especially as the airway obstruction becomes more severe [1]. Furthermore, comorbidities significantly increase the healthcare costs of COPD [2]. The present review summarises recent advances in this important area and addresses possible basic mechanisms responsible for them, acknowledging that these associations have only recently begun to be studied in depth.

There are two different views relating the observed associations between COPD and its manifestations and comorbidities. For many, they are the result of a systemic ''spill-over'' of the inflammatory and reparatory events occurring in the lungs of patients with COPD, with the disease remaining at the centre of the process (fig. 1), whereas for others the pulmonary manifestations of COPD are one more form of expression of a ''systemic'' inflammatory state with multiple organ compromise [3, 4]. Both views have merit

AFFILIATIONS
*National Heart and Lung Institute, Imperial College, London, UK.
#Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA.

CORRESPONDENCE
P.J. Barnes
Airway Disease Section
National Heart and Lung Institute
Dovehouse Street
London SW3 6LY
UK
Fax: 44 2073515675
E-mail: p.j.barnes@imperial.ac.uk

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TABLE 1 Systemic manifestations and comorbidities of chronic obstructive pulmonary disease

Skeletal muscle wasting
Cachexia: loss of fat-free mass
Lung cancer (small cell, nonsmall cell)
Pulmonary hypertension
Ischaemic heart disease: endothelial dysfunction
Congestive cardiac failure
Osteoporosis
Normocytic anaemia
Diabetes
Metabolic syndrome
Obstructive sleep apnoea
Depression

but imply different conceptual and important therapeutic consequences. In the former, the aims of therapy are primarily centred in the lungs whereas in the latter, the centre of therapy should be shifted to the systemic inflammatory state. It is very clear that the next decade will witness an explosion of information attempting to elucidate the associations between COPD and its systemic expressions, provide objective evidence of the mechanisms and, in the end, improve the management of patients with COPD. Another less likely possibility is that systemic inflammation may be beneficial and may play a protective role by enhancing defence and repair mechanisms, but this seems unlikely. The distinction between a systemic manifestation and comorbidity is difficult to define and for the purposes of the present review, the current authors consider them together.

SYSTEMIC INFLAMMATION

Patients with COPD, particularly when the disease is severe and during exacerbations, have evidence of systemic inflammation, measured either as increased circulating cytokines, chemokines and acute phase proteins, or as abnormalities in circulating cells [5–7]. Smoking itself may cause systemic inflammation, for example, and increased total leukocyte count, but in COPD patients the degree of systemic inflammation is greater. As discussed previously, it is still uncertain whether these systemic markers of inflammation are a spillover from inflammation in the peripheral lung, are a parallel abnormality, or are related to some comorbid disease that then has effects on the lung. In any case, the components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases. For this reason, there has been considerable interest in identifying the nature of systemic inflammations as this may help to predict clinical outcomes and responses to therapy and may identify new targets for therapy. Systemic inflammation appears to relate to an accelerated decline in lung function and is increased during exacerbations [8, 9].

Cytokines

Interleukin-6

Interleukin (IL)-6 is increased in the systemic circulation of COPD patients, particularly during exacerbations, and may account for the increase in circulating acute phase proteins such as C-reactive protein (CRP) found in COPD patients as it induces the release of acute phase proteins from the liver [10]. The functional effects of circulating IL-6, apart from increasing acute phase proteins, are not yet certain but there is evidence that it may be associated with skeletal muscle weakness. In an ageing population with or without airway obstruction, plasma IL-6 concentrations are related to decreased muscle strength measured by quadriceps strength and exercise capacity [11]. In rats, infusion of IL-6 induces both cardiac failure and skeletal muscle weakness [12]. Elevated circulating IL-6 concentrations are found in several comorbid diseases.

Tumour necrosis factor-α

Plasma tumour necrosis factor (TNF)-α and its soluble receptor are increased in COPD patients [13–15], and TNF-α is also released from circulating cells in COPD patients with cachexia [16]. Circulating TNF-α appears to be related, at least in part, to hypoxaemia [14]. Increased systemic TNF-α has been implicated as a mechanism of cachexia, skeletal muscle atrophy and weakness in COPD patients. Chronic administration of TNF-α in animals results in cachexia, anaemia, leukocytosis and infiltration of neutrophils into organs such as the heart, liver and spleen [17].

IL-1β

IL-1β has also been linked to cachexia, but increased plasma concentrations or decreased concentrations of its endogenous antagonist IL-1 receptor antagonist have not been found in COPD, although there is an association between COPD and a polymorphism of the IL-1β gene [15].

Chemokines

CXCL8 (IL-8) and other CXC chemokines play an important role in neutrophil and monocyte recruitment in COPD patients, but circulating CXCL8 concentrations are also increased in COPD patients and are related to muscle weakness [18].

Adipokines

Leptin is an adipokine (cytokine derived from fat cells) that plays an important role in regulating energy balance, and in COPD patients, plasma concentrations tend to be low and there is a loss of the normal diurnal variation [14, 15], but its role in cachexia is not certain. By contrast, circulating concentrations of ghrelin, a growth hormone-releasing peptide that increases food intake, is elevated in cachectic patients with COPD [19].

Acute phase proteins

CRP

CRP is an acute phase protein, which is increased in the plasma of COPD patients, particularly during acute infective exacerbations. In stable COPD, plasma concentrations are related to or cause mortality in mild to moderate patients [20], but not in severe and very severe patients [21]. Increased CRP is also related to health status and exercise capacity and appears to be a significant predictor of body mass index (BMI) [22]. But, although CRP is related to forced expiratory volume in one second (FEV_1) in cross-sectional studies, there is no association with the progressive decline of FEV_1 in longitudinal studies [23]. CRP is also increased in exacerbations of

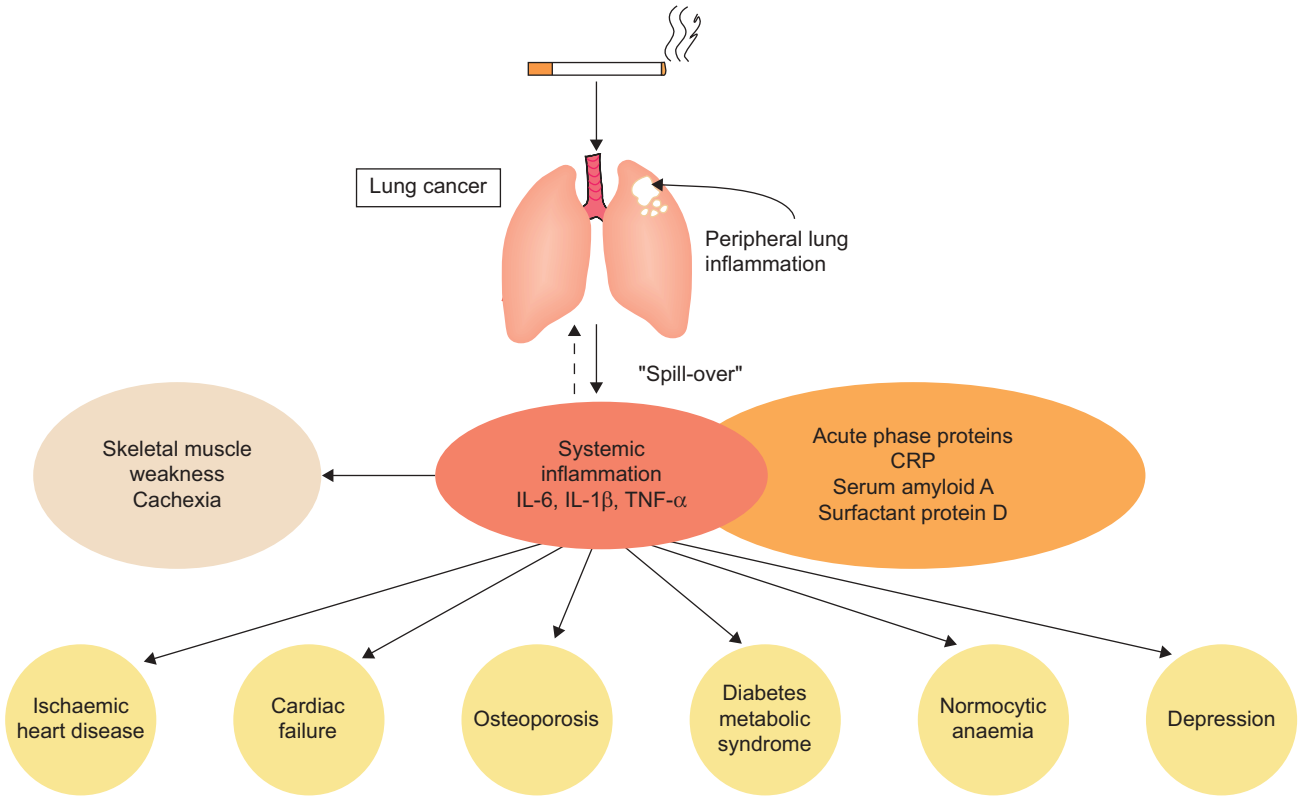

FIGURE 1. Systemic effects and comorbidities of chronic obstructive pulmonary disease (COPD). Peripheral lung inflammation may cause a ''spill-over'' of cytokines, such as interlukin (IL)-6, IL-1β and tumour necrosis factor (TNF)-α, into the systemic circulation, which may increase acute-phase proteins such as C-reactive protein (CRP). Systemic inflammation may then lead to skeletal muscle atrophy and cachexia and may initiate and worsen comorbid conditions. Systemic inflammation may also accelerate lung cancer. An alternative view is that systemic inflammation causes several inflammatory diseases, including COPD.

COPD, due to viral or bacterial causes [9, 24] and a high concentration of CRP 2 weeks after an exacerbation predicts the likelihood of recurrent exacerbation [25].

The link between increased CRP and the prediction of cardiovascular risk has suggested that it might be an association between COPD and the increased incidence of cardiovascular disease, but this relationship may be confounded by established risk factors, such as smoking [26]. The functional role of CRP is uncertain and disputed. CRP binds to damaged tissue and leads to activation of the complement, resulting in endothelial injury and tissue inflammation. A small molecule inhibitor of CRP 1, 6-bis(phosphocholine)-hexane, counteracts the effects of CRP in animal models and therefore may be cardioprotective [27]. However, the role of CRP has been questioned by the recent demonstration that transgenic overexpression of human CRP in mice is neither pro-inflammatory nor pro-atherogenic [28]. Furthermore, there is evidence to suggest that CRP may play an important role in innate defence against *Streptococcus pneumoniae*, so that inhibiting CRP could have detrimental effects in COPD, since this organism commonly colonises the lower airways of these patients [29].

Fibrinogen

Plasma fibrinogen concentrations are increased in COPD patients with frequent exacerbations [8, 30, 31]. An elevated plasma fibrinogen in a population is related to worse FEV_1 and an increased risk of hospitalisation for COPD [32].

Serum amyloid A

Serum amyloid (SA)-A is an acute phase protein that is released by circulating pro-inflammatory cytokines from the liver but unlike CRP, also from inflamed tissue. Proteomic analysis of plasma has identified an increase in SA-A during acute exacerbations of COPD and its concentrations are correlated with the severity of exacerbations [33]. SA-A binds to Gram-negative bacteria and is part of the innate defence mechanism against bacterial infections, but it also has pro-inflammatory effects, including the activation of neutrophils, monocytes and T-helper cell (Th) type 17 [34]. It has recently been discovered that SA-A is an activator of Toll-like receptor (TLR)2, resulting in activation of the inflammatory transcription factor nuclear factor (NF)-κB [35].

Surfactant protein D

Surfactant protein (SP)-D is a glycoprotein member of the collectin family and is secreted mainly by type II pneumocytes and plays a role in innate defence against microorganisms. Serum SP-D concentrations are increased in patients with COPD and are better related to disease severity and symptoms than CRP [36]. Since SP-D is derived only from peripheral lung tissue it provides good evidence that lung inflammation can lead to inflammatory changes in the systemic circulation rather than *vice versa*.

Circulating cells

Various abnormalities in circulating leukocytes have been reported in patients with COPD. This may reflect systemic effects of inflammatory mediators derived from the lung on circulating cells or the bone marrow, or abnormalities in circulating cells may represent an underlying mechanism for amplifying inflammation in the lungs in response to cigarette smoking. Abnormalities in circulating leukocytes may have effects on organs other than the lung and therefore may be contributory to comorbidities. An integral part of the systemic inflammatory response is the activation of the bone marrow, which results in the release of leukocytes and platelets into the circulation. The blood leukocyte count is a predictor of total mortality independent of cigarette smoking in a large population-based study [37, 38].

Monocytes

Circulating monocytes in the lung are recruited by chemotactic factors such as CXCL1 (growth-related oncogene-α) and chemokine (C-C motif) ligand (CCL)-2 (monocyte chemotactic protein-1) into the lungs, where they differentiate into the macrophages that drive the disease [39]. Monocytes from COPD patients show enhanced chemotactic responses to CXCL1 and the related chemokine CXCL7 (neutrophil activating protein 2) compared with monocytes from nonsmokers and normal smokers, but normal responses to CXCL8 and CXCL5 (epithelial neutrophil activating peptide of 78kD). There is no increase in expression of their common receptor CXCR2 and the enhanced chemotactic response to CXCL1 appears to be explained by increased turnover of CXCR2 [40]. This abnormality suggests that there may be some intrinsic abnormality in circulating monocytes that could account for the greater accumulation of macrophages in the lungs of COPD patients than in normal smokers [41]. Circulating monocytes also release more matrix metalloproteinase (MMP)-9 spontaneously after lipopolysaccharide stimulation in cells from COPD patients compared with cells from nonsmokers [42].

A major function of alveolar macrophages is phagocytosis of inhaled particles, including bacteria. Alveolar macrophages show decreased phagocytosis of bacteria, such as *Haemophilus influenzae* and *S. pneumoniae*, which colonise the lower airways of COPD patients and may be involved in bacterial exacerbations and in driving the immune inflammatory response. Monocytes from COPD patients have a similar phagocytic potential to cells from normal smokers and nonsmokers, but when transformed into macrophages, show the same defect in phagocytosis as observed in alveolar macrophages [43]. This does not appear to be a generalised defect in phagocytosis as the uptake of inert particles is not impaired. The defect cannot be accounted for by a defect in scavenger receptors and may be due to an intracellular defect in the phagocytic machinery required to take up bacteria. This suggests that there may be an intrinsic defect in monocytes once they differentiate to macrophages in the lungs that may result in impaired innate immunity against bacteria.

Neutrophils

Circulating neutrophil numbers are not increased in COPD patients but there is an inverse correlation between neutrophil numbers in the circulation and FEV_1 [44]. There may be an increased turnover of neutrophils in smokers since neutrophils appear to marginate in the pulmonary circulation and are then replaced in the periphery by increased bone marrow production [45]. In rabbits, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) increase production from the bone marrow in association with downregulation of L-selectin on circulating neutrophils and promoting preferential sequestration in the pulmonary microcirculation [46, 47]. Chemotactic responses to formyl-methionyl-leucyl-phenylalanine and proteolytic activity of circulating neutrophils are increased in patients with emphysema compared with normal smokers and nonsmokers, indicating an abnormality in circulating cells [48]. Neutrophils from COPD patients also show an enhanced production of reactive oxygen species in response to stimulatory agents [49]. Although no difference in spontaneous apoptosis of circulating neutrophils has been reported in COPD patients compared with normal smokers, there is a reduction in L-selectin and an increase in Mac-1 (CD11b) expression [50].

Lymphocytes

Changes in circulating lymphocytes are difficult to interpret as they may reflect a recruitment of circulating lymphocytes into the lungs. In some studies there is no change in total T-cell population but an increase in B-lymphocytes in COPD patients [51, 52]. There is also an increase in apoptosis of peripheral T-lymphocytes from COPD patients, with increased expression of Fas, TNF-α and transforming growth factor (TGF)-β [53]. A more recent study reports an increase in CD8+ cells, particularly those expressing Fas, indicating that there may be an increase in apoptosis of CD8+ T-cells [54]. Subset analysis has shown a slight increase in CD4+ cells expressing interferon (IFN)-γ and a decrease in cells expressing IL-4, indicating Th1 predominance in the peripheral circulation, with no changes in CD8+ cell subsets [55]. Circulating γδ T-cells are increased in normal smokers but not in COPD patients [56].

Natural killer cells

A reduction of cytotoxic and phagocytic function of circulating natural killer cells has been reported in COPD, but the significance of this observation is uncertain [57, 58].

COPD AND IMPAIRED FUNCTIONAL CAPACITY

Functional capacity relates to the ability to perform physical functions. Primarily investigated in patients with cardiac failure, the concept has been associated with the ability to perform predominantly aerobic work (cellular use of oxygen) and practically measured as exercise capacity. The assessment of functional capacity is achieved with the use of a formal cardiopulmonary exercise test and the measured peak oxygen uptake being the gold standard. Simple field tests such as the 6-min walk distance (6MWD) or the shuttle walk test provide limited physiological information, but have excellent prognostic power and clinical applicability. The recent introduction of portable pedometers and accelerator-based activity monitors may better help determine the actual level of activity and functional capacity of patients with COPD. Interestingly, results from one study suggests that the 6MWD correlates well ($r=0.76$) with 24-h activity level and may serve as a surrogate marker for the actual measurement of continuous activity

level [59]. More studies will help clarify the role of the new activity-measuring devices.

The capacity to perform exercise depends on the ability of the respiratory system and the cardiovascular pump to deliver oxygen to the working muscles. The specific details of the response to exercise in normal subjects and patients with COPD is beyond the scope of the current paper and the reader is referred to reviews that specifically address this area [60]. It is clear that functional impairment is critical in patients with clinical COPD and, although in part attributable to the compromise of respiratory function, increasing evidence supports a role for the concomitant presence of systemic components. Recognition of these factors provides a more comprehensive assessment of COPD severity. Decreased exercise capacity measured as decreased peak oxygen uptake and decreased 6MWD predict mortality better than FEV_1 [61, 62]. Pulmonary rehabilitation with exercise training has been shown to increase exercise capacity and thus, it is possible to modify the functional capacity of patients [63, 64]. Whether this will impact on outcome needs to be formally tested, although preliminary results from an uncontrolled trial suggest that pulmonary rehabilitation may improve survival.

Pulmonary factors

The pulmonary physiological factors contributing to functional limitation are all inter-related and it is very hard to separate the independent effect of each factor on overall functional capacity. Although COPD has classically been defined, staged and followed using the degree of FEV_1 limitation [65], an increasing body of evidence shows that static and dynamic hyperinflation is more important in determining functional dyspnoea than the actual degree of obstruction [66]. Likewise, the functional level of dyspnoea is a better predictor of mortality than the degree of airflow obstruction. The level of arterial oxygen and carbon dioxide are important contributors to overall functional compromise in patients with COPD and, although little explored, it is possible that some of the decreased functional capacity of patients with COPD relates to compromised cardiac function secondary to hyperinflation and increased cardiac load resulting from large swings in intra-thoracic pressures.

Systemic factors

The advent of devices capable of measuring and recording activity over long periods of time has shown that patients with COPD are extremely inactive [59]. It is now accepted that some patients with severe COPD develop associated loss of muscle mass and overt malnutrition [67]. Whether the result of systemic inflammation or disuse atrophy, or a combination of both, it is known that the exercise capacity as demonstrated by low peak exercise oxygen uptake during a cardiopulmonary exercise test or decreased 6MWD, are important factors predictive of poor outcome [68]. Interestingly, in patients with severe COPD who have little room to loose more lung function, the decline in FEV_1 slows over time, whereas the decrease in 6MWD continues and may actually help assess the progression of disease [69]. Other factors contribute to decreased functional capacity, including anaemia, osteoporosis and cardiovascular compromise. The use of multidimensional tools such as the BODE (BMI, degree of obstruction, dyspnoea and exercise capacity) index can improve the capacity to express the multidimensional nature of COPD [70]. Other tools such as the health-related quality of life questionnaires, for example the St George's Respiratory Questionnaire and the Chronic Respiratory Questionnaire, also provide a global description of the disease and can be very useful to better represent the complex nature of COPD.

MUSCLE DYSFUNCTION AND MALNUTRITION IN COPD

Skeletal muscle weakness is one of the main systemic effects of COPD and is often accompanied by loss of fat-free mass (FFM) [67]. However, muscle weakness may precede general cachexia [71]. Skeletal muscle accounts for ~40–50% of the total body mass in a male with normal body weight. Skeletal muscle protein turnover is a dynamic process balancing protein synthesis and breakdown. However, many acute and chronic illnesses share the feature of loss of muscle mass due to net breakdown of muscle proteins. In acute illnesses, such as multiple trauma and sepsis, this loss is usually large and occurs rapidly. In chronic illnesses like COPD, loss of muscle mass occurs at a slower rate. A very slow yet substantial loss of muscle mass can be found during ageing, a process called sarcopenia. Several studies have shown that skeletal muscle function and structure are altered in COPD patients. Data from human studies clearly indicate that atrophy of skeletal muscles is apparent in COPD and is specific to muscle fibre type IIA/IIx [72]. Furthermore, these abnormalities are related to respiratory function, exercise intolerance, health status, mortality and healthcare resource utilisation [73]. Muscle wasting is associated with loss of muscle strength, which in turn is a significant determinant of exercise capacity in patients with COPD independent of disease severity. In severe COPD, muscle wasting also has profound effects on morbidity, including an increased risk for hospital readmission after exacerbation as well as an increased need for mechanical ventilatory support. Furthermore, muscle wasting has been identified as a significant determinant of mortality in COPD, which is independent of lung function, smoking and BMI [74, 75].

Mechanisms

Even though peripheral muscle dysfunction is probably the most extensively studied systemic effect of COPD, its mechanisms are still poorly understood, but inactivity appears to be an important factor, as muscles that are active, such as the diaphragm and adductor pollicis, are not usually weak in contrast to inactive muscles, such as quadriceps and vastus lateralis [76]. Furthermore, the deltoid and diaphragm do not show the biopsy characteristics exhibited by the quadriceps [77]. Patients with COPD are very immobile and this is further reduced around the time of exacerbation [59], and patients loose quadriceps strength rapidly around the time of acute exacerbation [18]. Whether by inactivity, heightened inflammation or both, the exercise capacity is significantly decreased during an exacerbation and fails to return to normal up to 1 yr after the episodes [78].

The signal transduction pathways in skeletal muscle weakness are now better understood [79]. Protein degradation in skeletal muscle occurs through several proteolytic systems, including the lysosomal pathway, calcium-dependent proteases, calpain and the 26S ubiquitin proteasome pathways. Loss of muscle

mass is a complex process involving changes in the control of substrate and protein metabolism as well as changes in muscle cell regeneration, apoptosis and differentiation. Impaired protein metabolism may result in muscle atrophy when protein degradation exceeds protein synthesis. However, it is unclear what parts of this balance are disturbed in COPD and whether this is consequent to decreased protein synthesis or increased protein degradation. Increased myofibrillar protein breakdown has been demonstrated in cachectic COPD patients but unfortunately no data are available regarding protein synthesis [80]. There is increased apoptosis of skeletal muscle cells in severely underweight COPD patients [81]. However, this observation has not yet been confirmed in weight-stable COPD patients suffering from muscle wasting [72]. *In vitro* and animal studies suggest that impaired muscle cell differentiation and regeneration may contribute to skeletal muscle atrophy but the relevance of these findings in COPD remains to be determined.

Several studies suggest that systemic inflammation is an important factor involved in the pathogenesis of weight loss and wasting of muscle mass [67]. NF-κB activation in the skeletal muscle of COPD patients may be sufficient for the induction of muscle atrophy [82, 83]. Conversely, inhibition of NF-κB restores muscle mass in a number of experimental models of atrophy, implying an important role for NF-κB in this process. Recently, it has been recognised that physical inactivity itself may induce systemic inflammation and that this may be mediated by reduced function of the transcription factor peroxisome proliferator-activated-γ coactivator (PGC)-1α [84], which is reduced in the skeletal muscle of COPD patients [85].

In addition to inflammation, the development and progression of skeletal muscle dysfunction in COPD has also been strongly associated with enhanced oxidative stress, with increased reactive oxygen species (ROS) production and/or reduced antioxidant capacity. Oxidative stress may be enhanced in skeletal muscle of COPD patients as peroxidation products are elevated in the plasma of COPD patients at rest, after submaximal exercise and during exacerbations of the disease [86]. ROS can increase muscle proteolysis, inhibit muscle-specific protein expression and increase muscle cell apoptosis [87]. Skeletal muscle biopsies from COPD patients show increased protein carbonylation as evidence of increased oxidative stress [88]. Moreover, inducible nitric oxide synthase expression and nitrotyrosine formation are enhanced in the skeletal muscle of COPD patients showing that, in addition to oxidative stress, skeletal muscle is also exposed to nitrosative stress, which may also contribute to protein degradation [82]. Little is known about changes in antioxidant defences in the skeletal muscle of COPD patients but there is evidence of an increase in antioxidants in muscle, presumably reflecting the increased oxidative stress [89].

Treatment

Pulmonary rehabilitation improves skeletal muscle dysfunction of patients with COPD as supported by improvement in exercise capacity and increases in the content of oxidative enzymes in the mitochondria of biopsies of the vastus lateralis muscle [90]. However, the function never returns to normal even after lung transplantation. Perhaps the development of medications that can help reduce oxidative stress or alter the basic pathophysiological mechanisms responsible for the peripheral muscle dysfunction, may help restore full muscle function and improve outcomes.

CARDIOVASCULAR DISEASE

The anatomical and functional relation that exists between the lungs and the heart is such that any dysfunction that impacts in one of the organs is likely to have consequences on the other. This interaction is important in patients with COPD and can be summarised in two types of association. First, one that relates pathologies that share similar risks, such as cigarette smoke and coronary artery disease (CAD), or congestive heart failure and COPD; and secondly, those that result in dysfunction of the heart from primary lung disease, such as secondary pulmonary hypertension and ventricular dysfunction due to increased intra-thoracic mechanical loads.

CAD and atherosclerosis

COPD and CAD are both highly prevalent and share common risk factors, such as exposure to cigarette smoke, older age and sedentarism. It has become increasingly evident that patients with airflow limitation have a significantly higher risk of death from myocardial infarction and this is independent of age, sex and smoking history [91]. In the Lung Health Trial [92], which enrolled almost 6,000 patients and followed them over 14 yrs, FEV_1 was an independent predictor of the probability of dying from a myocardial infarction. This was present even when allowing for smoking history [92]. Patients with milder COPD actually have a higher chance of dying of a cardiovascular cause than from respiratory insufficiency [93]. There is a clear overlap between the risk factors associated with the development of COPD and atherosclerotic vascular disease. Clinically there is a strong correlation between impaired lung function (FEV_1) and cardiovascular morbidity and mortality. However, there is an increased risk of fatal myocardial infarction independent of smoking status in COPD patients [94]. A large population study showed that patients with severe and very severe COPD had a >2-fold greater risk of cardiovascular disease and a 1.6-fold increased prevalence of hypertension, as well as a higher risk of hospitalisation [1]. The most attractive link is the presence of low-grade systemic inflammation in COPD and atherosclerotic cardiovascular disease, which could potentially be the factor driving both pathologies. This systemic inflammation in COPD has been implicated in the pathogenesis of ischaemic heart disease and atherosclerosis in patients with COPD [67]. Atherosclerotic plaques show a low-grade inflammation, with increased numbers of macrophages and IFN-γ secreting Th1 lymphocytes, similar to that in the peripheral lungs of COPD patients [95, 96]. Although the strength of the associations and the mechanisms responsible have not been entirely elucidated, evidence suggest that patients with COPD should be screened for the presence of concomitant atherosclerosis and just as importantly, patients evaluated for the presence of atherosclerotic heart disease should be investigated for the concomitant presence of airflow.

Heart failure

Much less evidence exists for an association between COPD and left ventricular congestive failure. Although, at the centre of the theory that presents COPD as one of a group of diseases

that share a common inflammatory background, the actual prevalence of decreased left ventricular function in patients with COPD is largely unknown and clinically poorly defined. One study showed a prevalence of left ventricular failure of ~20% among COPD patients who had not previously had this diagnosis [97]. However, the diagnosis of heart failure in COPD is complicated by the overlap in symptoms and signs. Measurement of B-type natriuretic peptide or N-terminal prohormone brain natriuretic peptide (NT-proBNP) is a good way to discriminate heart failure in COPD patients [98] and may be useful to distinguish acute COPD exacerbations from decompensated heart failure [99]. An elevated plasma NT-proBNP is correlated with poor physical activity in COPD patients, suggesting that left defective left ventricular function may contribute to reduced performance [100]. There is some evidence that, if anything, the cardiac size is decreased at least in patients with emphysema and that the actual volume of intra-thoracic blood is also decreased in patients with hyperinflation. The increase in intra-thoracic blood volume after lung volume reduction surgery and the suggested improvement in left ventricular function improvement appear more related to changes in intra-thoracic pressures than to a parallel pathological deterioration of lung and cardiac function with inflammation at its centre.

Pulmonary arterial hypertension

Although clinical pulmonary arterial hypertension (PAH) at rest is uncommon in patients with mild to moderate stages it can develop during exercise. However, there is a subset of patients (1–3%) with severe PAH that is disproportionate to the degree of airway impairment who behave like patients with primary pulmonary hypertension [101]. Approximately 50% of patients with very severe COPD who undergo lung volume reduction surgery (LVRS) or lung transplantation have moderate to severe PAH [102]. In these patients with end-stage COPD and pulmonary hypertension or cor pulmonale, *post mortem* studies show deposition of muscle, fibrosis and elastosis that produce the enlargement of the intima in pulmonary muscular arteries [101]. Compared with mild COPD, lung tissue specimens obtained during LVRS show enlarged intima with reduced medial thickness. In mild to moderate COPD, pulmonary muscular arteries have an enlarged intimal layer, due to the proliferation of poorly differentiated smooth muscle cells and deposition of elastic and collagen fibres, with reduction of the lumen and arteriolar muscularisation. The contribution of hypoxic vasoconstriction to the ventilation–perfusion ratio balance tends to be greater in less severe COPD but is less active in advanced stages. Endothelial dysfunction, with changes in the expression and release of endothelium-derived vasoactive mediators that regulate cell growth, is a common feature in COPD and may appear early in the natural history of the disease. This dysfunction provides the basis for further changes in vascular structure and function induced by additional factors. There is emerging evidence that the initial event in the natural history of PAH in COPD could be endothelial injury by cigarette-smoke products with the subsequent down regulation of endothelial nitric oxide synthase and prostacyclin synthase expression and the impairment of endothelial function [103]. When the disease progresses, sustained hypoxaemia and inflammation may induce further pulmonary vascular remodelling, thereby amplifying the initial effects of cigarette smoke [104].

Despite evidence of PAH, systemic and selective vasodilators are not routinely recommended for the treatment of PAH in COPD, since the induction of mild decreases in pulmonary arterial pressure (with or without increased cardiac output) is usually associated with deterioration in gas exchange and no evidence of clinical benefit during long-term treatment. The long-term effect on outcomes with the use of selective vasodilators remains to be established. Long-term oxygen therapy appears to be the most effective treatment for PAH in hypoxaemic COPD patients because its administration slows down the progression of PAH. The potential of new targeted agents for the treatment of pulmonary hypertension in COPD needs to be approached with caution as some of these drugs might inhibit hypoxic pulmonary vasoconstriction and induce further worsening of gas exchange.

The contribution of systemic inflammation to PAH in COPD patients is not yet clear. The inflammation in pulmonary vessels of COPD patients has the same cells as seen in peripheral airways and parenchyma, namely macrophages, CD8+ T-lymphocytes and neutrophils, even in mild COPD patients [104].

Cardiac function at rest

The majority of patients with milder COPD have normal right heart function at rest. In some, but not all patients, there is a development of right ventricular dysfunction as the disease progresses in severity (more airflow limitation). In a recent review of patients undergoing right side cardiac catheterisation as part of the evaluation for LVRS, the prevalence of mild pulmonary hypertension defined as mean pulmonary artery pressure of >25 mmHg (>3.33 kPa) is ~50% [102]. There is a modest but statistically significant relationship between FEV_1 and pulmonary artery pressure. Conversely, the prevalence of significant pulmonary hypertension as defined by a mean pressure of >35 mmHg (>4.65 kPa) is small and appears not to be related to the degree of airflow limitation, suggesting that there may be an independent phenotype of patients with COPD who manifest pulmonary hypertension with COPD rather than as a result of it. The prevalence of true cor pulmonale with its clinical expression of the blue-bloated patient seems to be decreasing. The exact reason for this is not clear but could be related to the early supplementation of oxygen in patients with hypoxaemia, thus preventing a major cause of pulmonary vascular constriction, or to the overall effect of better therapy for patients with COPD.

Cardiac function during exercise

The response of the pulmonary circulation and the heart to exercise is more complex. As COPD progresses, exercise capacity decreases and in more severe COPD, the factor limiting exercise is the ceiling imposed by ventilatory limitation. This means that patients become dyspnoeic and are unable to continue exercising at lower levels of exercise [66]. However, additional mechanisms may also impact on cardiovascular function during exercise. During exercise, patients develop relatively high intra-thoracic pressures due to impedance to increased ventilatory demands and as a consequence of dynamic hyperinflation. In a study of patients with severe

COPD undergoing cardiopulmonary exercise tests, swings in intra-thoracic pressures measured with oesophageal balloons ranged from negative pressures of -16 cmH_2O (-2.13 kPa) during inspiration to as high as 24 cmH_2O (3.19 kPa) during exhalation [105]. The variables most intimately related to exercise capacity and oxygen pulse are changes of the intra-thoracic pressures during inspiration and the pressure at the end of inspiration. These findings are best explained by an incapacity of the heart to normally raise the cardiac output with exercise as its function is impaired by the pressure that surround it. Indeed, right heart catheterisation shows that patients with severe COPD who hyperinflate either during exercise or by voluntary hyperventilation develop high negative intra-thoracic pressures resulting in increased pulmonary and capillary wedge pressures, suggestive of left ventricular dysfunction [106]. Taken together these studies suggest that the function of the heart is mechanically constrained by the dynamic hyperinflation that is associated with exercise or increased ventilatory demand in patients with COPD whose resting hyperinflation is already a limiting problem. Indeed, the most hyperinflated patients manifest a decreased oxygen pulse (an indirect measure of stroke volume) during an isowork cardiopulmonary exercise test compared with patients with similar airflow limitation but less hyperinflation. The fact that intra-thoracic blood volume and cardiac function improve after LVRS supports this hypothesis [107].

Arterial stiffness and endothelial function

Arterial stiffness as a result of vascular disease is a good predictor of cardiovascular events and can be assessed noninvasively by measuring aortic pulse wave velocity or radial artery tonometry [108]. Arterial stiffness is increased in patients with COPD compared with normal smokers and nonsmokers and is unrelated to disease severity or circulating CRP concentrations [109, 110]. The increased arterial stiffness may predispose patients to systemic hypertension and an increased risk of cardiovascular disease in COPD patients [111]. Arterial stiffness may reflect common pathological mechanisms, such as abnormalities in connective tissue or inflammation, or may be a response to the systemic inflammation associated with COPD. One mechanism for reduced arterial stiffness is impaired endothelial NO production. COPD patients with emphysema have impaired flow-mediated vasodilatation, which may reflect a generalised impairment in endothelial function, possibly in response to systemic inflammation [112]. The defect in endothelial function may reflect a reduction in circulating endothelial progenitor cells that repair endothelial injury and maintain normal function [113].

NORMOCYTIC ANAEMIA

Contrary to common teaching, recent studies have shown that there is a high prevalence of anaemia in COPD patients, ranging 15–30% of patients, particularly in patients with severe disease, whereas polycythaemia (erythrocytosis) is relatively rare (6%) [114–116]. The level of haemoglobin is strongly and independently associated with increased functional dyspnoea and decreased exercise capacity, and is therefore an important contributor to functional capacity as well as a poor quality of life [115, 117]. In some studies, anaemia is an independent predictor of mortality [118]. The anaemia is usually of the normochromic normocytic type characteristic for diseases of chronic inflammation and appears to be due to resistance to the effects of erythropoietin, the concentration of which is elevated in these patients [119]. Whether the treatment of anaemia will result in improvement in functional outcome measures remains to be determined. Treatment with erythropoietin is unlikely to be useful as there is end-organ resistance, indicating that blood transfusion may be necessary. In a small study in anaemic COPD patients, blood transfusion improved their exercise performance [120]. Iron supplements are likely to be detrimental as iron cannot be utilised correctly and may increase systemic oxidative stress.

OSTEOPOROSIS

Several studies have shown a very high prevalence of osteoporosis and low bone mineral density (BMD) in patients with COPD, even in milder stages of disease [121]. Over half of patients with COPD recruited for the large TORCH (Towards a Revolution in COPD Health) trial (6,000 patients) had osteoporosis or osteopenia as determined by dual-energy radiograph absorptiometry (Dexa) [93]. In a cross-sectional study the prevalence of osteoporosis was 75% in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV disease and was strongly correlated with reduced FFM [122, 123]. Interestingly, the prevalence is high for males and even higher for females. The incidence of traumatic and nontraumatic fractures is similar for both sexes. The relationship between osteoporosis and functional limitation is uncertain but likely to be important as fractures remain a daunting problem in the elderly. Vertebral compression fractures are relatively common among COPD patients and the resultant increased kyphosis may further reduce pulmonary function [124].

Mechanisms

COPD patients have several risk factors for osteoporosis, including advanced age, poor mobility, smoking, poor nutrition, low BMI and high doses of inhaled corticosteroids as well as courses of oral steroids. Low BMD is correlated with reduced FFM in COPD patients [125]. However, COPD itself may be a risk factor for osteoporosis and this may be related to systemic inflammation. Using computed tomography (CT) to determine bone density of thoracic vertebrae, there is a significant correlation between CT-measured emphysema and bone density, supporting the view that osteoporosis is related to emphysema [126]. There is some evidence that osteoporosis is also associated with an increased risk of atherosclerosis and heart disease in patients without COPD [109]. The association between osteoporosis and increased arterial wall stiffness as well as between these variables and the systemic level of IL-6 suggests a common association with the degree of systemic inflammation. Indeed, several inflammatory mediators, including TNF-α, IL-1β and IL-6 act as stimulants of osteoclasts, which cause bone resorption [127]. Osteoclasts are regulated by a receptor activator of NF-κB (RANK) and the TNF-like RANK ligand, which synergise with TNF-α and are inhibited by osteoprotogerin, another TNF-like cytokine, which is regulated by TGF-β [128].

Therapy

BMD should be measured, either by Dexa or CT, in all patients with GOLD grade III and IV, particularly in patients with a low FFM. Evidence from the trials of inhaled steroids in patients

with COPD suggests that it does not result in an increased incidence in osteoporosis or fractures over 3 yrs, although there may be a reduction in plasma osteocalcin [93, 129]. Regardless of sex, patients with COPD attending clinics should be treated with a bisphosphonate, as recommended by current guidelines [130]. A trial of alendronate in patients with COPD showed some improvement in BMD in the lumbar spine but not the hip over 1 yr of therapy [131].

DEPRESSION

Due to their physical impairment, patients with COPD are frequently isolated and unable to engage in many social activities. It is not surprising that anxiety and depression are very frequent in patients with COPD and appear to be more prevalent than in other chronic diseases. Anxiety and depression symptoms may be confused with symptoms of COPD, so these psychiatric problems are often undiagnosed and untreated in clinical practice. Depressive symptoms that are clinically relevant are estimated to occur in 10–80% of all patients. Conversely, in clinically stable outpatients with COPD, the prevalence of major depression (that requires medical intervention) ranges 19–42% [132, 133]. There is no standardised approach for the diagnosis of depression in patients with COPD because of the differences in methodology and variability of the screening questionnaires in cut-off points to determine a diagnosis of depression. However, several simple tools can help the clinician screen for depression and if in doubt, referral to the appropriate specialist can have important beneficial effects for individual patients.

Mechanisms

The mechanisms responsible for depression in patients with COPD are unknown and likely to be multifactorial [134]. Depression may precede the development of COPD and there might be shared genetic factors but smoking is more frequent in patients with anxiety and depression. ''Reactive'' depression associated with declining health status is more common. The effects of ageing, smoking and hypoxaemia on brain function are likely to contribute to its genesis. There is growing evidence that systemic inflammation may result in depression and IL-6 appears to play a particularly important role in humans and in animal models of depression [135].

Treatment

Whatever the cause, untreated depression increases the length of hospital stay, frequency of hospital admissions, and leads to impaired quality of life and premature death [133]. However, depression often remains untreated in COPD patients. The benefit of antidepressants in the treatment of depression in COPD has been inconclusive in several small clinical trials, although these have often been poorly designed and there is a need for larger properly controlled trials in the future. Several studies have shown that pulmonary rehabilitation alone improves depression and anxiety. In a recent study, the improvement in depression and anxiety after rehabilitation was unrelated to the improvement in dyspnoea, suggesting that if present, depression itself should be targeted for therapy independent of the treatment offered for the other better known manifestations of COPD [136]. Psychotherapy added to pulmonary rehabilitation significantly reduces depression in COPD patients [137]. Cognitive behavioural therapy also improves the quality of life in COPD patients with depression [138]. Finally, if depression is caused by systemic inflammation then treating lung inflammation or systemic anti-inflammatory treatments should also be effective and depression needs to be measured in controlled trials in COPD patients once these drugs are in large clinical trials.

LUNG CANCER

Patients with COPD are 3–4 times more likely to develop lung cancer than smokers with normal lung function [139, 140] and lung cancer is a common cause of death in COPD patients, particularly those with severe disease [93, 141]. There is an increased risk of small cell and squamous cell cancers to a greater extent than adenocarcinomas. Smoking cessation does not appear to reduce the risk of lung cancer [92]. Interestingly, lung cancer was also more common in patients with COPD who had never smoked in a large prospective trial of almost half a million nonsmokers [142]. Females may have a greater risk of COPD and lung cancer, possibly due to hormone-stimulated metabolism of carcinogens in tobacco smoke [143].

Mechanisms

The increased prevalence of lung cancer in COPD patients is probably linked to the increased inflammation and oxidative stress in COPD (fig. 2) [144]. NF-κB activation may provide a link between inflammation and lung cancer [145]. Pro-inflammatory cytokines may also promote tumour angiogenesis, which accelerates cell growth and metastases. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates multiple antioxidant and detoxifying genes, is functionally defective in COPD lungs [146] and may contribute to the increased susceptibility of COPD patients to lung cancer, since Nrf2 plays an important role in defence against certain carcinogens in tobacco smoke by regulating the expression of several detoxifying enzymes [147]. Epidermal growth factor receptors (EGFR), which promote epithelial proliferation, show an increased expression in COPD patients [148].

Therapy

Since the increased risk of lung cancer in COPD may reflect inflammation in the lungs, then anti-inflammatory therapies or antioxidants should theoretically decrease the risk of lung cancer. Inhaled corticosteroids do not appear to reduce lung cancer mortality, presumably as they do not suppress inflammation in COPD patients [93]. Patients with nonsmall cell lung cancer and adenocarcinoma who have activating mutations of EGFR may benefit from treatment with an EGFR tyrosine kinase inhibitor, such as erlotinib or gefitinib, and these treatments could also be of benefit in treating mucus hypersecretion [149].

DIABETES

Large population studies show that there is an increased prevalence of diabetes among COPD patients (relative risk 1.5–1.8), even in patients with mild disease [1, 150]. The reasons for this association are not yet understood. It is unlikely to be explained by high doses of inhaled corticosteroids, as patients who are steroid-naïve with mild disease also have an increased risk of diabetes. Interestingly, patients with asthma do not have an increased risk of diabetes, so this may suggest a link to the different pattern of inflammation in COPD compared with

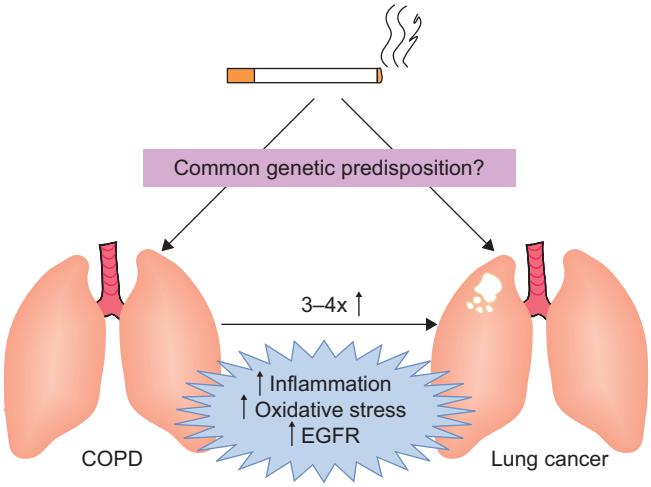

FIGURE 2. Increased lung cancer in chronic obstructive pulmonary disease (COPD). Inflammation and increased oxidative stress in COPD may enhance the growth and metastasis of lung cancer. In addition, increased expression of epidermal growth factor receptors (EGFR) may accelerate cancer growth. Small arrows: increase.

asthma and may be related to systemic inflammation. Pro-inflammatory cytokines, including TNF-α and IL-6, induce insulin resistance by blocking signalling through the insulin receptor and increase the risk of type 2 diabetes [151]. Increased plasma CRP, TNF-α and IL-6 concentrations are also seen in the metabolic syndrome, which includes insulin resistance and cardiovascular disease [152]. The metabolic syndrome also appears to be more common among COPD patients, reflecting the concurrence of diabetes and cardiovascular disease with airway obstruction [153].

OBSTRUCTIVE SLEEP APNOEA

Epidemiological studies have shown that ~20% of patients with obstructive sleep apnoea (OSA) also have COPD, whereas ~10% of patients with COPD have OSA independent of disease severity [154]. OSA patients also share several of the comorbidities of COPD, such as endothelial dysfunction, cardiac failure, diabetes and metabolic syndrome [155]. There is recent evidence that OSA patients have local upper airway inflammation, as well as systemic inflammation and oxidative stress [156, 157].

IMPLICATIONS FOR THERAPY

As comorbidities and systemic features of COPD are very common it is important to consider both in the management plan for COPD. The first approach involves suppression of pulmonary inflammation to prevent associated systemic diseases if they are due to or exacerbated by spill-over of inflammatory mediators from the lung into the systemic circulation. The second is to treat the systemic disease and to see whether this reduces features of COPD pulmonary disease. However, it has proved difficult to discover novel treatments for COPD, other than bronchodilators [158]. The other aspect that is now emerging is that treatments for certain comorbidities may also unexpectedly benefit COPD and indeed may provide the basis for future therapeutic approaches [159, 160].

Current therapies for COPD and their effects on important outcomes are shown in table 2.

Treatment of systemic effects with current COPD therapy

Inhaled therapy may reduce inflammation in the lung and thereby reduce systemic inflammation that results from spill-over from the lungs into the systemic circulation. Alternatively, inhaled drugs may reach the systemic circulation after absorption from the lungs or from the gastrointestinal tract after swallowing.

Inhaled corticosteroids

High-dose inhaled corticosteroids (ICS) are widely used in the management of COPD, either alone or combined with a long-acting β_2-agonist (LABA). ICS, even in high doses, fail to suppress inflammation in COPD lungs and airways and this may be due to an active resistance mechanism linked to a reduction in histone deacetylase 2 expression [161]. Observational studies suggested that ICS reduces all causes of mortality in COPD patients, including cardiovascular mortality [162], and ICS have been shown to reduce markers of systemic inflammation, such as CRP [163]. However, a prospective study of high-dose ICS in COPD patients (TORCH study) showed a minimal reduction in all causes of mortality, indicating that it is unlikely that there is a significant clinical benefit of ICS on COPD comorbidities such as cardiovascular disease or lung cancer, which are the commonest causes of death [93]. A controlled trial of high-dose ICS with or without a LABA showed no reduction in systemic inflammation in COPD patients, as measured by circulating IL-6 and CRP concentrations, indicating likely corticosteroid resistance of systemic as well as local inflammation in COPD patients [164]. However, there was a reduction in SP-D, indicating that ICS may reduce the production of lung-specific markers of inflammation.

LABAs

LABAs are useful bronchodilators in COPD patients, but it is uncertain whether they have anti-inflammatory effects. The combination inhaler, salmeterol/fluticasone, reduces inflammation in COPD airways [165, 166], whereas an ICS alone is ineffective [166]. This suggests either that there is a synergistic interaction between the LABA and the corticosteroid, or that the LABA is responsible for the anti-inflammatory effects. Whether inhaled LABA or oral β_2-agonists have any beneficial effects of systemic features of COPD has not yet been systematically investigated. There is evidence that various β_2-agonists increase skeletal muscle mass and strength, and prevent fatigue [167], suggesting that there is potential for improving skeletal (and respiratory) muscle weakness in COPD patients. However, cardiovascular complications of systemic β_2-agonists may be a problem, although the sustained effects over 24 h of the pro-drug bambuterol are relatively well tolerated in COPD patients, in whom it is an effective bronchodilator [168].

Anticholinergics

There is considerable evidence that acetylcholine can be released from non-neuronal cells, such as epithelial cells and macrophages, and that it may activate muscarinic receptors on inflammatory and structural cells, including neutrophils,

TABLE 2 Respiratory and systemic effects of current therapies for chronic obstructive pulmonary disease

Therapy	Respiratory effects	Systemic effects
Bronchodilators	Improve airflow obstruction	Improve quality of life
	Decrease static and dynamic hyperinflation	May cause anxiety, tremors and dry mouth
	Decrease exacerbations	
	Increase exercise endurance	
	Decrease functional dyspnoea	
ICS and LABA	Improve airflow obstruction	Improve quality of life
	Decrease static and dynamic hyperinflation	May decrease inflammatory markers (CRP and TNF-α)
	Decrease CD8+ lymphocytes in airway biopsy	Increase risk of pneumonia
	Decrease exacerbations	
	Increase exercise endurance	
	Decrease functional dyspnoea	
Lung volume reduction surgery	Improves airflow obstruction	Increases BMI
	Decreases static and dynamic hyperinflation	Improves osteoporosis
	Improves gas exchange	Improves quality of life
	Decreases functional dyspnoea	Improves BODE scores
	Improves respiratory muscle function	May improve survival
	Increases exercise endurance	Risk of surgical complications and mortality
Pulmonary rehabilitation	Delays dynamic hyperinflation	Improves BODE scores
	Improves exercise endurance	May improve survival
	Decreases functional dyspnoea	
Oxygen therapy	Prevents progression of pulmonary hypertension	Improves survival
	Increases exercise endurance	
	Decreases exercise dyspnoea	

ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; CRP: C-reactive protein; TNF-α: tumour necrosis factor-α; BMI: body mass index; BODE: body mass index, airflow obstruction, dyspnoea and exercise capacity.

macrophages, T-lymphocytes and epithelial cells [169]. This suggests that anticholinergics have the potential for anti-inflammatory effects in COPD, particularly since tiotropium bromide reduces exacerbations. However, tiotropium has no effect on inflammatory markers in sputum (IL-6, CXCL8 and myeloperoxidase) or in the circulation (IL-6 and CRP) of COPD patients, despite a reduction in exacerbations [170]. Anticholinergics (and other bronchodilators) may reduce the mechanical forces in the lung due to airway closure and this might reduce the expression of TGF-β and other mediators released in response to the mechanical strain of epithelial cells [171, 172]. This may have beneficial effects on systemic inflammation.

Theophylline

Theophylline has more potential as a treatment for lung inflammation in COPD, since low-dose oral theophylline reduces neutrophilic inflammation and sputum CXCL8 in COPD patients [173]. However, it is not known whether theophylline has any beneficial effects on systemic features or comorbidities of COPD. High doses of theophylline were shown to increase diaphragm strength in COPD patients, but this was not confirmed in other studies [174]. Low-dose theophylline has the potential to reverse corticosteroid resistance in COPD.

LVRS

Compared with patients remaining on medical therapy, the patients who have undergone LVRS have improved BMI associated with a better metabolic profile [175], improved osteoporosis, increased intra-thoracic lung volume and cardiac function, and improved overall BODE index and long-term survival [176]. These observations are important as they suggest that therapy primarily directed at altering lung structure and function can have systemic consequences independent of a primary effect on the inflammatory events occurring within the airways themselves. Unfortunately, none of the large pharmacological trials have been designed to evaluate this hypothesis and more research addressing these effects is needed.

Pulmonary rehabilitation

The results of over 30 randomised trials of pulmonary rehabilitation have shown that it is possible to beneficially impact on functional capacity, health-related quality of life, perception of dyspnoea, healthcare utilisation and on the BODE index with minimal, if any, impact on lung function, thus supporting the argument that it may be possible to modulate the course of COPD with therapies aimed at improving the nonpulmonary domains of COPD [177].

Treatments for comorbidities that may benefit COPD outcomes

It is now becoming clear from a number of observational studies that treatment of comorbid diseases may have some unexpected benefit on COPD. Observational and epidemiological studies have suggested that some treatments, such as statins and angiotensin converting enzyme (ACE) inhibitors,

used for comorbid diseases, may apparently benefit COPD, with a reduction in exacerbations and mortality [178–180]. This may reflect beneficial effects of these drugs on the comorbidities, associated with COPD, such as cardiovascular disease, but there may also be a therapeutic effect on the inflammatory disease process of COPD.

Statins

Although 3-hydroxy-3-methyl-3-glutaryl coenzyme A reductase inhibitors (statins) reduce cholesterol, they have several other pharmacological actions that might be beneficial in COPD, including antioxidant, anti-inflammatory and immunomodulatory effects (fig. 3). Many of these pleiotropic effects of statins are mediated by the inhibition of isoprenylation of small guanosine-5′-triphosphate-binding signalling molecules, such as Rho, Ras and Rac [181]. Through these mechanisms, statins reduce the expression of adhesion molecules, such as inter-cellular adhesion molecule 1, vascular cell adhesion molecule 1 and E-selectin, that are involved in the recruitment of inflammatory cells (neutrophils, monocytes and lymphocytes) from the circulation into the lungs. Statins also reduce the expression of chemokines, such as CCL2 and CXCL8, and MMPs, such as MMP-9, all of which are increased in COPD [182]. Some of these effects may be mediated *via* activation of peroxisome proliferator-activated receptors (PPAR)-α and -γ and some *via* inhibition of NF-κB. Statins prevent the development of emphysema in mice exposed to cigarette smoke and this is associated with a reduction in the expression of TNF-α, IFN-γ and MMP-2, -9 and -12 and a reduction in neutrophils in bronchoalveolar lavage fluid [183]. Statins also prevent elastase-mediated emphysema in mice and are associated with evidence for proliferation and regeneration of alveolar epithelial cells [184]. At a cellular level, statins inhibit the effects of IL-17 and TGF-β in stimulating mediator release from primary airway epithelial cells, indicating their potential to modulate the inflammatory response and small airway fibrosis in COPD [185]. Statins also stimulate the uptake of apoptotic neutrophils by alveolar macrophages (efferocytosis), an effect that is mediated *via* inhibition of the prenylation and activation of RhoA, which is involved in the phagocytosis of apoptotic cells [186]. Phagocytosis of apoptotic cells is impaired in COPD [187], which suggests that statins may accelerate the resolution of neutrophilic inflammation in COPD. Recently, statins have been shown to inhibit Th17 cells though an inhibitory effect on their regulatory transcription factor retinoic acid orphan receptor γt [188]. Th17 cells may play a role in orchestrating neutrophilic inflammation in COPD through the effect of IL-17 on epithelial cells to release CXCL1 and CXCL8 [189]. All of these studies on the pleiotropic effects of statins suggest that they may have a beneficial effect in COPD and this may contribute to the reduction in exacerbations in COPD patients treated with statins in observational studies [178–180, 190]. Through their pleiotropic effects, statins may have beneficial effects not only on cardiovascular disease but also other comorbidities associated with COPD, including diabetes, osteoporosis and lung cancer [191]. Prospective controlled trials are now needed to establish whether statins have beneficial effects in COPD patients, especially those with systemic complications and comorbidities. The dose-response for the pleiotropic effects of statins has not yet been established and may differ from their cholesterol lowering effects. High doses of statins may have adverse effects, particularly on skeletal muscles, so it is possible that statins could be delivered by the inhaled route.

ACE inhibitors

ACE inhibitors are widely used to treat hypertension and heart failure, and in observational studies these drugs have been associated with reduced exacerbations and mortality of COPD patients [178]. ACE inhibitors reduce pulmonary hypertension but may have other beneficial effects in COPD as angiotensin II may have pro-inflammatory effects [192]. Indeed, an angiotensin II receptor antagonist irbesartan has been shown to reduce hyperinflation in COPD patients, although its mechanism of action is uncertain [193]. Polymorphisms of the ACE gene have been linked to increased susceptibility to COPD [194] and quadriceps strength in COPD patients [195]. Since ACE inhibitors are routinely used in the management of hypertension, cardiac failure and diabetes, all of which are common comorbidities of COPD, prospective trials of ACE inhibitors in COPD patients are now warranted.

PPAR agonists

PPARs play an important role in the regulation of cellular metabolism and energy homeostasis and have been implicated in several systemic manifestations of COPD, including cachexia, skeletal muscle weakness and systemic inflammation [85]. Several anti-inflammatory mechanisms of PPAR agonists have now been documented, including suppression of adhesion molecule expression, chemokine secretion and TLR (fig. 4) [196]. The immunomodulatory effects of PPAR agonists on IL-17 and IFN-γ secretion is of particular relevance to COPD. There is reduced expression of PPAR-α and PPAR-δ in skeletal muscle of COPD patients who have cachexia, as well as

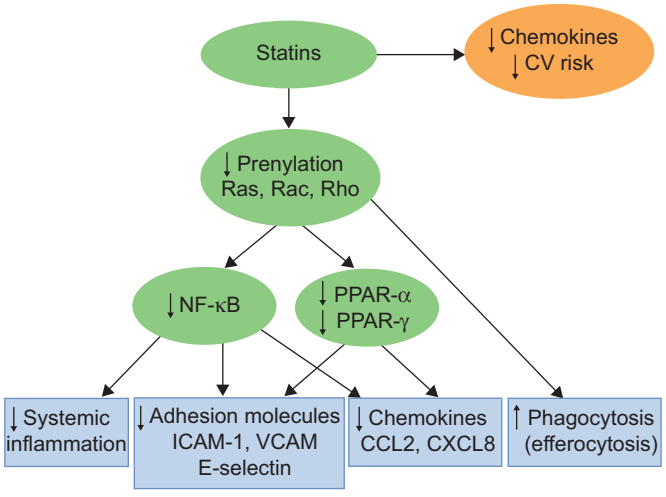

FIGURE 3. Beneficial effects of statins in chronic obstructive pulmonary disease (COPD). Statins reduce cholesterol and thus cardiovascular (CV) risk, but also have pleiotropic effects mediated though inhibition of prenylation and isoprenylation of small GTPases, such as Ras, Rac and Rho. This may enhance phagocytosis of apoptotic cells (efferocytosis), or decrease inflammation through inhibition of nuclear factor (NF)-κB and activation of peroxisome proliferator-activated receptors (PPAR) to decrease inflammatory cytokines, chemokines and adhesion molecules. Small arrows indicate an increase or decrease. ICAM-1: intercellular adhesion molecule 1; VCAM: vascular cell adhesion molecule.

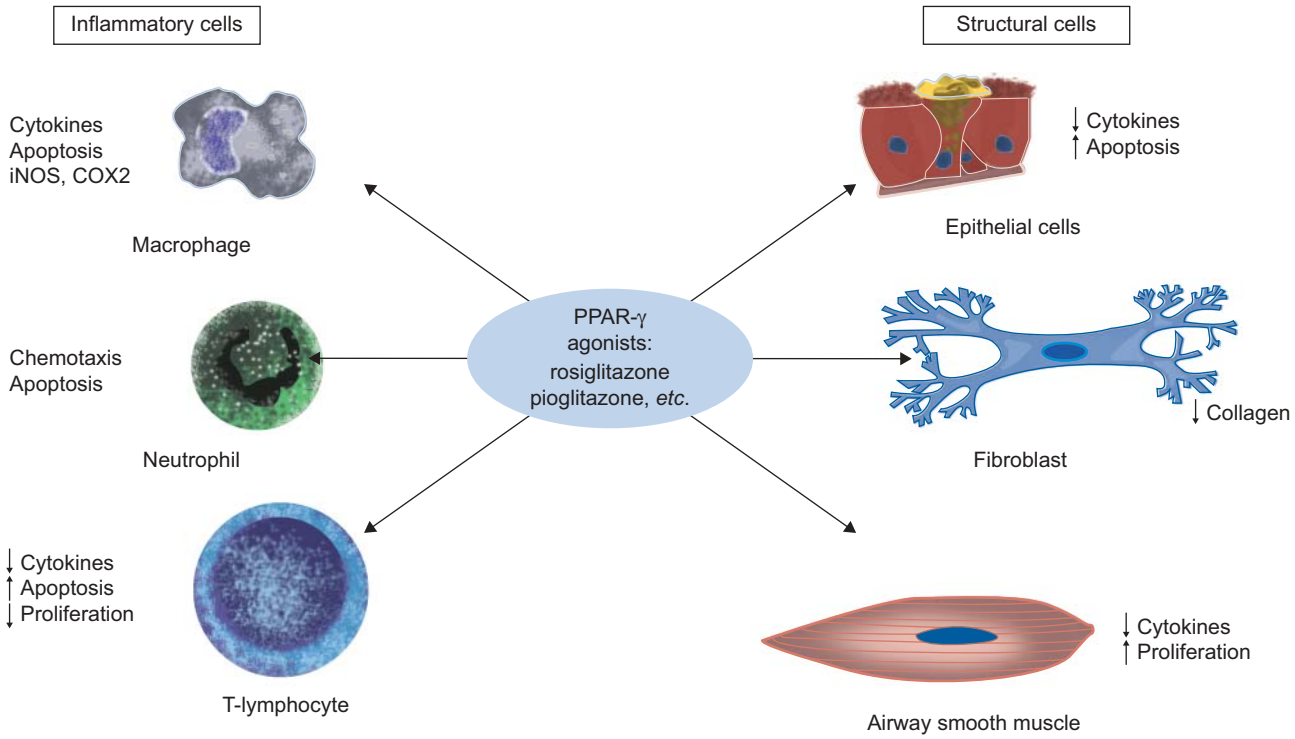

FIGURE 4. Peroxisome proliferator-activated agonist (PPAR)-γ effects on inflammatory and structural cells. iNOS: inducible nitric oxide synthase; COX: cyclooxygenase. Small arrows indicate an increase or decrease.

reduced expression of PGC-1α [197]. Reduced PPAR-α expression is correlated with cachexia and systemic inflammation, suggesting that PPAR-α agonists, such as clofibrate and fenofibrate, may have therapeutic potential in treating the systemic features of COPD. PPAR-α and PPAR-γ agonists inhibit the expression of several inflammatory genes in inflammatory cells such as macrophages, suggesting that they have the potential for treating pulmonary inflammation in COPD as well as systemic effects. PPAR-γ agonists, such as rosiglitazone, which are used to treat diabetes, reduce neutrophilic inflammation in the lungs of mice exposed to intratracheal endotoxin and this is associated with a reduction in CXC chemokines and GM-CSF [198]. PPAR-γ agonists inhibit the profibrotic effect of TGF-β on fibroblasts and have been shown to reduce pulmonary fibrosis in animal models [199]. Rosiglitazone inhibits the effects of TGF-β on the differentiation and collagen secretion by human lung fibroblasts and myofibroblasts [200, 201] and in animal models of bleomycin-induced pulmonary fibrosis [201]. This suggests that PPAR-γ agonists might reduce small airway fibrosis in COPD, which is currently untreatable. So far no trials of PPAR-α agonists (fibrates) or PPAR-γ agonists (thiazolidinediones) in COPD have been reported. Concern about the cardiovascular side-effects of thiazolidinediones has recently limited their use in the treatment of diabetes, but it is possible that these drugs may work by inhalation to avoid any cardiovascular risk in a high-risk population such as COPD patients.

New therapies

As corticosteroids fail to suppress inflammation effectively in COPD, in marked contrast to asthma, several alternative anti-inflammatory approaches are currently being investigated [158]. These drugs have largely been developed as systemic treatments and would therefore be expected to reduce systemic inflammation and perhaps treat systemic manifestations of COPD, such as skeletal muscle weakness and osteoporosis. However, a major limitation of the broad spectrum anti-inflammatory treatments currently in development has been side-effects, which have limited the doses that can be given. This has led to a search for inhaled anti-inflammatory drugs that are retained in the lung or inactivated in the systemic circulation. Broad spectrum anti-inflammatory treatments, such as phosphodiesterase (PDE)4, p38 mitogen-activated protein kinase (MAPK) and NF-κB inhibitors have been in development for oral administration and are therefore suitable for suppressing systemic inflammation and thus comorbid diseases. Unfortunately, because the targets for these drugs are widely distributed, side-effects and toxicological problems have proved a major barrier to clinical development.

PDE4 inhibitors

PDE4 inhibitors are the most developed of the novel anti-inflammatory treatments for COPD. A selective PDE4 inhibitor, roflumilast, inhibits lung inflammation and emphysema in a smoking model of COPD in mice [202]. In COPD patients, oral roflumilast given over 4 weeks significantly reduces the number of neutrophils (by 36%) and CXCL8 concentrations in sputum [203]. In clinical trials, roflumilast given over 6 or 12 months improves lung function in COPD patients to a small extent but has no significant effect in reducing exacerbations or improving health status [204, 205]. These results are likely to reflect the fact that side-effects, particularly nausea, diarrhoea and headaches, limit the dose that can be tolerated. This indicates that it may not

be possible to reach an oral dose that is effective and acceptable to patients. This could be overcome by inhaled delivery, but to date two inhaled PDE4 inhibitors have been found to be ineffective, although well tolerated. Systemic inflammation or effects on skeletal muscles or comorbidities in COPD patients have not yet been assessed. However, in rats a PDE4 inhibitor prevented bone loss and increased skeletal muscle mass in ovariectomised animals, suggesting that PDE4 inhibitors have the potential to prevent osteoporosis and skeletal muscle wasting in COPD patients [206].

NF-κB inhibitors

NF-κB regulates the expression of chemokines, TNF-α and other inflammatory cytokines, as well as MMP-9. NF-κB is activated in macrophages and epithelial cells of COPD patients, particularly during exacerbations [207]. NF-κB activation is also implicated in mediating systemic inflammation and may be involved in skeletal muscle weakness in COPD patients [82]. NF-κB activation is important in skeletal muscle atrophy and the inhibition of NF-κB may prevent this in animals [83]. NF-κB activation has also been implicated in several of the comorbidities associated with COPD, including cardiovascular disease, lung cancer, osteoporosis and diabetes [208]. Although there are several possible approaches to inhibition of NF-κB, small molecule inhibitors of NF-κB kinase (IKK)2 are the most promising. Although several IKK2 inhibitors are now in development, so far none have been tested in COPD patients. This suggests that IKK2 inhibitors may also treat some of the systemic complications of COPD. However, there is concern that long-term inhibition of NF-κB may result in immune suppression and impair host defences, since mice that lack NF-κB-associated genes succumb to septicaemia.

p38 MAPK inhibitors

The p38 MAPK is activated by cellular stress and regulates the expression of inflammatory cytokines, including CXCL8, TNF-α and MMPs. p38 MAPK (measured by phosphorylated p38 MAPK) is activated in alveolar macrophages of COPD lungs, indicating the activation of this pathway in COPD [209]. Several small molecule inhibitors of p38 MAPK have now been developed. A potent inhibitor of p38-α isoform, SD-282, is effective in inhibiting TNF-α release from human lung macrophages *in vitro* [210] and the same inhibitor is also effective in suppressing inflammation in a smoking model of COPD in mice in which corticosteroids are ineffective [211]. The role of p38 MAPK in mediating systemic effects of COPD has not yet been determined. Several p38 MAPK inhibitors have now entered clinical trials but there have been major problems of side-effects and toxicity, indicating that it is probably necessary to deliver these drugs by inhalation to reduce systemic exposure.

Antioxidants

Reduction in oxidative stress in COPD patients should provide clinical benefit by reducing inflammation and reversing corticosteroid resistance. Since systemic oxidative stress may be an important part of systemic inflammation, which is also corticosteroid-insensitive, antioxidants are an attractive therapeutic approach. Currently available antioxidants, such as N-acetyl cysteine, have proved to be disappointing in reducing the progression of lung function decline and exacerbations of COPD [212]. However, these glutathione-based antioxidants are consumed by oxidative stress so may not be efficient in the face of continued high ROS exposure. It has been difficult to find new more effective antioxidants that are not toxic [213]. A more attractive approach may be to restore the reduced Nrf2 levels in COPD lungs to normal. This has been achieved *in vitro* and *in vivo* by isothiocyanate compounds, such as sulforaphane, which occurs naturally in broccoli [146].

FUTURE DEVELOPMENTS

More effective anti-inflammatory treatments are needed for COPD inflammation with the prospect that such treatments will also suppress systemic inflammation and therefore treat comorbid diseases and systemic manifestations of the disease [160]. Novel broad spectrum anti-inflammatory treatments currently in clinical development for oral administration appear to have significant side-effects so that it may be necessary to develop inhaled drugs, but as discussed previously, this also has the prospect of treating systemic inflammation due to spillover from the lungs. Another approach is to develop drugs that reverse corticosteroid resistance, which is a major barrier to therapy [161]. Understanding the molecular mechanisms of corticosteroid resistance may lead to new therapeutic approaches in the future.

A further area of development is to consider COPD and several of its comorbidities, such as cardiac failure, osteoporosis and diabetes as disease of accelerated ageing. The molecular pathways of ageing are now much better understood and have revealed novel targets for therapeutic intervention, such as the anti-ageing molecules sirtuin 1 and peroxisome proliferator-activated-γ coactivator 1α [214].

IMPORTANT QUESTIONS

1. Are systemic manifestations of COPD and comorbidities all explained by overspill of inflammatory mediators from peripheral lungs? More studies with lung-specific biomarkers such as SP-D are needed.

2. Are there common genetic factors predisposing to COPD and comorbid diseases? Identification of common susceptibilities may lead to more accurate phenotyping of COPD patients in the future and may lead to identification of novel targets to treat these shared diseases.

3. Are long-acting bronchodilators able to reduce comorbidities by mechanical effects, such as reducing airway closure and epithelial stress and reducing strain on cardiovascular function? More research is needed on how mechanical factors associated with the structural changes of COPD may drive inflammation and abnormal repair mechanisms.

4. Will treatment of pulmonary inflammation in COPD patients also treat or ameliorate comorbid diseases? This will depend upon the development of effective inhaled anti-inflammatory treatments or reversing corticosteroid resistance in COPD patients.

5. Will treatments developed for comorbid diseases, such as statins, ACE inhibitors and PPAR-agonists, also have beneficial

effects on COPD lung disease? Properly controlled randomised trials of these therapies in COPD patients are now needed.

6. Will a better understanding of the molecular pathways involved in ageing lead to novel treatment for COPD and its comorbidities? Several novel therapeutic targets from ageing biology have already been discovered and novel drugs are in development.

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