



Identifying a Neurophenotype in Severe Asthma

Understanding why excessive symptoms and frequent exacerbations are poorly controlled in patients with severe asthma is a major unmet need. Uncontrolled daily symptoms despite high-dose inhaled (or oral) corticosteroids with or without bronchodilators impose a major burden on the lives of patients, with implications for their work and social and family life, and exacerbations are costly for healthcare systems (1–4).

Symptoms are difficult to measure because they are highly subjective and can be confounded by anxiety or depression. Cough is a common troublesome asthma symptom that can be experimentally evoked by inhaled cough stimuli (5) and objectively quantified by 24-hour cough monitoring (6). Capsaicin is a commonly used cough challenge agent that is known to activate TRPV1 (transient receptor potential vanilloid-1), which is found predominantly on unmyelinated c-fibers (7). Hence, capsaicin cough challenge can be used as an experimental model to investigate functional nerve responses in patients with asthma.

In a study presented in this issue of the *Journal*, Kanemitsu and colleagues (pp. 1068–1077) investigated the associations of capsaicin cough reflex sensitivity, as measured by the concentration of capsaicin causing two or five coughs (C2/C5), with clinical, physiological, and inflammatory features in patients with severe asthma (8). The clinical features were divided into two groups based on a combination of the degree of asthma control as measured by Asthma Control Questionnaire (>1.5) or Asthma Control Test (<20), exacerbation frequency (≥ 2 burst of oral steroids for ≥ 3 d), and hospitalizations (≥ 1). In a univariate analysis, heightened cough reflex sensitivity (lower C2/C5) and higher absolute serum neutrophil counts ($>5,000/\mu\text{L}$) were associated with poor asthma control, frequent exacerbations, and hospitalizations. However, this was confined mainly to nonatopic patients, where the mechanisms of clinical features remain poorly understood. In a multivariate analysis, heightened C5 increased the odds of poor asthma control (odds ratio [OR], 4.83), exacerbations (OR, 2.83), and a trend toward hospitalization (OR, 3.43). When compared with other variables, poor asthma control (Asthma Control Test < 20) was most strongly influenced by heightened cough reflex sensitivity (C5), followed by $\text{FEV}_1 < 80\%$ predicted, with some borderline significant contributions from being a nonatopic, ex-smoker with higher serum neutrophil counts. In contrast, greater exacerbation frequency (≥ 2) was most strongly influenced by $\text{FEV}_1 < 80\%$ predicted, followed by heightened cough reflex sensitivity and a borderline significant contribution from being female (OR, 3.34). Finally, hospitalizations were influenced most strongly by patients who were ex-smokers, with a $\text{FEV}_1 < 80\%$ predicted, raising the possibility these patients had chronic airflow limitation.

Ⓒ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202002-0228ED on February 12, 2020

This is the first study to show that heightened cough reflex sensitivity in patients with severe asthma is linked to clinical features such as poor asthma control and higher rates of exacerbations. This suggests that neuronal dysfunction is an important phenotype of severe asthma, and that novel treatments targeting excessive coughing may need to target peripheral airway nerves and/or the central pathways in the brainstem and higher cortical centers involved in the cough reflex.

Investigators have been reluctant to perform capsaicin cough challenges in subjects with severe asthma because of the risk of bronchoconstriction in those with persistent airway inflammation and lower FEV_1 . Only in the last few years have data emerged showing that capsaicin cough challenge does not cause bronchoconstriction in the vast majority of individuals with mild/moderate asthma (9), has no effect on airway hyperresponsiveness (10), is safe after induction of bronchoconstriction (10), and can be performed safely in patients with severe asthma (11). The only caveats are that FEV_1 should be checked before and after a challenge, and inhaled β_2 -agonists should be available in case there is a significant fall in FEV_1 associated with worsening symptoms. In this study, the investigators routinely gave salbutamol to every patient at the end of the capsaicin challenge without measuring FEV_1 , but, reassuringly, none of the patients required emergency treatment during the challenge itself.

As the authors recognize, the results should be interpreted with caution. This was a prospective observational study, and the authors did not assess airway inflammation in patients with severe asthma by measuring sputum differential cell counts. In addition, atopy was defined by negative specific serum IgE. The authors describe non-type 2 disease as the absence of atopy (i.e., non-IgE mediated) accompanied by low blood eosinophil counts, and this definition is imprecise. Patients were on moderate/high doses of inhaled corticosteroids, and it is not surprising that blood eosinophils were low and blood neutrophils were in the normal range. Previous observational data from subjects with mild/moderate asthma showed no relationship between capsaicin cough responses or 24-hour cough counts and blood (9) or sputum (12) eosinophil counts at baseline. However, after allergen challenge, an increase in sputum eosinophils after 24 hours was associated with increased capsaicin-evoked cough responses (13). This implies that inducing eosinophilic airway inflammation sensitizes the airway nerves. This notion was corroborated by a recent study that showed increased colocalization of eosinophils with airway nerves in patients with asthma (14).

Mucus or inflammatory cell debris in the airways as a plausible cause of coughing was not addressed. This was recently highlighted by elegant imaging studies that demonstrated ventilation heterogeneity (15) and reductions in total airway counts in patients with severe asthma (16). How these luminal and structural changes impact nerve structure and function remain unknown.

This study, as well as future mechanistic or interventional studies of cough in asthma, could be strengthened by measuring spontaneous objective 24-hour coughs. The relationship between

cough reflex sensitivity and spontaneous hourly cough rates is weak (17), although a distinction has to be made between cough reflex sensitivity (lower C2/C5) and cough hyperresponsiveness. The latter can only be demonstrated by performing a full capsaicin dose–response analysis to measure the maximum number of evoked coughs (Emax) (9). Whether inhibiting the cough reflex has any effects on reducing spontaneous objective cough rates is of questionable clinical utility. Two double-blind, randomized controlled trials of TRPV1 antagonists in patients with chronic refractory cough failed to show any impact on hourly cough rates, although one study using a highly potent TRPV1 antagonist demonstrated a significant reduction in capsaicin Emax (18, 19). However, these trials did not include patients with moderate or severe asthma; hence, TRPV1 antagonists could still play a role in asthma.

The concept of neurophenotypes in airway disease has previously been demonstrated in a study that used different cough challenge stimuli in airway diseases (20). The current study by Kanemitsu and colleagues further suggests that neuronal dysfunction is an important phenotype that influences asthma control and exacerbations. Broader questions remain as to whether the mechanism of TRPV1 hypersensitivity is peripherally and/or centrally driven, how type 2 and non-type 2 inflammatory cells and mucus affect airway nerves, and, importantly, whether any antitussives currently in development (e.g., P2X3 and NK-1 antagonists) or currently available biologics targeting IL-5 and IL-4/13 will improve cough in moderate-to-severe uncontrolled asthma. Future studies will be required to answer these important questions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Imran Satia, M.B. B.Chir., Ph.D.

Department of Medicine
McMaster University
Hamilton, Ontario, Canada

Firestone Institute for Respiratory Health
St. Joseph's Healthcare
Hamilton, Ontario, Canada
and

Faculty of Biology, Medicine and Health
University of Manchester, Manchester Academic Health Science Centre
Manchester, United Kingdom

Paul M. O'Byrne, M.B., F.R.C.P.(C.)

Department of Medicine
McMaster University
Hamilton, Ontario, Canada

ORCID ID: 0000-0003-4206-6000 (I.S.).

References

- Sadatsafavi M, Rousseau R, Chen W, Zhang W, Lynd L, FitzGerald JM. The preventable burden of productivity loss due to suboptimal asthma control: a population-based study. *Chest* 2014;145:787–793.
- Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J* 2007;16:22–27.
- Moy ML, Israel E, Weiss ST, Juniper EF, Dubé L, Drazen JM; NHLBI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;163:924–929.
- Adams RJ, Wilson DH, Taylor AW, Daly A, Tursan d'Espaignet E, Dal Grande E, et al. Psychological factors and asthma quality of life: a population based study. *Thorax* 2004;59:930–935.
- Morice AH, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol* 2001;52:365–375.
- Kelsall A, Decalmer S, Webster D, Brown N, McGuinness K, Woodcock A, et al. How to quantify coughing: correlations with quality of life in chronic cough. *Eur Respir J* 2008;32:175–179.
- Mazzone SB, Udem BJ. Vagal afferent innervation of the airways in health and disease. *Physiol Rev* 2016;96:975–1024.
- Kanemitsu Y, Fukumitsu K, Kurokawa R, Takeda N, Suzuki M, Yap J, 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.
- Satia I, Tsamandouras N, Holt K, Badri H, Woodhead M, Ogungbenro K, et al. Capsaicin-evoked cough responses in asthmatic patients: evidence for airway neuronal dysfunction. *J Allergy Clin Immunol* 2017;139:771–779.e10.
- Satia I, Badri H, Woodhead M, O'Byrne PM, Fowler SJ, Smith JA. The interaction between bronchoconstriction and cough in asthma. *Thorax* 2017;72:1144–1146.
- Wang R, Fowler S, Niven R, Ryan D, Holt K, Mitchell J, et al. Investigating the safety of capsaicin cough challenge in severe asthma. *Eur Respir J* 2018;52:PA4404.
- Marsden PA, Satia I, Ibrahim B, Woodcock A, Yates L, Donnelly I, et al. Objective cough frequency, airway inflammation, and disease control in asthma. *Chest* 2016;149:1460–1466.
- Satia I, Watson R, Scime T, Dockry RJ, Sen S, Ford JW, et al. Allergen challenge increases capsaicin-evoked cough responses in patients with allergic asthma. *J Allergy Clin Immunol* 2019;144:788–795.e1.
- Drake MG, Scott GD, Blum ED, Lebold KM, Nie Z, Lee JJ, et al. Eosinophils increase airway sensory nerve density in mice and in human asthma. *Sci Transl Med* 2018;10:eaar8477.
- Svenningsen S, Eddy RL, Lim HF, Cox PG, Nair P, Parraga G. Sputum eosinophilia and magnetic resonance imaging ventilation heterogeneity in severe asthma. *Am J Respir Crit Care Med* 2018;197:876–884.
- Eddy RL, Svenningsen S, Kirby M, Knipping D, McCormack DG, Liciskai C, et al. Is computed tomography airway count related to asthma severity and airway structure-function? *Am J Respir Crit Care Med* 2020;201:923–933.
- Marsden PA, Smith JA, Kelsall AA, Owen E, Naylor JR, Webster D, et al. A comparison of objective and subjective measures of cough in asthma. *J Allergy Clin Immunol* 2008;122:903–907.
- Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol* 2014;134:56–62.
- Belvisi MG, Birrell MA, Wortley MA, Maher SA, Satia I, Badri H, et al. XEN-D0501, a novel transient receptor potential vanilloid 1 antagonist, does not reduce cough in patients with refractory cough. *Am J Respir Crit Care Med* 2017;196:1255–1263.
- Belvisi MG, Birrell MA, Khalid S, Wortley MA, Dockry R, Coote J, et al. Neurophenotypes in airway diseases: insights from translational cough studies. *Am J Respir Crit Care Med* 2016;193:1364–1372.

Copyright © 2020 by the American Thoracic Society