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Is cough important in acute exacerbations of COPD?

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ABSTRACT

Chronic obstructive pulmonary disease is predicted to become the 4th leading cause of death worldwide by 2030. The natural history of the disease includes progressive symptoms punctuated by acute exacerbations during which symptoms rapidly deteriorate. The resulting disability places significant burden on health and social care systems. Cough is the second most common symptom reported by COPD patients, is a source of significant distress and is associated with adverse outcomes. We discuss the importance of cough in COPD, its mechanism and the relationship between cough and COPD exacerbations. We review the literature and present original data relating to the investigation of cough during COPD exacerbation, its associations and potential benefits of cough monitoring.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable chronic respiratory disease. In the developed world, it is largely caused by cigarette smoking in susceptible individuals and it is associated with significant morbidity and mortality. COPD was responsible for 3 million deaths worldwide in 2010 and is predicted to become the 4th leading cause of death by 2030 (Lozano et al., 2012; Mathers and Loncar, 2006). Breathlessness, cough, sputum production and wheeze are frequently experienced by people with COPD. Although symptom burden increases with disease severity, it is recognised that individuals experience significant symptom variability with periods of rapid worsening termed acute exacerbations (AECOPD). The combination of disability resulting from progressive symptoms and the tendency to exacerbations places a significant burden on health and social care services. As such, there is an urgent need to optimise COPD management to minimise patients' symptoms, reduce exacerbations and identify and treat them early when they occur. After breathlessness, cough is the second most commonly experienced symptom in COPD patients and it frequently worsens during exacerbation (Calverley et al., 2005). We discuss cough in COPD before focussing on potential ways that monitoring a patient's cough can be used to improve their management.

2. Cough in COPD

Cough is a common symptom in COPD with 60–80% of patients reporting having had a cough within the past 7 days (de Oliveira et al., 2013; Kessler et al., 2011). There is a diurnal variation with half of COPD patients reporting their cough to be most troublesome on waking in the morning (Kessler et al., 2011). Indeed, coughing at night is relatively rare, possibly due to increased vagal tone either diminishing cough reflex sensitivity or closure of the oesophageal sphincter (Fig. 1) (Crooks et al., 2016; Lee and Birring, 2010).

A chronic bronchitis phenotype is characterised by a cough with sputum production, occurring most days for three months for 2 consecutive years. Originally chronic bronchitis was claimed to have no adverse effects on COPD (Fletcher and Peto, 1977). However, later observational studies have demonstrated that cough with sputum production is associated with adverse outcomes including more frequent exacerbations (Burgel et al., 2009), accelerated lung function decline (Vestbo et al., 1996) and increased risk of mortality (Ekberg-Aronsson et al., 2005; Lahousse et al., 2017).

The cause of cough in COPD is likely to be multifactorial and vary significantly between individuals. Environmental exposures, altered respiratory mechanics due to hyperinflation, airway inflammation with mucus hypersecretion, and comorbidities all potentially impact cough in COPD patients.

A study by Sumner et al. utilised objective cough monitoring in 68 subjects with COPD and demonstrated cough frequency to be related to smoking history, current cigarette consumption and reported sputum production (Sumner et al., 2013). Only a weak correlation was observed with cough reflex sensitivity to capsaicin, however this is also true of other respiratory diseases associated with cough. In the 39 subjects that were able to provide a sputum sample for differential cell count, a trend towards a positive correlation between day time cough frequency and sputum eosinophils and neutrophils was observed. Multivariate analysis

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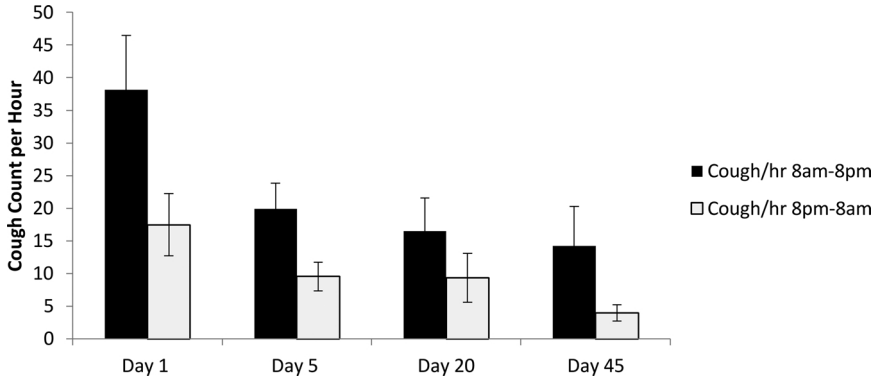

Fig. 1. Cough count per hour during the day (black bars) and night (grey bars) on days 1, 5, 20 and 45 following hospitalisation with AECOPD (n = 18).

suggested that current or past smoking and sputum production explained 45% of objective cough frequency variability in the full cohort. Past smoking history and sputum neutrophils explained 33% of cough variability in the group that were able to provide a sputum sample (Sumner et al., 2013). This study suggests that smoking history has a significant impact on cough in COPD. Indeed, cough frequency in current smokers was almost double that of ex-smokers with COPD. However, the disease process also plays a part with COPD ex-smokers having a similar cough frequency to current smokers without COPD who in turn had a significantly higher cough frequency than healthy non-smokers.

The relationship between cough and smoking is complex. A reduction in cough frequency is observed early following smoking a cigarette (Mulrennan et al., 2004). This is presumed to be due to reduced cough reflex sensitivity resulting from central stimulation of nicotine receptors since nicotine containing e-cigarettes produce a similar effect to tobacco where nicotine free e-cigarettes do not (Dicpinigaitis, 2017). Indeed, it is proposed that there is dual activity of nicotine, with peripheral protussive effects and central antitussive properties (Dicpinigaitis, 2017). This is illustrated by the immediate and transient cough that commonly occurs following e-cigarette consumption despite cough reflex sensitivity subsequently being observed to be reduced (Dicpinigaitis et al., 2016). A study in anaesthetised cats demonstrated that nicotine administered centrally to the brain stem circulation and ventral respiratory column had antitussive effects, emphasising the importance of central nervous system nicotine receptors in modulating cough reflex (Poliacek et al., 2015). The relationship between cough and cigarette smoking in COPD is therefore complex with an individual's propensity to cough based on the balance between peripheral protussive signals and nicotine's central effects on cough reflex sensitivity. Data from observational studies demonstrate the net effect of cigarette smoking to be in favour of increased cough frequency in COPD (Sumner et al., 2013).

COPD is associated with altered respiratory mechanics related to hyperinflation and dynamic airway collapse. Muscle dysfunction is also common in COPD patients (Charususin et al., 2018). The act of coughing occurs in three stages: inspiration, expiration against a closed glottis and explosive expiration following glottic opening. The high flow velocities generated by this process result in shearing of respiratory secretions from the bronchial wall, propelling them into the pharynx and mouth where they are either expelled or swallowed (Sivasothy et al., 2001). It is recognised in healthy subjects that the effectiveness of a cough is dependent on the operating volume (the volume inhaled prior to coughing) with influence on both the peak flow and volume of air expelled during a cough (Smith et al., 2012). It is also recognised that dynamic airway compression occurs during the expiratory phases of a cough that in healthy subjects contributes to the high expiratory flow rate (Knudson et al., 1974). Hyperinflation and dynamic airway collapse in COPD patients may negatively impact cough mechanics and coupled with altered sputum volume and viscosity, may reduce cough effectiveness.

Sputum overproduction is recognised in COPD patients with chronic bronchitis. In health, airway mucus has protective properties including innate immune functions and maintaining epithelial hydration (Martin et al., 2014). However, mucus hypersecretion and hyperconcentration occur in COPD contributing to disease pathogenesis and symptom burden (Anderson et al., 2015; Button et al., 2016). Mucus overproduction in the proximal airways is described in the context of the chronic bronchitis phenotype with neutrophil predominant inflammation observed in bronchial glands (Saetta et al., 1997). However, distal airway obstruction with mucus is not always associated with symptoms of cough and sputum production but is associated with adverse outcomes (Hogg et al., 2007). The mechanisms underlying mucus hypersecretion in COPD have been reviewed elsewhere (Hogg et al., 2007) and are beyond the scope of this review. However, changes in volume and consistency of airway mucus in COPD contributes to the disease process and impacts the frequency and effectiveness of cough.

There is current interest in the role of eosinophils in COPD because they appear to predict response to corticosteroids. However, there is considerable heterogeneity reported in the literature. Sumner et al. did not reveal a significant impact of sputum eosinophils on cough frequency using univariate or multivariate analysis. Similarly, no difference in the prevalence of a chronic bronchitis phenotype was seen in COPD patients with different levels of blood eosinophilia in a French observational study (Zysman et al., 2017). However, this study did not reveal any difference in exacerbation rate relating to blood eosinophil levels, a phenomenon that has been observed by others (Vedel-Krogh et al., 2016). A possible reason for the variability of findings amongst studies comparing patient characteristics in relation to their eosinophil counts is the way that eosinophilia is assessed. We have recently demonstrated that it is necessary to assess at least 2 previous eosinophil counts to distinguish eosinophilic versus non-eosinophilic COPD patients (Hamad et al., 2018). Therefore, the relationship between eosinophilia and cough and the chronic bronchitis phenotype remains unclear.

Cough reflex sensitivity in COPD has been examined in a number of studies utilising a range of cough challenges. A large study by Doherty et al. reported significantly increased cough reflex sensitivity compared to healthy controls in response to capsaicin (Doherty et al., 2000). However, the groups in this study were not well matched with COPD patients being predominantly older males (mean age 65 years, 75% male) and current smokers (40%) compared to the control group that consisted primarily of young females (mean age 38 years, 34% male) and only 17% current smokers. A subsequent study using capsaicin cough challenge assessed cough reflex sensitivity in COPD patients who otherwise did not report having a cough. This study revealed that COPD patients without persistent cough had a similar cough sensitivity to chronic smokers without airflow obstruction (Blanc et al., 2009). An earlier study by Wong and Morice (1999) comparing COPD patients with non-smoking controls did not demonstrate increased sensitivity to