

Interrupting the cough reflex in asthma

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Purpose of review

Although cough is one of the defining symptoms of asthma, wheeze, chest tightness and breathlessness have generally received more attention. The impact of coughing for patients may be more important than currently appreciated and has been rated more troublesome than wheeze, chest tightness or disturbance of sleep.

Recent findings

Studies objectively measuring cough in asthma reveal that cough frequencies vary from those similar to healthy volunteers to cough counts comparable to patients presenting with chronic cough, but the potential triggers for cough in asthma are poorly understood. This review discusses our current knowledge of cough in asthma, potential mechanisms that may provoke coughing, the effect of current treatments and possible future therapeutics.

Summary

Cough in some asthma patients is a significant problem, deserving further attention in both clinical practice and clinical research.

Keywords

asthma, asthma control, cough, cough reflex sensitivity

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Introduction

Cough is one of the defining symptoms of asthma [1] and although as such is frequently used in the diagnosis and monitoring of asthma, the symptoms of wheeze, chest tightness and breathlessness have generally received more attention. Some patients with asthma present with cough as an isolated troublesome symptom and so-called cough-variant asthma [2] is recognized as one of the three commonest causes of chronic cough alongside rhinosinusitis (or upper airways cough syndrome) and gastroesophageal reflux disease [3–6]. Why in some individuals asthma leads to such profound coughing but not significant wheeze is unclear.

The importance of cough in patient presenting with cough-variant asthma goes without question; however, the importance of this common symptom in patients with classical asthma may have been underestimated. A study by Osman *et al.* [7] performed a conjoint analysis of patients' symptom weightings in asthma and surprisingly found that cough and breathlessness were rated more troublesome than wheeze, chest tightness or disturbance of sleep. In this study, cough was the most troublesome symptom and patients were willing to trade higher levels of other symptoms for a reduction in coughing. There are a number of potential explanations for this: perhaps cough responds less well to current medications than wheeze or breathlessness; cough is a distinct, easily

identified problem and may correlate closely with other symptoms; and in some patients, cough is a dominant severe symptom and, therefore, results in the significant psychosocial and physical complications described in patients presenting with chronic cough [8]. A recent study [9] examined cough-specific quality of life in patients attending a general respiratory outpatient clinic and did not find significant differences in this setting between patients who had presented with asthma, chronic obstructive pulmonary disease bronchiectasis or even chronic cough.

In addition to its importance to patients, some evidence from epidemiological studies suggests that chronic cough may predict poor outcomes in asthma. In a study [10] that followed a cohort of asthma patients over a 9-year period, worsening of cough had the highest predictive weight for severe asthma.

The present review summarizes our current knowledge of the mechanisms underlying cough in asthma, the effectiveness of existing treatments and the potential targets for future treatments to interrupt the cough reflex in asthma.

Measuring cough in asthma

One of the barriers to a better understanding of the role of cough in asthma may be the lack of well validated

measures. Current outcome measures may not adequately emphasize the impact of cough as perceived by patients relative to their other asthma symptoms. Furthermore, when cough is assessed in both clinical practice and in clinical trials, subjective reporting using visual analogue scales or scoring systems has generally been relied upon. We have recently shown that subjective patient reports of cough frequency in asthma poorly represent objective cough rates [11[•]]. In some small studies, cough reflex sensitivity to tussive agents such as capsaicin or citric acid has been determined, and although mechanistically interesting, again we found these measures do not well represent the actual amount of coughing or its impact on patients [11[•]].

As can be seen in Fig. 1 [11[•],12], objective ambulatory measurement of cough using a digital sound recording device reveals a wide range in cough frequency in patients with classical asthma. Although cough frequencies for many asthma patients were similar to those in healthy volunteers, the higher cough rates in classical asthma were comparable to those we have observed in a cohort of patients presenting with chronic cough [12]. Cough-related quality of life was correlated with objective cough frequency in classical asthma [11[•]], implying that for patients with high objective frequencies, the impact of coughing was significant.

Mechanisms underlying cough in asthma

There are several possible mechanisms by which coughing in asthma might be triggered, and potentially provide targets for the treatment of cough in asthma. These

may, however, differ considerably between individual patients.

Sensitization of the cough reflex

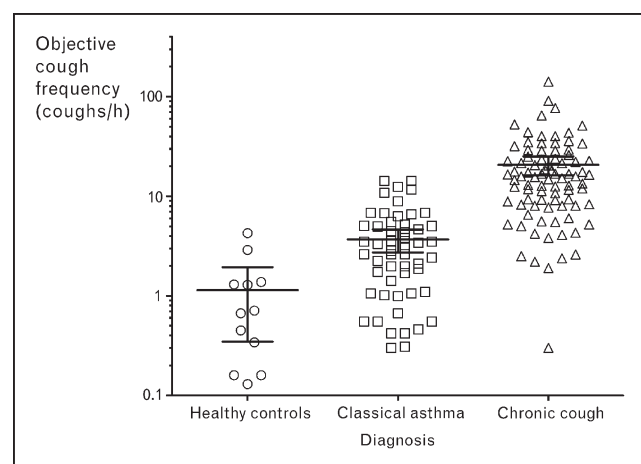
It is controversial whether hypersensitivity of the cough reflex contributes to cough in patients with either classical asthma or cough-variant asthma. Some studies have suggested that asthma patients have a sensitized cough reflex [13] compared with healthy volunteers and that cough reflex sensitivity improves following asthma treatment [9], whereas several studies by Fujimura [14,15] have suggested that asthma patients have similar cough reflex sensitivity to that in normal volunteers. In patients with cough-variant asthma, the cough reflex sensitivity was reduced by zafirlukast [16] but in a separate study of classical asthma, this effect was not seen [17]. In contrast, a recent study [18] found improvement in cough was not associated with improved cough reflex sensitivity in cough-variant asthma. Many of these studies contain a small number of patients and patient selection likely explains the contradictory findings. In our experience, cough reflex sensitivity in classical asthma is correlated moderately with objective cough counts [11[•]]; hence, if patients with high cough rates happen to be selected, cough reflex sensitivity will probably be heightened compared with healthy volunteers. Until cough reflex sensitivity is measured in a large group of unselected well characterized patients and compared with that in healthy volunteers of similar age and sex, this issue will not be resolved.

Airway inflammation

Asthma is a chronic inflammatory disease of the airways and is usually associated with eosinophilic inflammation, which can be demonstrated in sputum and airway biopsies. Cough in patients with classical and cough-variant asthma is generally reported to respond well to treatment with antiinflammatory agents [5], which produce reductions in eosinophil counts. Furthermore, eosinophilic bronchitis, a condition defined by eosinophilic airway inflammation in the absence of airway hyperresponsiveness, may account for up to 13% of patients presenting with chronic cough [19]. These observations raise the possibility that eosinophilic inflammation may be responsible for cough via influences on airway afferent nerves.

In addition to cellular inflammation, asthma patients exhibit increases in concentrations of mediators known to be involved in the activation and sensitization of airway nerves, for example, prostaglandin E₂ [20] and bradykinin [21]. One study [22] has suggested that mast cell-derived mediators histamine and PGD₂ are increased in chronic cough patients of all causes compared with healthy controls. In a separate study, these mediators were not elevated in classical asthma, suggesting these mediators could be involved in provoking excessive coughing.

Figure 1 Comparison of objective cough frequency in healthy controls, patients with classical asthma and patients presenting with chronic cough



Note logarithmic scale on Y-axis. Data adapted from previous publications [11[•],12].

Airway mucus

Patients with classical asthma generally expectorate only small volumes of sputum and the precise role of mucus hypersecretion as a trigger for symptoms such as cough is unknown [23^{••}]. In the small airways, excessive mucus produced by the epithelium may become impacted leading to closure of the small airways and contributing to airflow obstruction. These smaller airways are thought to have a lower density of afferent fibers capable of responding to the mechanical effects of mucus plugging [24]; however, coughing may be required to clear such impactions by a squeezing action on the airway wall.

Comorbidities

It is frequently reported that apart from asthma, nasal disease and gastroesophageal reflux disease constitute the two other commonest diagnoses found in patients presenting with chronic cough. Both of these conditions are known to have an increased prevalence in asthma and it is interesting to speculate that high cough rates in asthma may be due to these comorbidities. The mechanisms via which nasal disease and reflux provoke coughing and why some patients present with severe coughing as a consequence of these conditions, whereas many do not are poorly understood. Recent studies on asthma have failed to demonstrate a role for reflux in poorly controlled asthma but have not specifically assessed cough or weakly acid reflux events (pH 4–7) [25]. Bronchiectasis is another complicating condition in asthma patients, which may affect up to a quarter of patients with severe asthma [26], with larger volumes of mucus leading to increased cough and expectoration.

Asthma exacerbations

Exacerbations of asthma are common and are clearly associated with increased coughing, which is likely to be due to many of the mechanisms described above, that is, increased airway inflammation, mucus production and possibly also heightening of cough reflex sensitivity. The majority are related to viral infections, which even in the absence of asthma, can produce severe and sometimes prolonged coughing [27]. In experimental rhinovirus infections, lower respiratory symptoms (including cough) are markedly increased for asthma patients compared with healthy volunteers [28^{••}]. The precise mechanisms via which viruses induce coughing and whether this is a direct or indirect effect on airway nerves are not known [29].

Cough and measures of asthma severity

The severity of asthma involves not only the severity of the underlying disease process but also how well the disease responds to therapy. As such Global Initiative for Asthma (GINA) guidelines suggest asthma severity is based upon the frequency of symptoms, number of exacerbations, medication use and impairments/variability in forced

expiratory volume in 1 s (FEV1) or peak expiratory flow rate (PEFR) [1]. In a recent cross-sectional study [11[•]] of patients, we explored the relationships between objective cough frequency and standard measures of asthma severity, including pulmonary function and airway responsiveness. We found no significant correlations between cough frequency and FEV1 or methacholine challenge. A number of studies [30–32] have demonstrated that the underlying mechanisms of cough and bronchospasm are mediated by different sensory pathways in keeping with this finding.

There was, however, a weak association between increasing nocturnal cough frequency and dose of inhaled corticosteroid, which may be explained by poor asthma control correlating with both greater treatment requirements and higher cough frequency. Alternatively, patients with higher cough rates may be given additional asthma treatment in an unsuccessful attempt to control the cough. Of interest, cough frequency in this group of asthma patients was more influenced by age and sex than by standard measures of asthma, with cough rates tending to be higher in female patients and older patients, similar to that we have observed in chronic cough [12].

Cough and asthma control

Asthma control may be defined as how the symptoms and pathophysiological features of the disease are suppressed by therapy and therefore may vary over time. As such objective cough frequency may be a useful surrogate objective indicator of asthma control. We have recently investigated this hypothesis by examining the relationships between objective cough rates and disease control in 89 asthma patients using both a clinical measure (GINA classification: ‘controlled’, ‘partly controlled’ and ‘uncontrolled’) [33] and a validated questionnaire-based measure (Asthma Control Questionnaire, ACQ) of asthma control [34]. We found statistically significant differences in log total cough rates across GINA control groups with ‘uncontrolled’ asthma patients having significantly higher cough rates than those ‘partly controlled’ or ‘controlled’. There were also weak but statistically significant positive correlations between ACQ score and objective cough rates over 24 h and for day and night cough rates individually. Indeed, British Thoracic Society (BTS) treatment step [35], smoking history (pack years), sputum eosinophil count and log total cough rate all significantly independently predicted ACQ scores. This observation suggests cough frequency and eosinophilic inflammation may be operating a different paradigm.

Current and future treatments for cough in asthma

As already mentioned, it is generally accepted that cough in both classical asthma and cough-variant asthma

responds well to treatment with inhaled corticosteroids and bronchodilators. If this impression is correct, it might be assumed that patients with treated asthma, who still have cough, have poorly controlled disease. Further work is required to better understand to what extent cough rates in asthma may be a consequence of inadequate treatment, comorbid conditions or a failure of existing treatments to fully control the mechanisms driving cough in asthma. It is noteworthy that a recent observational study [36] of asthma patients in France found over a quarter were dispensed antitussive agents. In patients in whom a diagnosis of asthma is confirmed but cough remains refractory to standard treatment, there is some evidence to suggest that leukotriene receptor antagonists may be of benefit, by reducing cough reflex sensitivity [16].

In recent years, considerable progress has been made in animal models identifying specific airway afferent nerve subtypes and the channels which they express [37[•],38[•]]. This has allowed the identification of a number of potential targets for novel antitussive agents, including transient receptor potential receptors (TRPV1 and TRPA1), Nociceptin Opioid 1 (NOP1) receptors, tachykinin receptors, cannabinoid receptors and a variety of modulators of ion channels (for a recent comprehensive review, see reference [39[•]]). Whether promising results using drugs targeting these receptors in animal studies will translate into effective human treatments and whether such treatments will have a role in the management of classical asthma remain to be seen.

Conclusion

In summary, rates of cough in asthma are extremely variable and the potential triggers for cough numerous. In the patients with higher cough rates, the impact upon patients is currently underestimated and further investigation is required to understand the mechanisms driving cough in these patients and hence identify targets to improve treatment.

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J.A.S. is an inventor on a patent describing a novel method for cough detection, filed by the University Hospital of South Manchester and licensed to Vitalograph Ltd, UK. J.A.S. has an industrial collaboration with Vitalograph Ltd, UK to develop a commercial cough monitoring system.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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