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REVIEW ARTICLE

Mechanisms of acute exacerbation of respiratory symptoms in chronic obstructive pulmonary disease

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ABSTRACT

Exacerbations of chronic obstructive respiratory disease (ECOPD) are acute events characterized by worsening of the patient's respiratory symptoms, particularly dyspnoea, leading to change in medical treatment and/or hospitalisation. AECOP are considered respiratory diseases, with reference to the respiratory nature of symptoms and to the involvement of airways and lung. Indeed respiratory infections and/or air pollution are the main causes of ECOPD. They cause an acute inflammation of the airways and the lung on top of the chronic inflammation that is associated with COPD. This acute inflammation is responsible of the development of acute respiratory symptoms (in these cases the term ECOPD is appropriate). However, the acute inflammation caused by infections/pollutants is almost associated with systemic inflammation, that may cause acute respiratory symptoms through decompensation of concomitant chronic diseases (eg acute heart failure, thromboembolism, etc) almost invariably associated with COPD. Most concomitant chronic diseases share with COPD not only the underlying chronic inflammation of the target organs (i.e. lungs, myocardium, vessels, adipose tissue), but also clinical manifestations like fatigue and dyspnoea. For this reason, in patients with multimorbidity (eg COPD with chronic heart failure and hypertension, etc), the exacerbation of respiratory symptoms may be particularly difficult to investigate, as it may be caused by exacerbation of COPD and/or $\geq$ comorbidity, (e.g. decompensated heart failure, arrhythmias, thromboembolisms) without necessarily involving the airways and lung. In these cases the term ECOPD is inappropriate and misleading.

Keywords Airway inflammation, chronic bronchitis, chronic heart failure, emphysema, infections.

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In the coming decades, chronic obstructive pulmonary disease (COPD) is expected to occur with increasing frequency, resulting in enormous healthcare expenditures and high mortality. Thus, COPD presents a challenge for clinicians and is a leading public health problem worldwide [1]. However, COPD is almost invariably associated with other chronic conditions and is thus an important component of the epidemy of multimorbidity (due to ageing, smoking, indoor and outdoor pollution, alcohol, inactivity and other risk factors) that affects elderly patients [1].

The disease trajectory in COPD is usually marked by a gradual decline in health status and increasing symptoms, punctuated by acute exacerbations that are associated with an increased risk of death [1]. In clinical trial, exacerbations of COPD (ECOPD) are defined as 'acute events characterized by worsening of the patient's respiratory symptoms, beyond day-to-day variations, leading to a change of medication' [1], thus without any description of their pathophysiology or mechanisms. ECOPD are the main cause of hospitalization in patients with COPD, resulting in higher in-hospital mortality, which in turn significantly increases the use of healthcare resources and thus the economic burden [2–5].

Exacerbations of chronic obstructive pulmonary disease result not only in an increased risk of mortality during the acute event but also a long-term risk of death [5]. Concomitant chronic diseases are another important feature of COPD, as they affect patients' quality of life, symptoms, exacerbations and survival. Furthermore, comorbidities share the common chronic inflammatory nature [6,7] and have a complex relationship with ECOPD, affecting the frequency, clinical severity and prognosis of these events [1,8,9].

Mechanisms of COPD exacerbation

Historically, bacterial infections, viral infections and environmental pollutants have been implicated as the most important

causative agents of ECOPD [1]. All of these agents can result in the transient acute inflammation of the airways and lung that develops on top of the chronic inflammation present in stable conditions [10,11]. Some immune response abnormalities may facilitate viral and bacterial airway infections in patients with COPD [12,13]. However, although there is a strong association between viral/bacterial infections and ECOPD, a causal relationship is difficult to prove [14,15]. Experimental rhinovirus infection has been recently shown to provide a human model of COPD exacerbation [16].

Acute airway and lung inflammation resulting from both bacterial and viral infections in ECOPD consists in a significant increase in the number of inflammatory cells and also in inflammatory mediators. Bacterial exacerbations are associated with significantly greater increases in neutrophilic airway inflammation, with higher levels of sputum neutrophil elastase, IL-8, IL-1β and tumour necrosis factor-alpha (TNF-α) [14,15]. Virus-associated ECOPD are seen as significant elevations in sputum levels of interferon-gamma-inducible protein 10 (IP-10), which correlates with human rhinovirus viral load [17]. Recent research has defined the most important biological clusters in ECOPD: bacterial-predominant, viral-predominant, eosinophilic-predominant and a biological cluster characterized by limited changes in the inflammatory profile, known as 'pauci-inflammatory' [15]. In addition to airway infection, exposure to air pollutants was implicated as a trigger of ECOPD. Exposure to particulate matters and organic compounds may cause cytotoxicity, along with damage to macrophages and bronchial epithelial cells with increasing oxidative stress, by production of reactive oxygen species [18]. Oxidative stress is involved in pathogenesis of ECOPD, regardless of aetiology, by enhancing the influx of inflammatory mediators to the airway, in condition of alteration in the functioning of the antioxidant system [19]. The increased activation of redox-sensitive transcription factors, such as nuclear transcription factor, NF-Kb, may explain the high levels of pro-inflammatory gene products such as IL-8 and TNF-α [20]. Both amplified inflammation and oxidative stress in the airways of patients with ECOPD trigger complex mechanisms resulting in the worsening of respiratory symptoms [21–24] (Fig. 1).

Systemic consequences of airway inflammation

Airway inflammation during acute infections or exacerbations of chronic airway diseases also causes an elevation in systemic inflammation, revealed by the levels of pro-inflammatory mediators in circulation. ECOPD are associated with an elevation in serum C-reactive protein, IL-6, myeloid progenitor inhibitory factor-1, pulmonary and activation-regulated chemokine (PARC), adiponectin and soluble intercellular

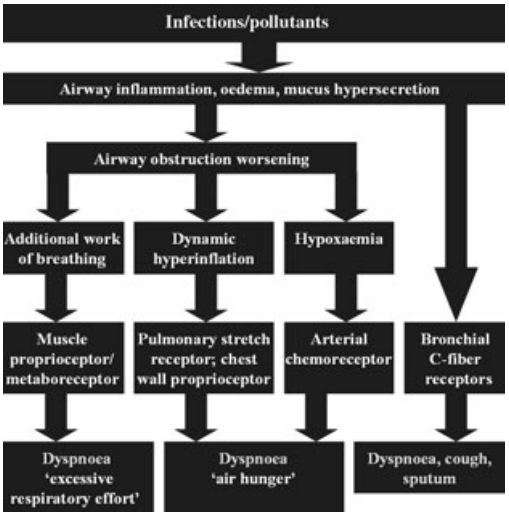

Figure 1 Mechanisms of respiratory symptoms in exacerbations of airway inflammation in COPD. The mechanisms triggered by infections or pollutants lead to injury of the airway mucosa, airway inflammation with oedema and mucus hypersecretion, resulting in the worsening of airway obstruction and respiratory symptoms such as cough with sputum and, more importantly, dyspnoea. Increased airflow resistance leads to an additional burden of breathing, producing a specific afferent feedback from proprioceptors and metaboreceptors from the respiratory muscles, perceived as dyspnoea and specifically described as an excessive respiratory effort. Consequently, air trapping and dynamic hyperinflation develop as the airflow resistance becomes greater. Dynamic hyperinflation decreases the efficiency of respiratory muscles, which now work at an ineffective length. This determines the activation of chest wall proprioceptors and pulmonary stretch receptors (slowly adapting stretch receptors, SARs, and rapidly adapting stretch receptors, RARs). The result is an elevation in corollary discharge by the breathing movements command, also perceived as dyspnoea, specifically described as 'air hunger'. In severe ECOPD, hypoxaemia with or without hypercapnia may stimulate arterial chemoreceptors, increasing the respiratory drive and sharpening the sensation of air hunger. The mechanisms of dyspnoea in ECOPD also involve bronchopulmonary C-fibers, which are vagal afferents innervating the mucosa of the respiratory tree. Exogenous or endogenous factors that appear in ECOPD, such as chemical irritants, infectious agents and inflammatory mediators, cause the activation of the bronchial C-fiber receptors. The main effects of their activation are bronchoconstriction with an elevation in bronchial tone, hypersecretion in the mucosa, cough and dyspnoea. Exogenous or endogenous factors also cause the inflammation-induced hypersensitivity of C-fibers even to normal physiological stimuli, such as common inspiration, by activating C-fiber receptors and causing exaggerated sensory and reflex responses.

adhesion molecule-1 [20,25]. The acute increase in cellular and molecular determinants of airway and systemic inflammation may result in such systemic manifestations as fever, tachycardia/bradycardia or hypertension/hypotension [24,26–29] (Fig. 2). Acute respiratory infections, including ECOPD induced by infections, may have significant systemic effects on non respiratory organs. For example, acute respiratory tract infections and exacerbations of COPD increase the risk of myocardial infarction and stroke [30]. The mechanisms underlying this association may involve prothrombotic and haemodynamic effects of acute respiratory infections [31]. A transient increase in the risk of cardiovascular events (myocardial infarction and stroke) was determined during the first 3 days after a diagnosis of respiratory tract infection [32]. These effects might explain the high incidence of non respiratory causes of death, especially cardiovascular, in influenza epidemics [33].

The role of concomitant disorders of COPD in mimicking ECOPD

Concomitant chronic diseases are a significant feature of COPD, meaning that in most cases they are just one component of the multimorbidity that affects an increasing number of people, particularly the elderly. These diseases have a significant, negative influence on the natural course of COPD and the patients' quality of life and survival [9,34]. Cardiovascular and metabolic diseases, osteoporosis, depression and lung cancer are the most frequent concomitant chronic diseases in patients with COPD [34–36]. The results from Towards a Revolution in COPD Health (TORCH) trial revealed that patients with COPD die not only of respiratory failure associated with COPD, but mostly of other causes, particularly cardiovascular diseases such as myocardial infarction and stroke or cancer [37].

Exacerbation of concomitant disorders in patients with COPD may present clinically with not only organ-specific but also organ-nonspecific symptoms, particularly dyspnoea. These symptoms may mimic the dyspnoea occurring in COPD patients with respiratory infections and/or exposure to pollutants, in that exacerbations in both cases are focused on the airways and lung. While the latter should continue to be considered an exacerbation of COPD, the former is rather an exacerbation of respiratory symptoms, particularly dyspnoea, in patients with COPD.

In other words, the acute events occurring in chronic diseases associated with COPD may trigger dyspnoea by different pathways, with particularities determined by the specific pathogenic mechanisms of each disease, leading to some diagnostic uncertainty regarding the nature of the exacerbations.

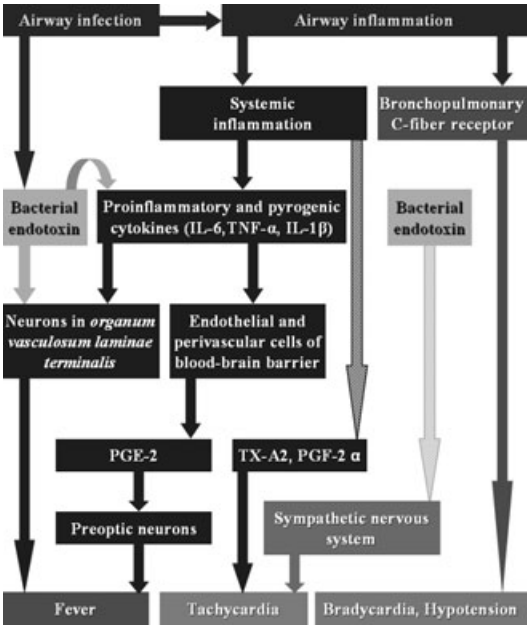

Figure 2 Mechanisms of systemic consequences in exacerbations of airway inflammation in COPD. Fever may be caused by the pyrogenic properties of some cytokines released during systemic inflammation: TNF-α, IL-1β and IL-6. These cytokines activate neurons in *organum vasculosum laminae terminalis*, one of the circumventricular organs of the brain, which is interconnected with the median preoptic nucleus of the hypothalamus and acts as a coordinating centre in thermoregulation. The pyrogenic effects were demonstrated not only for cytokines but also for bacterial endotoxin released in the systemic circulation, which may occur in acute infections of the airway. Prostanoids, including prostaglandin (PG)D2, PGE2, PGF2α, PGI2 and thromboxane A2, were shown to be potential inducers of various adaptive responses in systemic inflammation. In the endothelial and perivascular cells of the blood–brain barrier, upstream pro-inflammatory cytokines are switched to a downstream mediator, PGE2. The receptor for PGE2 of preoptic neurons seem to be the primary 'fever receptor' in the febrile response induced by bacterial endotoxins. The production of thromboxane A2 and PGF2α during systemic inflammation may cause tachycardia by a direct action on the heart, independent of sympathetic nervous system activity. This direct mechanism does not exclude the role of the sympathetic nervous system in tachycardia associated with systemic inflammation. Beta-blockade attenuated tachycardia induced by bacterial lipopolysaccharide, showing that the sympathetic nervous system may be involved in triggering systemic effects of infection. There is evidence that respiratory reflexes also result in systemic effects during airway inflammation and infection. Thus, the activation of bronchopulmonary C-fibers in ECOPD may lead to bradycardia and hypotension. Furthermore, the inflammation-induced hypersensitivity of C-fibers results in amplification of the systemic consequences.

Extrapulmonary comorbidities

Gastroesophageal reflux

One of the major risk factors for COPD exacerbations is gastroesophageal reflux disease (GERD) [20,25], and gastroesophageal reflux disease is one of the most commonly diagnosed diseases seen in outpatient clinics with the estimated prevalence of 14–20% in the adult general population [25,38]. Patients with a variety of chronic respiratory diseases, including asthma, cystic fibrosis and idiopathic pulmonary fibrosis (IPF), have a higher prevalence of GERD compared with general population [25,38]. The exact mechanisms of the observed associations between GERD and pulmonary diseases or symptoms are still unknown. Respiratory symptoms might be related at least in part with a higher intra-abdominal pressure, caused by hyperinflation and respiratory muscle effort, causing reflux with subsequent microaspiration of the gastric contents.

Cardiovascular disorders

Cardiovascular disorders such as hypertension, chronic heart failure, ischaemic heart disease and arrhythmia are the most frequent disorders seen in patients with COPD [9,34–36]. In the natural course of these cardiovascular chronic diseases occur acute events, which may result in respiratory symptoms [21,23,24] (Fig. 3).

Hypertension

Hypertension, the most prevalent concomitant disease in COPD, is reported in up to 60% of patients with COPD [35,36]. The pathophysiological link between COPD and hypertension might be determined by the systemic elevation in proteolytic activity, resulting in increased elastin degradation in various organs, including the arterial wall, with an increase in arterial stiffness, which correlates with emphysema severity [39]. Flow-mediated mechanism of vascular dilation is impaired in COPD, this alteration correlating with levels of systemic inflammation markers (IL-6 and C-reactive protein) in ECOPD [40]. This could be important in exacerbations of respiratory symptoms caused by acute inflammation of the airways and lung in patients with COPD, associated with concomitant systemic inflammation, which may result in an imbalance of vascular reactivity and elevation in arterial pressure.

Independent of the course of COPD, a patient with concomitant arterial hypertension may develop a hypertensive crisis. This event results from imbalance in renin–angiotensin axis and other neurohumoral pathways, causing an acute intravascular volume overload and further acute elevation in blood pressure. Patients with decreased systolic and diastolic capacity to adapt to acute changes in loading subsequently experience left ventricle overload, systolic and diastolic dysfunction, elevation in pulmonary venous pressure and fluid

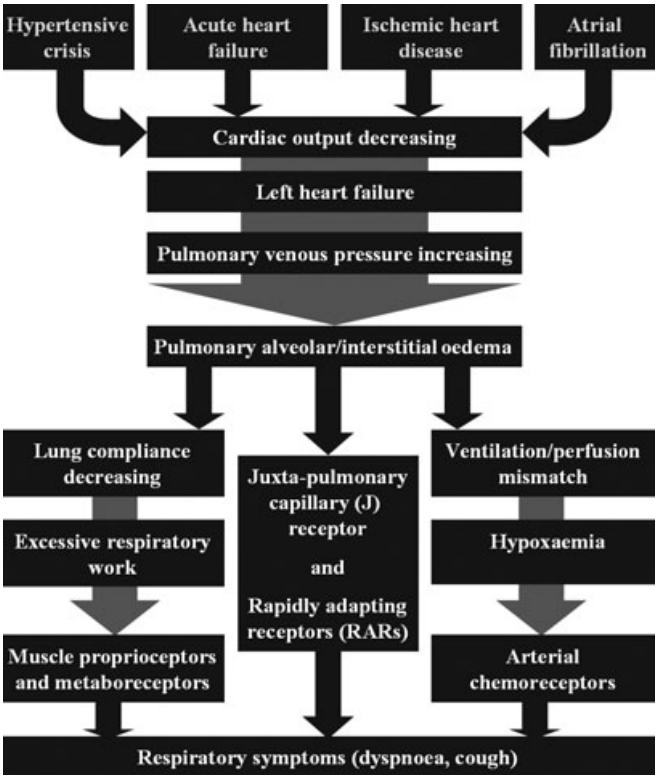

Figure 3 Mechanisms of respiratory symptoms determined by acute cardiovascular events. Hypertensive crisis, acute decompensated heart failure, angina pectoris, myocardial infarction and atrial fibrillation are specific acute events that may occur in chronic cardiovascular disorders. As a common pathway in determining dyspnoea, these acute events share acute dysfunction of the left ventricle, resulting in pulmonary congestion and activation of the specific receptors in the lung and respiratory muscles. In particular, the accumulation of interstitial fluid activates juxtapulmonary capillary (J) receptors. J receptors are a category of pulmonary C-fiber receptors, located close to the alveolar capillaries, which, in conditions of pulmonary oedema, may contribute to dry cough and dyspnoea. Pulmonary oedema also results in mismatch in the ventilation/perfusion ratio and, consequently, hypoxaemia and dyspnoea. Rapidly adapting stretch receptors (RARs), located in the region of the airways close to bronchial venules, also detect changes in extravascular fluid volume. Pulmonary venous congestion causes the increase in extravascular fluid in the airways, and the activation of RARs is responsible for dyspnoea on exertion. At the same time, the increased work of breathing, caused by the alteration in lung compliance, may result in dyspnoea by the activation of muscle proprioceptors and metaboreceptors, perceived by the patient as excessive respiratory work.

extravasation from pulmonary capillaries, with respiratory symptoms and pulmonary oedema [41].

Heart failure

Heart failure, most often left ventricular systolic dysfunction, is a frequently unrecognized comorbidity in COPD with a prevalence that varies considerably (10–46%) among the results of clinical studies [42]. Emphysema and hyperinflation seem to affect haemodynamic mechanisms, with an important role in promoting heart dysfunction in patients with COPD. In mild emphysema, endothelial dysfunction of the pulmonary microvasculature and loss of pulmonary capillary bed may result in impaired left ventricular filling. During exacerbation of respiratory symptoms in patients with COPD, the worsening of hyperinflation may trigger the acute decompensation of heart failure. Severely increased hyperinflation results in the significant elevation in intrathoracic end-expiratory pressure, consequently altering pulmonary vascular compliance. This results in an elevated right ventricular load, a reduced right ventricular stroke volume and impairment of left ventricular filling [43,44]. Even when is unrelated to an increase in airway and lung inflammation, acute decompensation of heart failure may still cause respiratory symptoms. The decompensation of left ventricular systolic function results in a decrease in cardiac output, an increase in left ventricle filling pressure and the elevation in the subsequent retrograde pulmonary venous pressure; fluid extravasations into the interstitial and/or alveolar space; oedema; and respiratory symptoms such as dyspnoea and orthopnoea.

The supine position brings about a redistribution of blood volume from the lower extremities and splanchnic beds to the lungs, enhancing pulmonary oedema and causing a marked decrease in expiratory reserve volume. This mechanism explains orthopnoea in acute decompensation of heart failure. Furthermore, the decrease in functional residual capacity may result in airway closure, causing a limitation in tidal flow. This produces a mismatch in the ventilation/perfusion ratio, with alteration in gas exchanges and worsening of hypoxaemia and dyspnoea [45,46].

Ischaemic heart disease

Ischaemic heart disease, a frequent comorbidity in COPD, is associated with worse health status, such as more severe dyspnoea and longer exacerbations [47]. The most important pathogenic mechanism of ischaemic heart disease is coronary atherosclerosis, but arterial spasm or embolism may also cause this disorder. Oxidative stress resulting most often from smoking, a commonly shared risk factor, and systemic inflammation have been reported to represent pathophysiological links between COPD and atherosclerosis [48]. Acute airway and lung inflammation in ECOPD is associated with systemic inflammation and systemic effects such as fever or tachycardia. Tachycardia causes reduced diastolic filling time and elevated cardiac workload. This may result in a mismatch in the myocardial supply/demand ratio, in patients with coronary artery disease, and subsequently in myocardial ischaemia and angina pectoris. Exertion and psychological stress may also produce myocardial ischaemia by similar mechanisms, completely unrelated to acute inflammation of the airways and lung. Myocardial ischaemia determines lactate accumulation, acidosis and may result in contractile dysfunction. Sudden onset of myocardial ischaemia usually appears as angina pectoris, a clinical syndrome of precordial discomfort or pain. In some cases, myocardial ischaemia may manifest as a syndrome of painless dyspnoea. The main mechanism of this syndrome is determined by a wide area of ischaemic myocardium with left ventricle regional dysfunction, resulting in the elevation in left ventricle end-diastolic pressure and subsequent pulmonary congestion. Ischaemia that affects papillary muscle could result in mitral regurgitation with severe dyspnoea. A neurogenic mechanism involving a crosstalk phenomenon for pain signals from ischaemic myocardium in thoracic sympathetic ganglions may also result in a false perception of dyspnoea [49].

Sixteen percentage of patients with severe exacerbation of COPD have increased serum troponin values, which is accompanied by an increase in mortality at 30 days [50]. One in 12 patients with severe ECOPD had raised troponin, chest pain and/or serial ECG changes and therefore met the criteria for myocardial infarction [51].

Atrial fibrillation

Analysis of the data from the Copenhagen City Heart Study revealed an elevated frequency of atrial fibrillation in patients with COPD, the alteration in lung function being a predictor for the occurrence of this arrhythmia [52]. Atrial fibrillation involves the loss of the contribution of atrial contraction to ventricular filling, leading to a decrease in cardiac output. This is clinically significant, particularly at the onset of atrial fibrillation or when ventricular rate suddenly rises, because it may lead to left heart failure, producing consequences for retrograde pulmonary circulation with pulmonary congestion, generating dyspnoea.

Pulmonary embolism

Clinical studies proved a prevalence of pulmonary embolism of 3·3% in patients admitted to the emergency departments for ECOPD [53] and 25% in patients hospitalized for severe ECOPD of unknown origin [54]. In the acute setting of pulmonary embolism, the obstruction of a pulmonary artery causes a sudden increase in anatomical dead space in the lung parenchyma, determined by ventilation without perfusion. This produces

acute hypercapnia that may activate the carotid arterial chemoreceptors, resulting in dyspnoea. Pulmonary embolism causes alveolar haemorrhage, destruction of the alveolar–capillary interface, loss of surfactant and atelectasis. The stimulation of bronchopulmonary C-fibers by local injury may produce bronchoconstriction, mucus secretion, cough and tachypnoea. Atelectasis and bronchoconstriction cause a mismatch in the ventilation/perfusion ratio and subsequent arterial hypoxaemia; the activation of vascular chemoreceptors results in dyspnoea. The activation of vagal receptors (RARs and J receptors) in the injured parenchyma may also generate dyspnoea [55].

Depression

Screening for depression in patients with COPD has shown a 25% incidence of any mood disorder and an 11% incidence of major depressive disorder [56]. Depressive symptoms have a significant effect on the intensity of dyspnoea and on the length of hospitalization in patients with ECOPD [57]. Breathing is under the physiological control of respiratory centres. Medullary, cortical and limbic centres control cognitive, affective and autonomic aspects of breathing. Dyspnoea may be generated by respiratory stimuli, acting in the airway and lung, and by the cognitive and affective framing of experience. Panic, anxiety or depression may result in dyspnoea [58]. As a concomitant disorder in patients with COPD, depression may not only worsen the dyspnoea related to chronic lung disease, but may also intensify dyspnoea by its psychological effect, independent of COPD. Furthermore, exacerbations of depression may occur, thereby increasing dyspnoea and mimicking ECOPD.

Although depressive symptoms have a significant impact on dyspnoea, this just does not fully explain the increased risk of exacerbations, hospitalizations and especially mortality observed in depressed patients [9,59,60]. Actually, depression is considered by many authors a disease with an inflammatory component, because i) even in the absence of medical illness, depression is associated with raised inflammatory markers; ii) inflammatory medical illnesses (COPD, ischaemic heart disease) are associated with greater rates of major depression; iii) patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness [61].

Concomitant pulmonary diseases

Asthma

Obstructive airway disease may be a combination of asthma and COPD (overlap syndrome). Data obtained in a cross-sectional study revealed a prevalence of the overlap syndrome in general population that varies from 13%, prior to age of 40 years, to 21.7%, when no age restriction was used in the definition of asthma [62].

Overlap syndrome determines an increased variability concomitant with an incomplete reversibility of the airway obstruction [63]. It also causes recurrent exacerbation of respiratory symptoms, making it difficult to distinguish those produced by COPD from those produced by asthma. In both asthma and COPD, fixed airflow obstruction is associated with increased lung function decline and frequency of exacerbations. Even though there are differences between the inflammation seen in COPD and in asthma, the episodes of disease exacerbation are characterized by similar patterns of inflammation and symptoms such as cough with sputum and dyspnoea [64,65]. Airway obstruction, air trapping and dynamic hyperinflation in asthma exacerbations result in additional work of breathing, leading to specific afferent feedback from muscle proprioceptors and metaboreceptors, perceived by the patient as excessive respiratory effort. The activation of chest wall proprioceptors and pulmonary stretch receptors results in sensory perception of dyspnoea, manifested as air hunger. This symptom can also result from an increase in respiratory drive, produced by the activation of arterial chemoreceptors in hypoxaemia and/or hypercapnia [21]. A pathognomonic feature in asthma is airway hyper-reactivity, which appears to be associated with airway inflammation and remodelling. Even though additional research is needed, some studies support the hypothesis of airway 'hyper-reactivity' determined by parasympathetic 'hyper-reflexivity' in asthma [66]. The perception of dyspnoea by the patient is more specific for asthma than for COPD. It is experienced as 'tightness' during the early stages of an asthma attack, associated with bronchoconstriction, and resulting from the stimulation of RARs and C-fiber vagal receptors in the airway [21,22].

Pneumonia

Patients with COPD have a higher risk of developing pneumonia than general population. Previous incidents of severe ECOPD requiring hospitalization, as well as the existence of comorbidities in COPD, result in additional risk for pneumonia (odds ratio 2·7, 95% confidence interval 2·3–3·2) [67]. In bacterial pneumonia, the infectious agent induces the migration of neutrophils into the alveolar space and the release of cytokines, resulting in acute inflammation. The neutrophils phagocytize bacteria, and the alveolar space is filled by inflammatory exudate containing antibodies, complement proteins, C-reactive protein and pentraxin, which are involved in opsonic, bacteriostatic and microbicidal functions [68]. Dyspnoea, cough and sputum are the main symptoms of pneumonia and may create diagnostic difficulties in patients with COPD because of the clinical similarities with ECOPD. Some similarities in the response during oxygen therapy may also create diagnostic confusion. In the affected parenchyma, pneumonia causes abnormal gas exchanges characterized by

marked increases in intrapulmonary shunt, combined with ventilation/perfusion mismatch, resulting in hypoxaemia with or without hypercapnia. Research has shown that high-concentration oxygen therapy decreases hypoxic pulmonary vasoconstriction. However, this may alter the dispersal of pulmonary blood flow by worsening the ventilation/perfusion mismatch, without influencing intrapulmonary shunt and resulting in increased hypercapnia. This effect is similar to that of high-concentration oxygen therapy in patients with ECOPD [69]. In pneumonia, dyspnoea may be produced by activation of arterial chemoreceptors in hypoxaemia or hypercapnia and also by vagal receptors (RARs and J receptors) in the injured parenchyma.

Bronchiectasis

Bronchiectasis is a comorbidity in 30–50% of patients with COPD. The coexistence of the two diseases may increase the duration of hospitalization, even though it has not been clearly proved to have an influence on mortality [70]. Bronchiectasis is characterized by marked inflammation of the bronchial wall, mainly in the smaller airways, by bronchial dilation and alterations caused by postinfectious or systemic disorders, which impair airway clearance and physiological defence. Neutrophils are the most prominent cell type in the bronchi, producing proteases, elastases and matrix metalloproteinases. The result is epithelial injury, mucus hypersecretion, altering of the mucociliary clearance and plugging of the airway. Bronchiectasis is often complicated by Gram-negative or mycobacterial infections [71]. The infections may be involved in the acute exacerbations of bronchiectasis, characterized by increased airway inflammation and mucus hypersecretion, worsening of the obstructive dysfunction and clinically reflected in the aggravation of cough and dyspnoea [72]. COPD and bronchiectasis share the main respiratory symptoms, particularly dyspnoea, but also cough with sputum, which may result in diagnostic difficulties during exacerbations. In exacerbations of bronchiectasis, respiratory symptoms such as cough and dyspnoea may be caused by the activation of bronchial C-fiber receptors triggered by airway infection and/or inflammation. Depending on the severity of the obstruction, a decrease in lung compliance may cause the activation of RARs, muscle proprioceptors and metaboreceptors, with worsening of the dyspnoea. This symptom may also result from activation of arterial chemoreceptors in severe exacerbations associated with hypoxaemia with or without hypercapnia.

Idiopathic pulmonary fibrosis

Pulmonary fibrosis and emphysema may combine in a distinct entity characterized by severe impairment of gas exchange, a high prevalence of pulmonary hypertension and poor survival [73]. COPD and IPF seem to share abnormalities in the mechanisms of normal lung ageing, including oxidative stress, regulation of telomere length, immuno- and cellular senescence, and changes in anti-ageing molecules and in the extracellular matrix [74]. IPF is characterized by episodes of acute exacerbation, defined by significant, acute worsening of the patient's clinical condition without an identified cause. Rapidly progressive dyspnoea is the most prevalent symptom and may be associated with cough and fever. The major histological finding is diffuse alveolar damage. A criterion for diagnosis is abnormal gas exchange or a decrease in PaO_2 [75]. The upregulation of genes related to stress response and mitosis-related genes in alveolar epithelium proves the central role of epithelial injury in acute exacerbations of IPF. Widespread apoptosis of epithelial cells results in epithelial proliferation, as a potential compensatory response to injury. Gene expression pattern research did not indicate bacterial or viral infections as causes of epithelial injury in acute exacerbations of IPF, even though this could not rule them out. Furthermore, the research did not find upregulation of inflammation-related gene expression (IL-1, IL-6, TNF-α or NF-κB) [76]. If IPF is concomitant with COPD, its exacerbation may mimic the exacerbation of COPD, resulting in a diagnostic problem. In IPF exacerbation, dyspnoea may be caused mainly by hypoxaemia resulting from abnormal gas exchange, triggering the activation of vascular chemoreceptors.

Pneumothorax

Clinical research has shown an association between spontaneous pneumothorax and COPD in 8.7% of cases [77]. Bullous emphysema in COPD is an important cause of pneumothorax. The acutely installed symptoms caused by spontaneous pneumothorax in a patient previously known to have COPD may mimic ECOPD. The most important symptom of pneumothorax, dyspnoea, is generated by various mechanisms. Sudden deflation of the lung activates the RARs in the affected lung, with known effects in acute dyspnoea. The absence of ventilation creates the shunt effect because of the area of parenchyma that has normal perfusion but is not ventilated. The vascular shunt results in hypoxaemia, activating arterial chemoreceptors and producing dyspnoea [22].

Systemic inflammation – a pathogenic link between COPD and comorbidities

Exacerbations of chronic obstructive pulmonary disease are characterized by additional elevation in airway, lung and systemic inflammation compared with baseline COPD [20,25]. Systemic inflammation may be the pathogenic link between COPD and the coexisting diseases. Furthermore, the additional systemic inflammation associated with ECOPD may be the pathogenic link between exacerbation and the concomitant

acute decompensation of comorbidities. The cardiovascular diseases involving atherosclerosis as the main pathogenic mechanism are important comorbidities of COPD. C-reactive protein and IL-6 – biomarkers of systemic inflammation in COPD and its exacerbations—are also biomarkers of atherosclerosis, correlating with the severity of peripheral arterial disease and with the progression of atherosclerotic lesions, respectively [78]. Analysis of data from the Edinburgh Artery Study demonstrated the importance of systemic inflammation in determining the risk of acute cardiovascular events. Hazard ratios for myocardial infarction and stroke correlated with levels of inflammation markers: C-reactive protein, IL-6 and fibrinogen [79]. Clinical research has shown the association between ECOPD and various pathogenic mechanisms, determining the risk of acute cardiovascular events [80–85] (Fig. 4). There is also some evidence for the inverse relationship between pre-existing systemic inflammation and ECOPD. Serum fibrinogen, a marker of systemic inflammation, is a predictor for the occurrence of severe ECOPD [86]. Analysis of the effects of metabolic syndrome, a disorder that may

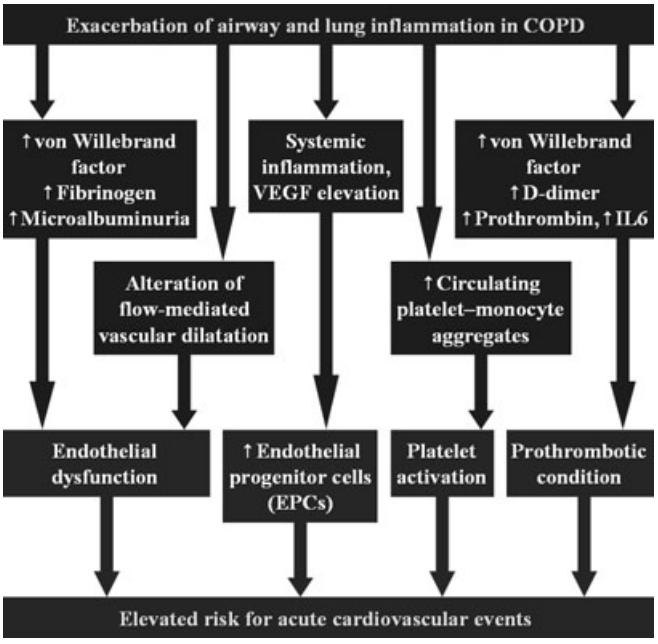

Figure 4 Mechanisms of risk elevation in acute cardiovascular events, associated with ECOPD. The vascular endothelium is an important site in which the effects of enhanced systemic inflammation in ECOPD may occur. The increase in plasma von Willebrand factor and fibrinogen and 24-h urine microalbuminuria indirectly demonstrate the endothelial dysfunction in ECOPD. Furthermore, this dysfunction was also proved by the alteration in the mechanism of flow-mediated vascular dilatation. Endothelial progenitor cells (EPCs) are a special type of stem cells found in the bone marrow and peripheral blood. Even though the pathways involving EPCs are only partially understood, they are known to be involved in protection and repair of dysfunctional endothelium, including protection against atherosclerosis. The capacity of EPCs to repair is altered in patients with COPD. This might result in elevated susceptibility for injury to the vascular endothelium, including atherosclerotic lesions. Although it has not been proved that EPC dysfunction is a cause or an effect of COPD pathogenesis, it is clear that EPCs constitute a pathogenic link between chronic lung disease and coexistent cardiovascular disorders. Furthermore, EPC levels are higher during exacerbation of respiratory symptoms than in stable COPD and that elevation in plasma vascular endothelial growth factor (VEGF) is associated with systemic inflammation. Interestingly, acute cardiovascular events such as coronary artery disease involve a similar pathogenic pathway, including systemic inflammation with plasma VEGF elevation resulting in increased numbers of EPCs. An important mechanism in the pathogenesis of atherothrombosis involves the interaction of inflammatory cells with activated platelets, resulting in an increase in the level of circulating platelet–monocyte aggregates. Levels of platelet–monocyte aggregates are increased in COPD compared with non-COPD and in ECOPD compared with baseline COPD. This proves the activation of atherosclerotic mechanisms in ECOPD. ECOPD are also an important prothrombotic condition, being associated with significantly elevated levels of von Willebrand factor, D-dimer, prothrombin fragment 1 + 2 and a cytokine with prothrombotic effects, IL-6. The disorder of endothelial structures and the increased levels of circulating platelet–monocyte aggregates and prothrombotic mediators may explain the risk of acute cardiovascular events in ECOPD, including myocardial infarction and stroke.

appear as a comorbidity of COPD, demonstrated that patients with COPD and metabolic syndrome present more frequent acute exacerbations than do patients with COPD without this comorbidity. Increased serum C-reactive protein in patients with metabolic syndrome is significantly correlated with ECOPD frequency [87]. More studies are needed to clarify the effect of systemic inflammation in the pathogenesis of ECOPD.

Conclusions

Exacerbations of chronic obstructive pulmonary disease are complex events in the natural history of COPD, dramatically affecting lung function decline, patients' quality of life and long-term mortality. ECOPD are heterogeneous events with respect to associated inflammatory response and aetiology. Biological and clinical phenotypes in ECOPD are determined by intricate interactions between different aetiological pathogenic factors and individual response. The pathogenic relationship between ECOPD and comorbidities is extremely complex and poorly understood. The direction of this relationship is sometimes uncertain, and the interactions between diseases appear to be reciprocal. However, it has clearly been proved that comorbidities affect ECOPD frequency and severity and alter the long-term prognosis.

The clinical presentation of ECOPD can be determined not only by acute 'bronchitis' or 'alveolitis' induced by infections or pollutants, that is, the properly named exacerbations of COPD, but also by acute decompensation of respiratory or non respiratory concomitant disorders, that is, the more properly named exacerbations of respiratory symptoms in patients with COPD [88]. This distinction generates diagnostic and therapeutic issues, and more comprehensive approaches are needed. Not only the baseline lung disease but also the comorbidities must be considered. More sensitive and specific biomarkers are necessary to identify and establish the real weight of every concomitant pathogenic entity in the clinical presentation of ECOPD.

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Conflict of interest

None declared.

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References

1 Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A *et al*. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, GOLD executive summary. *Am J Respir Crit Care Med* 2013;**187**:347–65.
2 García-Sanz MT, Pol-Balado C, Abellás C, Cánive-Gómez JC, Antón-Sanmartin D, González-Barcala FJ. Factors associated with hospital admission in patients reaching the emergency department with COPD exacerbation. *Multidiscip Respir Med* 2012;**7**:6.
3 Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:653–61.
4 Ozkaya S, Findik S, Atici AG. The costs of hospitalization in patients with acute exacerbation of chronic obstructive pulmonary disease. *Clinicoecon Outcomes Res* 2011;**3**:15–8.
5 Gudmundsson G, Ulrik CS, Gislason T, Lindberg E, Brøndum E, Bakke P *et al*. Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: a prospective observational study in the Nordic countries. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:571–6.
6 Agustí A, Faner R. Systemic inflammation and comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2012;**9**:43–6.
7 Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE *et al*. Evaluation of COPD longitudinally to identify predictive surrogate endpoints (ECLIPSE) investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS ONE* 2012;**7**:e37483.
8 Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;**380**:37–43.

9 Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;**186**:155–61.
10 Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1304–9.
11 Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2009;**360**:2445–54.
12 Singanayagam A, Joshi PV, Mallia P, Johnston SL. Viruses exacerbating chronic pulmonary disease: the role of immune modulation. *BMC Med* 2012;**10**:27.
13 Mallia P, Footitt J, Sotero R, Jepson A, Contoli M, Trujillo-Torralbo MB *et al.* Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in COPD. *Am J Respir Crit Care Med* 2012;**186**:1117–24.
14 Hurst JR, Perera WR, Wilkinson TM, Donaldson GC, Wedzicha JA. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;**173**:71–8.
15 Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;**184**:662–71.
16 Mallia P, Message SD, Gielen V, Contoli M, Gray K, Kebadze T *et al.* Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med* 2011;**183**:734–42.
17 Quint JK, Donaldson GC, Goldring JJ, Baghai-Ravary R, Hurst JR, Wedzicha JA. Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. *Chest* 2010;**137**:812–22.
18 Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. *J Toxicol* 2011;**2011**:487074.
19 Drost EM, Skwarski KM, Sauleda J, Soler N, Roca J, Agusti A *et al.* Oxidative stress and airway inflammation in severe exacerbations of COPD. *Thorax* 2005;**60**:293–300.
20 Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R *et al.* Evaluation of COPD longitudinally to identify predictive surrogate endpoints (ECLIPSE) investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;**363**:1128–38.
21 Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;**185**:435–52.
22 Nishino T. Dyspnea: underlying mechanisms and treatment. *Br J Anaesth* 2011;**106**:463–74.
23 Kappagoda CT, Ravi K. The rapidly adapting receptors in mammalian airways and their responses to changes in extravascular fluid volume. *Exp Physiol* 2006;**91**:647–54.
24 Lee LY. Respiratory sensations evoked by activation of bronchopulmonary C-fibers. *Respir Physiol Neurobiol* 2009;**167**:26–35.
25 Mackay AJ, Hurst JR. COPD exacerbations: causes, prevention, and treatment. *Med Clin North Am* 2012;**96**:789–809.
26 Ott D, Murgott J, Rafalzik S, Wuchert F, Schmalenbeck B, Roth J *et al.* Neurons and glial cells of the rat organum vasculosum laminae terminalis directly respond to lipopolysaccharide and pyrogenic cytokines. *Brain Res* 2010;**1363**:93–106.
27 Romanovsky AA, Almeida MC, Aronoff DM, Ivanov AI, Konsman JP, Steiner AA *et al.* Fever and hypothermia in systemic inflammation: recent discoveries and revisions. *Front Biosci* 2005;**10**:2193–216.
28 Takayama K, Yuhki K, Ono K, Fujino T, Hara A, Yamada T *et al.* Thromboxane A2 and prostaglandin F2α mediate inflammatory tachycardia. *Nat Med* 2005;**11**:562–6.
29 Nalivaiko E, Ootsuka Y, Blessing WW. Activation of 5-HT1A receptors in the medullary raphe reduces cardiovascular changes elicited by acute psychological and inflammatory stresses in rabbits. *Am J Physiol Regul Integr Comp Physiol* 2005;**289**: R596–604.
30 Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010;**137**:1091–7.
31 Bazaz R, Marriott HM, Francis SE, Dockrell DH. Mechanistic links between acute respiratory tract infections and acute coronary syndromes. *J Infect* 2013;**66**:1–17.
32 Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**:2611–8.
33 Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV *et al.* Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. *Eur Heart J* 2007;**28**:1205–10.
34 Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;**31**:204–12.
35 Corsonello A, Antonelli Incalzi R, Pistelli R, Pedone C, Bustacchini S, Lattanzio F. Comorbidities of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2011;**17**:S21–8.
36 Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL *et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013, [Epub ahead of print].
37 McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;**62**:411–5.
38 Rogha M, Behravesh B, Pourmoghaddas Z. Association of gastroesophageal reflux disease symptoms with exacerbations of chronic obstructive pulmonary disease. *J Gastrointestin Liver Dis* 2010;**19**:253–6.
39 Maclay JD, McAllister DA, Rabinovich R, Haq I, Maxwell S, Hartland S *et al.* Systemic elastin degradation in chronic obstructive pulmonary disease. *Thorax* 2012;**67**:606–12.
40 Eickhoff P, Valipour A, Kiss D, Schreder M, Cekici L, Geyer K *et al.* Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;**178**:1211–8.
41 Mărgulescu AD, Rimbaş RC, Florescu M, Dulgheru RE, Cinteză M, Vinereanu D. Cardiac adaptation in acute hypertensive pulmonary oedema. *Am J Cardiol* 2012;**109**:1472–81.
42 Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006;**8**:706–11.
43 Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA *et al.* Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010;**362**:217–27.
44 Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M *et al.* Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. *Chest* 2010;**138**:32–8.

45 Torchio R, Gulotta C, Greco-Lucchina P, Perboni A, Avonto L, Ghezzo H *et al.* Orthopnea and tidal expiratory flow limitation in chronic heart failure. *Chest* 2006;**130**:472–9.
46 Torchio R, Gulotta C, Greco-Lucchina P, Perboni A, Montagna L, Guglielmo M *et al.* Closing capacity and gas exchange in chronic heart failure. *Chest* 2006;**129**:1330–6.
47 Patel AR, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012;**141**:851–7.
48 Ghoorah K, De SA, Kunadian V. Increased cardiovascular risk in patients with chronic obstructive pulmonary disease and the potential mechanisms linking the two conditions: a review. *Cardiol Rev* 2012; doi:10.1097/CRD.0b013e318279e907. [Epub ahead of print].
49 Cheng TO. Acute dyspnea on exertion is an angina equivalent. *Int J Cardiol* 2007;**115**:116.
50 Chang CL, Robinson SC, Mills GD, Sullivan GD, Karalus NC, McLachlan JD *et al.* Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011;**66**:764–8.
51 McAllister DA, Maclay JD, Mills NL, Leitch A, Reid P, Carruthers R *et al.* Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *Eur Respir J* 2012;**39**:1097–103.
52 Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;**21**:1012–6.
53 Rutschmann OT, Cornuz J, Poletti PA, Bridevaux PO, Hugli OW, Qanadli SD *et al.* Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007;**62**:121–5.
54 Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB *et al.* Pulmonary embolism in patients exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006;**144**:390–6.
55 Moua T, Wood K. COPD and PE: a clinical dilemma. *Int J Chron Obstruct Pulmon Dis* 2008;**3**:277–84.
56 Julian LJ, Gregorich SE, Earnest G, Eisner MD, Chen H, Blanc PD *et al.* Screening for depression in chronic obstructive pulmonary disease. *COPD* 2009;**6**:452–8.
57 Papaioannou AI, Bartziokas K, Tsikrika S, Karakontaki F, Kastanakis E, Banya W *et al.* The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations. *Eur Respir J* 2012; doi:10.1183/09031936.00013112. [Epub ahead of print].
58 Neuman A, Gunnbjörnsdottir M, Tunsäter A, Nyström L, Franklin KA, Norrman E *et al.* Dyspnea in relation to symptoms of anxiety and depression: a prospective population study. *Respir Med* 2006;**100**:1843–9.
59 Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med* 2007;**167**:60–7.
60 Almagro P, Calbo E, Ochoa de Echagüen A, Barreiro B, Quintana S, Heredia JL *et al.* Mortality after hospitalization for COPD. *Chest* 2002;**121**:1441–8.
61 Krishnadas R, Cavanagh J. Depression: an inflammatory illness? *J Neurol Neurosurg Psychiatry* 2012;**83**:495–502.
62 Hardin M, Silverman EK, Barr RG, Hansel NH, Schroeder JD, Make BJ *et al.* The clinical features of the overlap between COPD and asthma. *Respir Res* 2011;**12**:127.
63 Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;**64**:728–35.
64 Contoli M, Baraldo S, Marku B, Casolari P, Marwick JA, Turato G *et al.* Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol* 2010;**125**:830–7.
65 Barnes PJ. Similarities and differences in inflammatory mechanisms of asthma and COPD. *Breathe* 2011;**7**:229–38.
66 Undem BJ, Nassenstein C. Airway nerves and dyspnea associated with inflammatory airway disease. *Respir Physiol Neurobiol* 2009;**167**:36–44.
67 Müllerova H, Chigbo C, Hagan GW, Woodhead MA, Miravitlles M, Davis KJ *et al.* The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012;**106**:1124–33.
68 Corrales-Medina VF, Musher DM, Shachkina S, Chrinos JA. Acute pneumonia and the cardiovascular system. *Lancet* 2013;**381**:496–505.
69 Wijesinghe M, Perrin K, Healy B, Weatherall M, Beasley R. Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. *J R Soc Med* 2012;**105**:208–16.
70 Gursel G. Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease? *Heart Lung* 2006;**35**:58–65.
71 Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. *Eur Respir J* 2008;**31**:396–406.
72 Kapur N, Masters IB, Chang AB. Exacerbations in noncystic fibrosis bronchiectasis: clinical features and investigations. *Respir Med* 2009;**103**:1681–7.
73 Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I *et al.* Combined pulmonary fibrosis and emphysema: a distinct under-recognised entity. *Eur Respir J* 2005;**26**:586–93.
74 Faner R, Rojas M, Macnee W, Agustí A. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;**186**:306–13.
75 Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr *et al.* Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007;**176**:636–43.
76 Konishi K, Gibson KF, Lindell KO, Richards TJ, Zhang Y, Dhir R *et al.* Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;**180**:167–75.
77 Khan N, Jadoon H, Zaman M, Subhani A, Khan AR, Ihsanullah M. Frequency and management outcome of pneumothorax patients. *J Ayub Med Coll Abbottabad* 2009;**21**:122–4.
78 Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. *Circulation* 2005;**112**:976–83.
79 Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. *Circulation* 2007;**115**:2119–27.
80 Polatli M, Cakir A, Cildag O, Bolaman AZ, Yenisey C, Yenicerioglu Y. Microalbuminuria, von Willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation. *J Thromb Thrombolysis* 2008;**26**:97–102.
81 Ozben B, Eryüksel E, Tanrikulu AM, Papila-Topal N, Celikel T, Başaran Y. Acute exacerbation impairs endothelial function in

patients with chronic obstructive pulmonary disease. *Turk Kardiyol Dern Ars* 2010;**38**:1–7.
82 Liu X, Xie C. Human endothelial progenitor cells isolated from COPD patients are dysfunctional. *Mol Cell Biochem* 2012;**363**:53–63.
83 Sala E, Villena C, Balaguer C, Ríos A, Fernández-Palomeque C, Cosío BG *et al*. Abnormal levels of circulating endothelial progenitor cells during exacerbations of COPD. *Lung* 2010;**188**:331–8.
84 Maclay JD, McAllister DA, Johnstone S, Raftis J, McGuinnes C, Deans A *et al*. Increased platelet activation in patients with stable and acute exacerbations of COPD. *Thorax* 2011;**66**:769–74.
85 Polosa R, Malerba M, Cacciola RR, Morjaria JB, Maugeri C, Prosperini G *et al*. Effect of acute exacerbations on circulating endothelial, clotting and fibrinolytic markers in COPD patients. *Intern Emerg Med* 2011; doi:10.1007/s11739-011-0636-1. [Epub ahead of print].
86 Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlösser NJ, Wouters EF. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest* 2008;**133**:350–7.
87 Küpeli E, Ulubay G, Ulasli SS, Sahin T, Erayman Z, Gürsoy A. Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. *Endocrine* 2010;**38**:76–82.
88 Beghé B, Verduri A, Roca M, Fabbri LM. Exacerbations of respiratory symptoms in COPD patients may not be exacerbations of COPD. *Eur Respir J* 2013, doi:10.1183/09031936.00180812.