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Cardiovascular mechanisms of death in severe COPD exacerbation: time to think and act beyond guidelines

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Three important studies on acute exacerbations of chronic obstructive pulmonary disease (ECOPD) have been published in *Thorax*. Two of them, by Chang *et al*¹ (see page 764) and Hoiset *et al*² (see page 775), show the importance of the cardiac biomarkers troponin T and NT-BNP (N-terminal pro-B-type natriuretic peptide) as strong predictors of the increased risk of death of patients hospitalised because of ECOPD.^{1,2} The third, by Maclay *et al*³ (see page 769), provides evidence that patients with stable chronic obstructive

pulmonary disease (COPD) have increased circulating platelet–monocyte aggregates—a potential specific pathogenic mechanism of atherosclerosis. These aggregates further increase during exacerbations, suggesting a plausible biological mechanism to explain the increased cardiovascular risk seen in ECOPD. Taken together, these studies confirm the view that ECOPD episodes requiring hospitalisation must be considered very severe events in the natural course of the disease because they are associated with such important outcomes as increased risk of mortality, reduced health status, impaired lung function, muscle weakness, and cardiopulmonary complications.⁴ The studies also suggest that the increased risk of death is often due to acute cardiovascular involvement, and they highlight the limitations of the current definition of ECOPD and the need to move towards a more comprehensive definition, diagnostic approach and treatment.

RISK OF DEATH AND EXACERBATIONS OF COPD

Several previous studies have clearly established that episodes of ECOPD are a major driver of mortality in this disease, especially during and immediately after the acute event. (The long-term effects are discussed in next paragraph.) For instance, in a cohort of 1016 patients hospitalised because of ECOPD with hypercarbia (PaCO₂ ≥ 50 mm Hg), Connors *et al*⁵ reported that mortality was 11% in hospital, and 20%, 33%, 43% and 49%, respectively, at 60 days, 180 days, 1 year, and 2 years after discharge. More recently, Chang *et al*⁶ reported that mortality during the first 30 days after hospitalisation varied between 2% and 21% according to the CURB65 score. CURB65 is a composite index based on confusion, blood urea, respiratory rate, blood pressure and age that was developed to predict mortality risk in community-acquired pneumonia.⁶ Together these studies demonstrate that mortality during and immediately after hospitalisation for ECOPD is remarkably high.

Episodes of ECOPD also affect long-term mortality. This is best illustrated by the study of Soler-Cataluña *et al*,⁷ who followed a cohort of 304 patients with COPD for 5 years and found that mortality increased in direct proportion to the frequency of ECOPD; that is, patients with frequent episodes (three or more) had the greatest mortality risk (HR 4.13; 95% CI 1.80 to 9.41). In agreement with Connors *et al*,⁵ Soler-Cataluña *et al* also found that arterial hypercarbia was an independent marker of poor prognosis (HR 1.07; 95% CI 1.02 to 1.12).

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CARDIOVASCULAR DISEASE AND EXACERBATIONS OF COPD

Cardiovascular disease (CVD) is an important cause of mortality in COPD,⁸ and, as recently shown by Donaldson *et al*,⁹ the risk of acute vascular events appears to be particularly high during episodes of ECOPD. After analysing data from 25 857 patients with COPD who were entered in the Health Improvement Network database over a 2-year period, Donaldson *et al* reported that the risk of myocardial infarction 1–5 days after an ECOPD episode increased 2.3-fold (95% CI 1.1 to 4.7; $p=0.03$), and that the risk of stroke 1–49 days after ECOPD increased 1.3-fold (95% CI 1.0 to 1.6; $p=0.05$).⁹ Furthermore, a 2009 retrospective post-mortem study of patients who died within 24 h of hospitalisation because of ECOPD showed that cardiac failure and thromboembolism were the principal causes of death.¹⁰

The mechanisms linking COPD and CVD are unclear, but the presence of low-grade chronic systemic inflammation is likely to be an important one.^{11–13} Systemic inflammation increases during ECOPD,^{14 15} providing a potential mechanism to explain the increased risk of vascular events associated with ECOPD.⁹ The three studies published in this issue provide new information that can contribute to a better understanding of the relationship between ECOPD, inflammation and cardiovascular events. The first two studies^{1 2} found that the plasma levels of the cardiac biomarkers NT-proBNP and troponin T were abnormal in a significant number of patients hospitalised because of ECOPD, and that both markers predicted mortality^{1 2} even after adjusting for other predictors of mortality such as PaCO₂ or CURB65 score.¹ The third study found that, compared with healthy controls, patients with COPD had increased circulating platelet–monocyte aggregates, which were further increased during ECOPD.³ Together these findings suggest that cardiovascular involvement in ECOPD may be an important determinant of prognosis and death, opening new avenues for research of novel diagnostic and therapeutic strategies.

LIMITATIONS OF THE CURRENT DEFINITION OF EXACERBATION OF COPD

Maclay *et al*³ studied only patients with ECOPD, excluding those with acute heart failure, pneumonia or pulmonary embolism. However, Chang *et al*¹ and Hoiset *et al*² do not provide detailed criteria of

inclusion and exclusion, nor the full range of examinations performed to exclude alternative or concomitant causes of an increase in respiratory symptoms that may mimic an episode of ECOPD.

Unfortunately, the current definition of ECOPD is still very much descriptive and clinical. Episodes of ECOPD are defined as acute events characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations; in a patient with underlying COPD, these events may warrant a change in medication.^{16–18} However, while this definition may be useful in epidemiologic studies,¹⁹ it is often of limited use in the clinical setting. It is suggested that more than half of ECOPD episodes are caused by viral and bacterial infections or pollutants.^{16–18} These exacerbations are most likely associated with the three cardinal respiratory symptoms, increased sputum, purulent sputum and dyspnoea. In these cases, dyspnoea most likely worsens because of increased inflammation of the airways and the lung due to the infection or pollutant. However, patients with COPD often have several concomitant disorders. Therefore acute inflammation of the airways and the lung may not only worsen dyspnoea by affecting the respiratory system, but may also have systemic effects because of acute systemic inflammation and thus cause dyspnoea by affecting the cardiovascular or metabolic system. Moreover, other conditions, such as pulmonary embolism, acute cardiac failure, pneumonia, pneumothorax and anaemia, can mimic ECOPD by precipitating respiratory symptoms, particularly dyspnoea. Considering this complexity of causes, we suggest that the term 'exacerbations of COPD' be changed to 'exacerbations of respiratory symptoms in patients with COPD'. For the same reason, there is great interest in identifying biomarkers that can facilitate a more precise diagnosis of ECOPD and its aetiology. The three studies published in this issue suggest that serum biomarkers such as troponin T and NT-BNP may not only identify patients at increased risk of death but may also help to determine the relative role of extra-respiratory events, such as acute heart failure or thromboembolism, and that of other causes of acute dyspnoea in patients with COPD.

NEED FOR A MORE COMPREHENSIVE DIAGNOSTIC AND THERAPEUTIC APPROACH

These three articles^{1–3} extensively discuss the mechanisms underlying the increased

levels of cardiac biomarkers and platelet activation during ECOPD, as well as their clinical significance. The increase in troponin T and NT-BNP may be due to several different causes, including systemic inflammation, respiratory failure, coronary artery disease, left ventricular dysfunction, right ventricular pressure overload due to pulmonary hypertension, or pulmonary thromboembolism. However, platelet activation might not only be due to systemic inflammation but also to other concomitant chronic conditions such as rheumatoid arthritis or diabetes, or acute conditions such as hypoxaemia, tachycardia and hyperglycemia, all predictors of poor outcome in patients with ECOPD.^{4 8}

Guidelines provide clear evidence-based recommendations on how to diagnose and treat respiratory abnormalities during ECOPD episodes, but provide little direction on how to deal with concomitant abnormalities in patients with COPD. Considering the high risk of cardiovascular complications and death from ECOPD, we agree with the authors of the three studies discussed here that, while awaiting the generation of the necessary scientific evidence, patients hospitalised because of ECOPD should be carefully examined for the relevant biomarkers and for any concomitant abnormality that may call for specific therapy. This in line with the recent editorial of FitzGerald²⁰ and comment by the Editors of Thorax²¹ who recommend replacing the term 'exacerbations' with the term 'lung attacks' to emphasise their severity, dramatic consequences, and need for more aggressive, comprehensive and prolonged treatment.

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Call for papers

The Editorial Board would like us to have a North American-ATS themed issue in April 2012, for distribution at the ATS in May. We are therefore inviting manuscripts which either originate from North America, or relate to work which will be presented at the ATS meeting. All manuscripts will of course be rigorously peer reviewed in the usual way. Deadline for consideration 1 December 2011; please mention this call in the cover letter. The Editors would be happy to discuss any potential submissions.