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Journal club

Is there clinical value in performing capsaicin cough challenges in patients with severe asthma?

Commentary on:
Kanemitsu Y, *et al*. Increased capsaicin sensitivity in patients with severe asthma is associated with worse clinical outcome. *Am J Respir Crit Care Med* 2020; 201: 1068–1077.

Context

Over 330 million people have been diagnosed with asthma worldwide [1], of whom 5–10% are classified as severe [2]. Despite use of high doses of inhaled corticosteroids (ICS), long-acting bronchodilators (LABA) and/or maintenance oral steroid use, patients with severe asthma account for over 50% of the asthma healthcare budget [3, 4]. Largely due to exacerbations requiring hospitalisation, and cost of treatments to control disease severity, the disease burden has serious implications for their health and quality of life [3–5].

Cough is a common, troublesome symptom in asthma which predicts poor prognosis and disease severity [6–9]. Almost 60% of patients with moderate-to-severe asthma reported cough as an ongoing symptom with a greater impact than wheeze or sleep disturbance [10]. The cough reflex is a neuronally mediated pathway whereby afferent C and Aδ fibres that innervate airway epithelial and subepithelial cells express ion channels that become activated by various stimuli, including capsaicin (chilli pepper extract) [11]. This can result in depolarisation of the afferent nerves that then synapse in the brainstem to interact with higher cortical pathways and efferent motor nerves that innervate respiratory muscles to produce cough [11]. Many patients with asthma demonstrate features of hypersensitivity and hyperresponsiveness of this reflex that is sometimes refractory to ICS treatment [12, 13]. It is unclear whether current asthma treatments target the cough reflex.

Cough challenge is a method used to evaluate mechanisms of chronic cough [14]. By inhaling agents known to activate particular ion channels, one can evaluate the cough response to this agent in health and disease. Capsaicin is a cough challenge agent that activates transient receptor protein vanilloid 1 (TRPV1) ion channels, found predominantly on unmyelinated C fibres, to evoke a cough response [15, 16]. It can therefore be used to investigate the cough reflex in asthma.

Prior work has demonstrated heightened cough response to capsaicin in patients with mild to moderate asthma, providing evidence of neuronal dysfunction in this disease [12]. Concerns about safety and tolerability of capsaicin challenge in the severe asthma population have been in part addressed by a small study suggesting that capsaicin challenge is safe and tolerable in this cohort [12, 17]. Kanemitsu *et al*. [18] are the first group to evaluate capsaicin cough sensitivity (C-CS) in the severe asthma population. They aimed to evaluate the association of features of poor asthma control, blood biomarkers and demographic features with C-CS.

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Heightened capsaicin cough sensitivity is independently associated with poor asthma control in moderate-to-severe asthma patients https://bit.ly/3mkbLkI

Table 1 *Odds ratio of clinical features of severity in patients with heightened C-CS (C5 dose ≤2.44 µM)*

	OR (CI)	p-value
Poor asthma control (ACT <20)	4.83 (1.97–10.4)	0.0004
Exacerbations ≥2 per year	2.83 (1.04–7.71)	0.04
Hospitalisations ≥1 per year	3.43 (0.91–12.9)	0.07

Methods

This study prospectively recruited patients with a prior diagnosis of asthma. This was confirmed by the combination of clinical symptoms of asthma, and either reversible airflow obstruction or a positive methacholine challenge [18]. Prior to enrolment, patients needed to have received ICS treatment for 1 year or more. Capsaicin cough challenge was performed by administering doubling concentrations of capsaicin *via* a tidal breathing method. Doubling concentrations of capsaicin were administered for 15 s followed by 45 s of saline inhalation until five coughs (C5) were reached. The concentration of capsaicin required to evoke two (C2) and five coughs was used to evaluate C-CS [18]. Univariate analyses were performed to assess associations of heightened C-CS with features including demographics, Asthma Control Test (ACT) score, number of exacerbations requiring oral prednisolone, number of hospital admissions, prevalence of comorbidities, and asthma biomarkers [18]. Multivariate analysis was then used to assess the degree of association between C-CS and ACT score, exacerbation frequency and number of hospital admissions [18].

Main results

Capsaicin cough challenge was performed on 157 patients, of whom 77.7% were classified as having severe asthma (Global Initiative for Asthma (GINA) 2015 guidelines steps 4 or 5). The population mean age was 55 years, with a female predominance (70.7%) and 28.7% had a prior smoking history. The most prevalent comorbidities were rhinitis (54.1%) and gastro-oesophageal reflux disease (27.4%). Non-atopic asthma (defined as all specific IgEs <0.35 IU·mL^{-1}) was more common in females (86.2%) and associated with poorer asthma control (ACT score <20; p=0.01) and increased likelihood of hospital admission (≥1 admission per year) due to asthma (p=0.03).

Geometric mean C5 was lower in the non-atopic group (6.64 *versus* 12.2 µM; p=0.03), indicating higher levels of cough hypersensitivity within this group. Those in the non-atopic group were also twice as likely as those in the atopic group to have a C5 dose ≤2.44 µM (40.7% *versus* 23.3%; p=0.02). Patients on GINA treatment step 5 had a trend towards lower C5 values indicating heightened C-CS in this group (p=0.06). This was also the case for those taking oral corticosteroids (p=0.04).

By stratifying biomarkers and comorbidities against clinical features of severe asthma (ACT score <20), exacerbations per year, admissions per year, and evidence of airflow limitation (forced expiratory volume in 1 s <80% predicted), the study demonstrated that heightened cough reflex sensitivity and higher absolute neutrophil counts were associated with poorer asthma control, higher exacerbations, and a greater likelihood of hospitalisation due to asthma in the non-atopic phenotype.

In a multivariate regression analysis, heightened capsaicin sensitivity (C5 dose ≤2.44 µM) was associated with increased likelihood of having poor asthma control, two or more exacerbations and one or more hospitalisation (table 1).

Commentary

This prospective observational study investigated cough reflex sensitivity and its association with asthma control and exacerbations in a cohort of well characterised asthma patients. The study reflected a real-world moderate-to-severe asthma population, with a 2:1 female predominance and a mean age of 55 years, which interestingly is similar to the demographics of the refractory chronic cough population seen in specialty clinics [2, 19].

This study supports previous evidence demonstrating neuronal dysfunction in stable asthma, also suggesting airway reflex sensitivity is greatest in female non-atopic asthma patients [12]. In 5–10% of patients with asthma, symptoms are refractory to maximum inhaled therapy [20]. This suggests, that despite reducing airway inflammation and bronchial hyperresponsiveness, a further mechanism may contribute to symptoms. This is the first study to suggest cough reflex sensitivity could be important in the pathophysiology in severe asthma, particularly in non-atopic females. This supports evidence from asthma population studies, where this cohort report high symptom burden despite low levels of airway inflammation [21]).

There were some limitations. First, it is not clear that the absence of raised blood eosinophils or serum specific IgE titres truly define non-type 2 inflammation asthma. ICS and oral steroids, doses of which were high in this study, can suppress these measurements. In a milder cohort of steroid naïve patients with asthma, methacholine and allergen challenge resulted in bronchoconstriction and recruitment of eosinophils to the airways, both challenges were associated with an increased capsaicin evoked cough response [22]. Thus, to fully establish that a distinct neuro-phenotype exists in this "non-atopic" group, eosinophilic inflammation would ideally need to be fully excluded with either sputum eosinophil counts or bronchoalveolar lavage.

Although one can hypothesise that increased C-CS in severe asthma correlates with increased cough frequency, this cannot be assumed without 24-h objective cough counts. A previous study in asthma suggested that C2 and C5 do not correlate well with objective 24-h coughs [9]. An alternative approach is to perform a full capsaicin dose–response curve, to establish the maximum number of evoked coughs (E_{max}) and the dose of capsaicin needed to evoke 50% of the maximal cough response (ED_{50}) [12]. These measurements have shown better relationships with objective cough frequency [14].

Implications for practice

Capsaicin cough challenge is not currently used in clinical practice. In clinical trials its use in the uncontrolled asthma population has been limited probably due to limited safety data. This study provides evidence for safety of capsaicin challenge in patients with moderate-to-severe asthma [17].

This study demonstrates that cough is an important clinical symptom and an independent predictor of poor asthma control. But the question remains whether capsaicin cough challenge has a role in clinical practice as a biomarker for disease severity or identifying a potential treatable trait. Specific details of how cough challenges can be used, and which is the optimum end-point in clinical practice also needs validation. A full dose capsaicin cough challenge to the maximum tolerated dose or 1000 $\mu M \cdot L^{-1}$ may take 30–45 min. This would allow calculation of E_{max} and ED_{50}. In contrast, calculation of C2/C5 may take less time but is highly variable, discriminates less between health and disease and relates less well to spontaneous objective cough frequency [8, 14, 22]. Studies are required to ascertain which of the cough end points (E_{max}, ED_{50}, C2 or C5) would be most feasible, reproducible, repeatable and provide meaningful utility for clinical purposes.

An alternative approach is to administer the single individualised ED_{50} dose and measure the number of coughs [22, 23]. This would take 2 min to perform, and this method could potentially be used longitudinally every time a patient comes to clinic. What is unknown is how the results could be used to target therapy or alter medication targeting the cough reflex. There may be scepticism towards capsaicin cough challenge, given two TRPV1 antagonist studies failed to improve coughing [24, 25] and even when TRPV1 was effectively blocked, this did not reduce objective 24-h cough frequency [24]. However, this has yet to be evaluated in the asthmatic population with uncontrolled eosinophilic inflammation [24]. Others may consider using citric acid, hypotonic solution or ATP challenge to identify specific treatable targets. This has become more relevant in the context of the novel P2X3 antagonist [26, 27].

Current biological therapies reduce exacerbations, but placebo-controlled trials evaluating the impact of anti-interleukin (IL)-5, anti-IL-5 receptor and anti-IL-4 receptor α therapy on objective coughs are needed. This work will help answer the crucial clinical question as to whether heightened neuronal sensitivity in asthma is driven by eosinophilic or non-eosinophilic processes and whether such treatments can be used to treat cough in asthma.

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Author contributions

All authors were involved in the selection of the article for journal club, analysis, interpretation and writing of the manuscript.

Conflict of interest

J. King has nothing to declare. J. Wingfield Digby has nothing to declare. I. Satia reports personal fees for educational talks for GPs from GSK and Astrazeneca, grants and personal fees from Merck Canada, a grant from ERS Respire 3 Marie Curie Fellowship, and a grant from E.J. Moran Campbell Early Career Award, Department of Medicine, McMaster University, outside the submitted work.

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