

Interfering with airway nerves in cough associated with asthma

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ABSTRACT

Cough is a troublesome and often refractory symptom of asthma, which is associated with poor control of disease. The pathogenesis of asthmatic cough has mainly been attributed to bronchoconstriction, but recent evidence indicate that cough reflex hypersensitivity or neuronal dysfunction is a feature of asthma, even in those with mild stable disease. This is likely resistant to the mainstay treatment ICS/LABA which inhibits classic asthmatic response. Such refractory cough might manifest more predominantly in the day-time rather than night-time. Treatment options of such refractory cough or cough reflex hypersensitivity in asthma targeting the nerves (LTRAs, tiotropium, and potentially bronchial thermoplasty) are discussed.

1. Introduction

Cough is the most commonly reported symptom of asthma [1]. Cough of the daytime had the greatest negative impact, and was of far greater importance than wheeze or sleep disturbance, among 1300 moderate asthmatic patients [2]. The presence of cough in asthma may be longitudinally associated with asthma severity and poor prognosis: in a 9-year study, worsening of cough had the highest predictive weight for severe asthma [3]. Despite clinical importance of cough in asthma, its mechanisms have been a subject of debate. We review the presence and relevance of airway nerve dysfunction (potentially associated with increased innervation) in the pathogenesis of cough in asthma; such features clinically present with heightened cough reflex sensitivity (CRS) to tussive stimuli such as capsaicin. We will further discuss the evidence of intervention on such dysfunction, a potentially relevant therapeutic target, leading to improvement of cough.

2. Mechanisms of cough in asthma

Cough, as well as wheeze, chest tightness, and shortness of breath, in asthma has been attributed to reversible airflow obstruction and airway inflammation, the latter of which is typically eosinophilic. Long-standing inflammation may lead to airway remodeling features such as epithelial shedding and increase of airway smooth muscle (ASM). These features are associated with the classical early- and late-phase asthmatic responses and airway hyperresponsiveness (AHR), typically following an allergen challenge (Fig. 1, left) [4]. This notion is supported by the response of asthmatic cough to short- and long-acting beta-agonists (SABAs and LABAs), the most potent bronchodilators, and inhaled corticosteroids

(ICSs), the mainstay anti-inflammatory medication for asthma.

However, cough of asthma cannot be exclusively explained by such traditional scenario. For example, asthmatic cough is often resistant to the standard ICS (with/without LABA) treatment (Table 1) [5]; this issue will be further discussed later. Furthermore, Purokivi and colleagues examined the determinants of asthma control measured by Asthma Control Questionnaire (ACQ). Interestingly, cough response to hypertonic saline and isocapnic hyperpnea, and Leicester Cough Questionnaire (LCQ) total scores significantly correlated with ACQ total scores, while variable or reversible airflow obstruction or airway inflammation, as measured as exhaled nitric oxide (FeNO), were unrelated to asthma control (Table 2) [6]. Likewise, objective cough frequency correlated with standard measures of asthma control, but not with FEV1 or sputum eosinophilia [7].

Apart from asthmatic response, increase of CRS is a central feature of chronic cough in general [8]. There are two subtypes of airway sensory nerve for initiating cough: nociceptors, which mainly detect a range of noxious chemical irritants, and mechanoreceptors which are very sensitive to touch-like mechanical stimuli. Mechanosensors are found in the larynx, the trachea and large bronchi, and sensitive to intraluminal irritants or particulate matter and mechanical irritants with signals conducted along myelinated Aδ fibers. Nociceptors found in the larynx, tracheal, bronchial, and alveolar walls are unmyelinated slow conducting C-fibers that respond to capsaicin, pro-inflammatory molecules including bradykinin, prostaglandins, leukotrienes and cytokines, and noxious irritants such as acid and nicotine. C-fiber sensors may release tachykinins, such as substance P, through an “axon reflex”, which in turn causes neurogenic inflammation, despite evidence is limited to guinea pigs. Several transient receptor potential (TRP)

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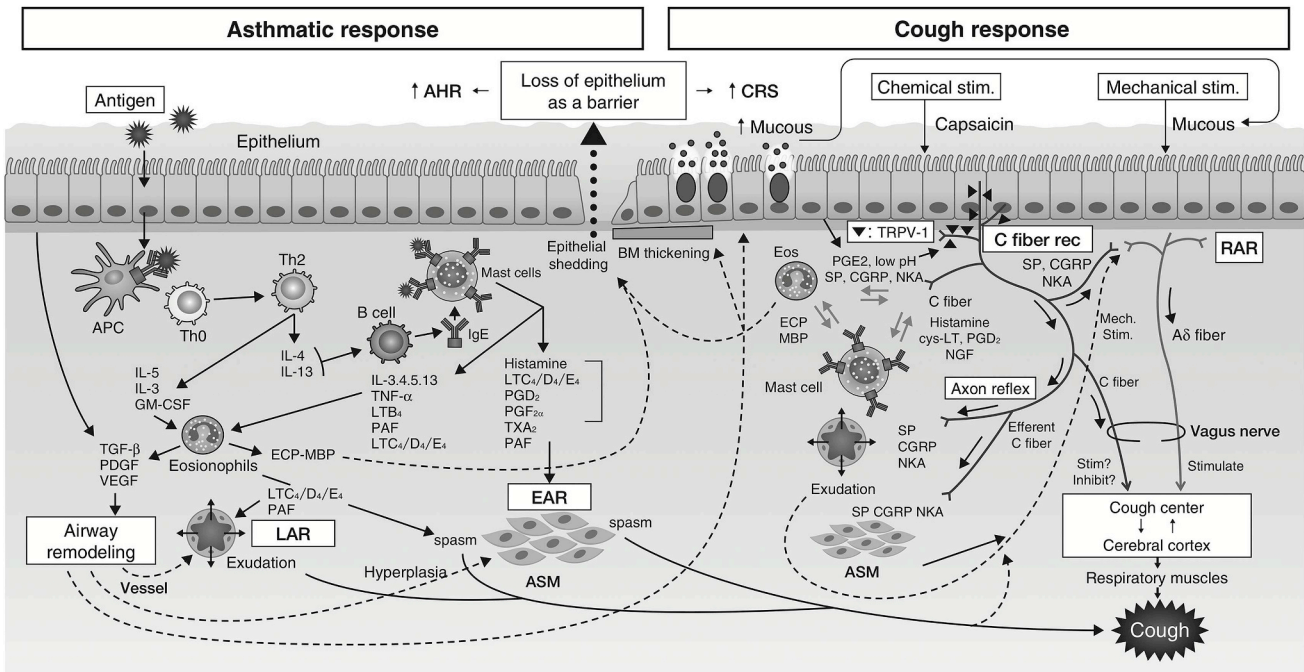


Fig. 1. Suggested mechanism of cough in asthma for the present (updates of our hypothesis [4]). The left-hand figure shows the classical asthmatic response which has been considered the mainstream mechanism for asthmatic cough. The right-hand figure represents the cough response that is focused in the present review. These mechanisms, however, may not be distinct from, but may be linked to, each other [41,42](see text for the details). Please also refer to the conclusion of the manuscript for the therapeutic implication of this discussion. Abbreviations used: APC: antigen presenting cell, AHR: airway hyperresponsiveness, CRS: cough receptor sensitivity, EAR: Early asthmatic response, LAR: Late asthmatic response, ASM: airway smooth muscle, TRPV1: Transient receptor potential vanilloid type 1, Stim.: stimuli/stimulate, Rec: receptor, RAR: rapidly adapting receptor, BM: basement membrane.

Table 1
Symptom scores in adult patients with chronic asthma before and after ICS treatment [ref 5].

Symptom	Initial	8 wk	Mean Difference	No.	P value
Cough	1.83 ± .21	1.68 ± .20	0.146	40	0.54
Wheeze	2.30 ± .20	1.60 ± .20	0.700	39	0.008
Chest tightness	2.10 ± .22	1.37 ± .22	0.732	40	0.009
Dyspnea	2.60 ± .20	1.88 ± .22	0.737	39	0.004
Sputum	1.75 ± .25	1.43 ± .23	0.350	39	0.32
Nocturnal awakening	2.20 ± .25	1.60 ± .26	0.585	40	0.055
Total	12.7 ± 1.0	9.6 ± 1.2	3.1	40	0.02

Cough was the most refractory symptom to ICS treatment.

Table 2
Determinants of asthma control measured by Asthma Control Questionnaire (ACQ^a) [ref 6].

PEF variation (%)	r = 0.04, p = 0.80
FEV ₁ bronchodilator reversibility (%)	r = 0.20, p = 0.25
FeNO (ppb)	r = -0.03, p = 0.84
Cough induced by hypertonic saline (No.)	r = 0.52, p = 0.001
Cough induced by isocapnic hyperpnea (No.)	r = 0.43, p = 0.008
LCQ ^b total score	r = -0.54, p = 0.001

In a cross-sectional study of 36 stable asthmatics taking ICS (26 females, mean age 41 years), cough, but not the classical features of asthma (variable airflow obstruction and inflammation), was the determinant of asthma control.

^a Asthma Control Questionnaire (ACQ): higher the worse asthma control.
^b Leicester Cough Questionnaire (LCQ): lower the poorer cough-specific QoL.

channels are found in C- and Aδ-nociceptors, namely TRPV-1 and TRPA1 receptors. TRPV-1 receptors are directly activated by capsaicin, and are sensitized or indirectly activated by heat, protons, bradykinin,

and arachidonic acid derivatives. TRPA1 is co-expressed and may interact with TRPV1 on many vagal C-fibers [8]. Reflex cough is integrated in the medulla oblongata where the afferent fibers for coughing first relay in the nucleus of the tractus solitarius (“cough center”). Afferent inputs to the brainstem are relayed to higher brain regions where inputs are integrated in pontine, subcortical and cortical nuclei. The motor outputs send motoneurons to the respiratory muscles, and to the larynx and bronchial tree, leading to cough [8].

CRS is commonly examined with inhalations of increasing doses of capsaicin, as determined by the lowest concentration causing 2, or 5, or more coughs (C2/C5). Whether CRS to capsaicin is heightened in asthma has been controversial [9,10], probably due to methodology issues, patient selection and concomitant medications. In a study of stable asthmatics, capsaicin C5 was heightened as compared with healthy controls and unrelated to ICS dose. Furthermore, C5 in asthma was related to symptomatic cough as measured by the diary scores and VAS, but independent of the degree of FEV1, PEF variability or AHR [9].

Recently, Satia and colleagues conducted a study of a doubling full dose capsaicin challenge which went beyond the C5 to investigate the maximum coughs evoked (Emax) and the dose causing half the response (ED50) in stable mild to moderate asthma patients not selected for symptoms of cough, and healthy controls [11]. This method is different to the conventional methods which stops at either 2 coughs or 5 coughs (i.e. it continues beyond C5), in stable asthma patients not selected for symptoms of cough, and healthy controls [11]. They revealed that CRS is increased in the asthmatic patients especially in female and nonatopic subjects, and is associated with poor asthma control but is independently of, airway inflammation, AHR, and airflow obstruction. These patients exhibited exaggerated capsaicin-evoked cough responses consistent with neuronal dysfunction [11]. These results indicated that cough response (Fig. 1, right), in addition to the mainstream asthmatic response (Fig. 1, left), is importantly involvement in the pathogenesis of cough in asthma.

3. Can standard anti-asthma medications modulate cough reflex sensitivity in asthma?

In a retrospective study of patients with cough variant asthma (CVA), ICS treatment attenuated methacholine AHR as expected, but capsaicin C5 was not affected [12]. In another study of asthma, three months of ICS treatment again failed to affect capsaicin C5 [13]. Also a SABA procaterol did not alter capsaicin CRS in asthmatic as well as bronchitic subjects [9]. In contrast, studies with cysteinyl-leukotriene receptor antagonists (LTRAs) showed positive results. Zafirlukast 20 mg bid for two weeks significantly improved cough scores and capsaicin CRS in eight patients with CVA as compared with placebo, while FEV₁ values were unchanged [14]. An observational study of 4 weeks' treatment with montelukast in 23 CVA patients resulted in decrease of cough VAS, sputum eosinophils, and attenuation of capsaicin CRS [15]. Spirometry, AHR, and measures of respiratory resistance and reactance as examined by impulse oscillometry (IOS) [16] were unchanged [15]. The antitussive effect of montelukast in CVA may therefore be attributable to attenuation of CRS, possibly through its anti-inflammatory ability, rather than bronchodilation [17]. These results indicate that CRS in patients with CVA can be modulated by LTRAs but not by ICSs or beta-agonists, the standard anti-asthma medications. However, although a reduction in capsaicin CRS was shown, it is currently unknown whether LTRA is clinically effective at reducing spontaneous objective coughing in patients with CVA or classical asthma.

4. Diurnal variation of cough and CRS, and factors contributing to ICS-refractory daytime and nighttime asthmatic cough

Asthma is characterized by variable airflow obstruction, as demonstrated by variations of peak expiratory flow [PEF] or bronchodilator responsiveness, or increased AHR, and airway inflammation. These pathophysiological hallmarks are associated with symptoms such as shortness of breath and wheezing, becoming most prominent in the midnight and early morning [18]. This most likely comes from circadian rhythm of circulating epinephrine, cortisol, eosinophils, and histamine. Also, nocturnal cough is considered a characteristic (and even diagnostic) feature of asthma. However, objective cough frequency in asthma in mild to moderately severe patients is actually reduced during the night due to sleep, as in healthy individuals and non-asthmatic chronic cough patients, but significantly increased at the time of waking between 6 a.m. and 8 a.m. [7,19,20]. Importantly, the degree of coughing does not correlate with airflow obstruction or its diurnal variation [7,19,20]. Furthermore, CRS as measured by inhalation of citric acid was reduced in patients suffering from aspiration pneumonia both at the daytime and nighttime, as compared with age-matched healthy elderly. CRS was attenuated in the nighttime as compared with the daytime in both subject groups [21]. Diurnal variation of cough or CRS is thus absolutely reversal of that of PEF/airflow limitation/AHR, the "classic" hallmarks of asthma. We hypothesized that the pathophysiology and refractoriness of cough in asthma to ICS may differ between the daytime and nighttime, and prospectively recruited consecutive asthmatics presenting solely or predominantly with chronic cough but not taking ICSs or LTRAs, between April 2012 and December 2014 [22]. All 55 patients, who were eligible for evaluation, were treated with ICS (mean dose 592 µg/day, fluticasone equivalent; also with LABAs in 31), for 12 weeks in an observational fashion. Lung function, capsaicin C2/C5, methacholine AHR (airway sensitivity and reactivity [23]), Japanese version of LCQ [24], and visual analogue scale (VAS) and numeric scores of cough [19] to separately evaluate daytime and nighttime cough symptoms, were measured at baseline and 12 weeks after treatment. When either the VAS or numeric scores showed a limited improvement of < 50% or < 2 points, patients were considered refractory to ICS treatment. Both cough VAS and cough scores decreased for the daytime and night-time. LCQ scores also improved (Fig. 2). AHR (airway reactivity), airway closure (R5 of IOS) and

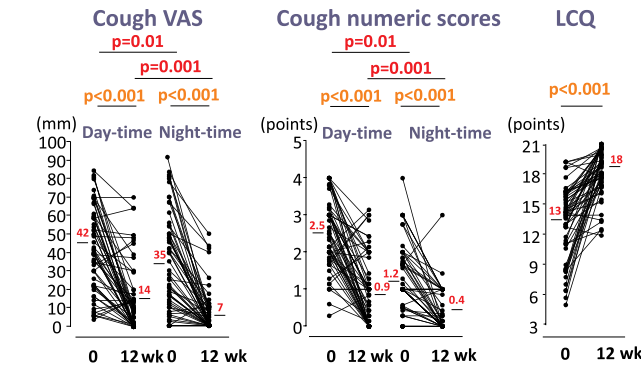


Fig. 2. Changes of cough VAS, cough scores, and LCQ scores before and after 12 weeks of ICS treatment in 55 mild-to-moderate asthmatic patients [22]. Both cough VAS and cough scores significantly decreased for the daytime and night-time. These cough indices were higher in the daytime vs night-time both before and after ICS treatment. LCQ scores also significantly improved.

inflammation (FeNO), but not capsaicin CRS, were responsive to ICS, all of which were consistent with literature. Cough VAS and scores were higher in the daytime vs night-time both before and after ICS (Fig. 2) [22]. Among the 55 patients, 16 (29%) and 8 (15%) were considered refractory to the 12 weeks' ICS treatment, for the day-time and night-time cough, respectively. Multivariate analysis revealed that lower C2 significantly contributed to residual daytime cough. Meanwhile, methacholine hyperreactivity and lower IgE levels were independent predictors of the nighttime residual cough (Table 3). We concluded that heightened cough reflex sensitivity is an independent factor of daytime asthmatic cough that is refractory to ICSs, and that AHR (airway hyperreactivity) and less atopic status (lower IgE) contribute to ICS-refractory nighttime cough [22]. These results indicate that day-time cough that is more prevalent, refractory and thus troublesome to asthmatic patients [2] may be attributable to the insensitivity of CRS to ICS. A limitation to this study was the lack of placebo and objective cough monitoring and subject scores whose minimally clinical important difference is unclear. Despite this, new therapeutic strategy of CRS in asthma, other than LTRAs, are awaited.

5. Novel anti-asthma treatment targeting cough reflex sensitivity: interfering with airway nerves

A substantial body of evidence from studies in animals and in experimentally induced cough in humans has supported antitussive activity of anticholinergics [25]. Tiotropium, a long-acting muscarinic M3 receptor antagonist (LAMA), inhibits citric acid- [26] and capsaicin-induced cough [27] in conscious guinea pig. Ipratropium, a short-acting muscarinic M3 receptor antagonist (SAMA) which is structurally similar to tiotropium, significantly lowered symptom scores for both daytime and nighttime cough in patients with post-viral cough, vs placebo [28]. Ipratropium also reduced cough number, cough index and CRS to citric

Table 3
Pre-treatment factors associated with the daytime and night-time cough refractory to ICS (multivariate regression analysis)[ref 22].

	OR	(95% CI)	P value
Day-time cough refractory to ICS, yes vs. no			
Sex, females	3.53	0.96–15.7	0.06
Capsaicin C2, µM	0.36	0.01–0.93	0.04
Night-time cough refractory to ICS, yes vs. no			
Sex, females	18.8	0.20–849	0.21
Use of LABA, yes	7.69	0.35–202	0.26
Log serum IgE, U/ml	0.009	0.00003–0.70	0.03
No of sensitized allergens, n	0.72	0.12–258	0.70
Airway reactivity (SGrs), L/sec/cmH ₂ O/m	32.7	2.24–776	0.002

acid in asthmatic patients but not in normal subjects while albuterol, a SABA, failed to show such effects [29]. Tiotropium alleviated capsaicin CRS of patients with acute viral cough without affecting lung function [30]. However, oxitropium bromide, which inhibits the cough response to ultrasonically nebulized distilled water, did not demonstrate antitussive activity in acute viral cough [31].

Despite such evidence, any antitussive effect of muscarinic receptor antagonists is unlikely to be a direct airway effect on the cough reflex, because there are no muscarinic receptors on airway afferent nerves [26]. In naive guinea pigs, tiotropium attenuated capsaicin-induced hyperdepolarization of vagal nerve *ex vivo*, which was exerted by modulation of TRPV-1 [26]. Such effect was not evident for other SAMAs or LAMAs, except for ipratropium [26]. Tiotropium may thus have off-target antitussive effects by altering CRS. Since the efficacy of tiotropium for asthmatic cough remained unknown, we evaluated the effects of tiotropium 5 mcg qd for 4–8 weeks on subjective cough measures (VAS and LCQ), capsaicin C2 and C5, lung function, and asthma control in 17 asthmatics with persistent cough despite ICS/LABAs, in an uncontrolled observational manner [32]. The mean dose of ICS was 651 µg/day, equivalent of fluticasone. Tiotropium significantly improved cough VAS, LCQ, and asthma control test (ACT) scores, but not FEV₁, C2 or C5 in the whole 17 patients. However, when the subjects were stratified into 11 responders defined by a Δcough VAS of > 15 mm, and the remaining 6 nonresponders, both C2 and C5 significantly increased in responders within the subgroup and also vs nonresponders (Table 4). The Δcough VAS of whole patients correlated with ΔC2, ΔC5 and ΔACT, but not with ΔFEV₁ (Fig. 3). The baseline C2 and C5 values were significantly lower in females and non-atopic subjects vs males and the atopics, in consistent with Satia et al. [10]. The C2 and C5 values tended to be lower, despite insignificantly, in responders than in nonresponders (data not provided in the paper). We concluded that tiotropium alleviates asthmatic cough refractory to ICS/LABA, by modulating CRS but not through bronchodilation; however, placebo-controlled studies in mild/moderate asthmatic patients are still required [32].

Bronchial thermoplasty (BT) is a novel treatment for severe asthma; heat therapy targeting ASM in the central airways. BT reduces the volume of increased ASM in severe asthmatic airways, leading to reduction of exacerbations and improved asthma control. Recently, a new

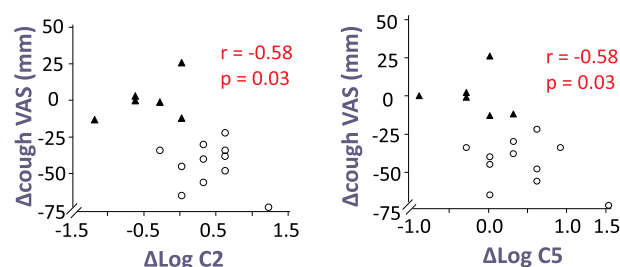


Fig. 3. Correlations between changes in cough VAS score and those in capsaicin cough reflex sensitivity after treatment with tiotropium, in 17 patients with asthmatic cough refractory to ICS/LABA [32]. ΔCough VAS negatively and significantly correlated with ΔC2 and ΔC5. Open circles and closed triangles represented 11 responders to tiotropium with an increase of cough VAS with treatment ≥ 15 mm, and the remaining 6 non-responders, respectively. ΔCough VAS did not correlate with ΔFEV₁ (data not shown). ΔACT scores correlated with Δcough VAS and ΔJ-LCQ (data not shown).

mechanism of BT has been demonstrated; the number of airway nerves in the submucosa and ASM, and also the number of epithelial neuroendocrine cells are decreased by BT, in association with reduction of exacerbations and improved asthma control [33] (increase of nerve tissues can be now considered airway remodeling changes of asthma, as will be discussed later). These pathological effects of BT persisted for at least 12 months, in parallel with clinical improvements [34]. We reported a 35 year-old lady with adult-onset asthma, presenting with severe cough, which was refractory to standard antiasthma treatments including high-dose ICS, LABA, LTRA and tiotropium (Fig. 4) [35]. This nonatopic patient had no indication of anti-IgE or anti-IL5, and gave a consent to undergo BT. After the first session of BT, coughing started to improve markedly, as demonstrated by cough VAS halving from 79 to 36 mm, and LCQ scores doubling from 7.9 to 16.8. Cough counts induced by the lowest dose of capsaicin of our protocol (0.61 mcg/ml) [32] were 10–20 before BT, but were markedly reduced to 3 and eventually 0 after BT [35]. Such effects may be due to the “denervation” effects as reported [33], but cannot be attributable to decrease of ASM.

The predominant cite of airway inflammation/involvement is

Table 4

Clinical indices before and after the tiotropium treatment between the responders and the non-responders.

	Responders (n = 11)			Non-responders (n = 6)			p value ^c
	Before	After	p value	Before	After	p value	
Age (years)	45.2 (16.4)	–	–	45.7 (25.0)	–	–	–
Sex (M/F), n	2/9	–	–	2/4	–	–	–
Smoking status (never/ex), n	9/2	–	–	3/3	–	–	–
Body mass index (kg/m ²)	22.7 (5.0)	–	–	21.8 (2.6)	–	–	–
Atopic, n (%)	5 (46)	–	–	3 (50)	–	–	–
Total IgE (IU/L) ^a	289 (5–1620)	–	–	37.6 (5–705)	–	–	–
Cough duration (month) ^a	6 (3–66)	–	–	18 (2–54)	–	–	–
ICS dose (FP equivalent), µg	650 (204)	–	–	653 (183)	–	–	–
Treatment with LTRA, n (%)	4 (37)	–	–	4 (67)	–	–	–
Cough VAS (mm)	54.6 (17.3)	11.5 (11.8)	< 0.0001	50.8 (23.8)	51.8 (23.5)	0.87	< 0.0001
J-LCQ	12.5 (3.4)	17.5 (2.2)	0.006	13.2 (4.1)	14.1 (3.7)	0.44	0.04
ACT scores	16.6 (2.3)	21.8 (4.1)	0.01	18.8 (3.5)	18.8 (3.9)	1.00	0.03
C2 (µM) ^b	0.36 (0.56)	0.74 (0.60)	0.01	0.84 (0.62)	0.39 (0.63)	0.06	0.004
C5 (µM) ^b	0.41 (0.64)	0.83 (0.65)	0.02	0.94 (0.64)	0.74 (0.79)	0.29	0.02
FEV ₁ (mL)	2918 (995)	2972 (950)	0.24	3083 (1112)	3115 (1177)	0.81	0.81
%FEV ₁ predicted (%)	102 (9.2)	105 (11.4)	0.11	108 (13.2)	109 (16.5)	0.74	0.67

Mean (SD).

ICS: inhaled corticosteroids, FP: fluticasone propionate, LTRA: leukotriene receptor antagonists.

VAS: visual analogue scale, J-LCQ: Japanese version of Leicester Cough Questionnaire.

ACT: asthma control test, FEV₁: forced expiratory volume in 1 s.

^a Median (range).

^b Log-transformed.

^c Comparison of the differences in clinical valuables between the responders and non-responders.

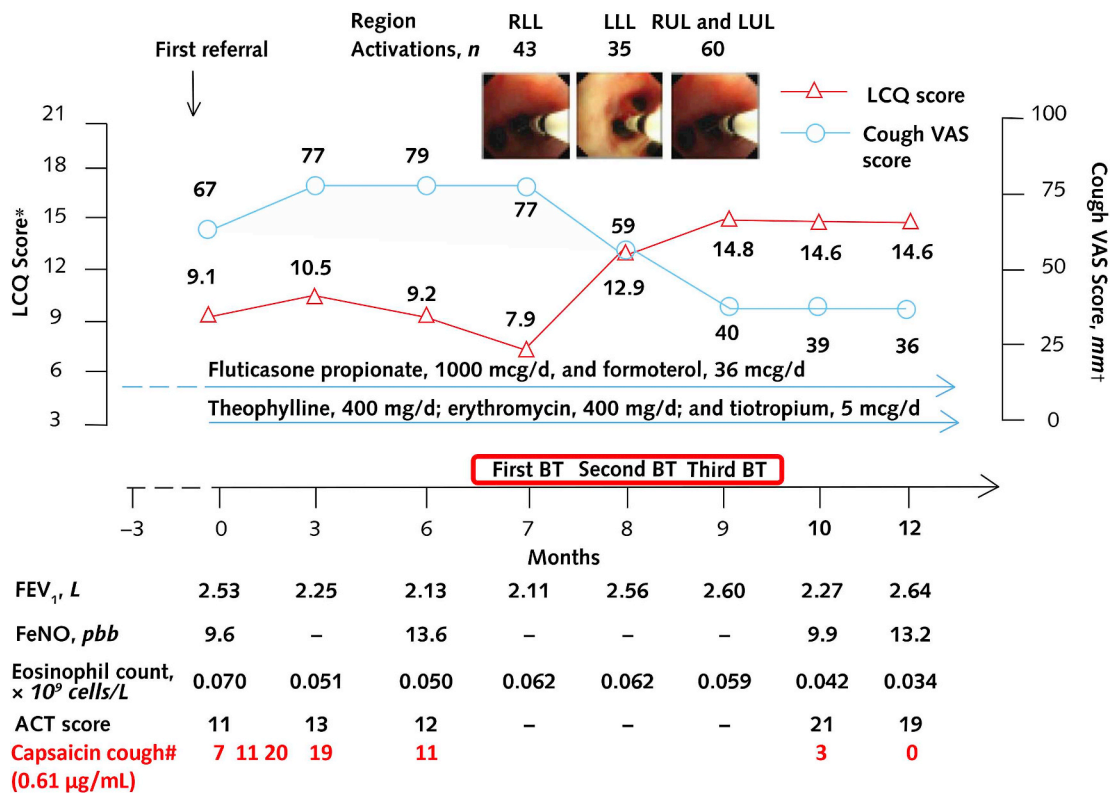


Fig. 4. Successful treatment of severe refractory cough with bronchial thermoplasty in a 35-year-old lady with nonatopic, non-eosinophilic asthma [35]. Cough VAS, LCQ scores, ACT scores and capsaicin-induced cough count markedly improved with BT, while FEV1, FeNO and blood eosinophil levels were not affected.

unknown for CVA, while small airways dysfunction has been associated with poor asthma control [36]. We conducted a modified fractional analysis of early- and late-phase induced sputum samples, which may differentially evaluate large and small airways inflammation [37] in patients with classic asthma and CVA [38]. They inhaled 3% hypertonic saline for 30 min, and coughed up sputum, being separately collected during the former and the latter 15 min for cell differentials. Among 119 patients examined, 47 successfully produced both early-phase and later-phase samples. After excluding 12 patients who had no eosinophils in either samples, the remaining patients were arbitrarily classified into “larger airway-eosinophils-predominant” group (early-phase eos% > late-phase eos%; n = 22) and “smaller airway-eosinophils-predominant” group (early-phase eos% < late-phase eos%; n = 13) for comparison. Although such classification is still preliminary and has not been validated, the latter group significantly differed from the former group for indices considered associated with small airway abnormality (frequency resonance [Fres] and low-frequency reactance area [AX] of IOS and alveolar nitric-oxide levels), and the prevalence of CVA [38] (Table 5). Spirometry indices, AHR, asthma control or exacerbation frequency were similar between the two groups. Our sputum-based novel phenotyping of asthma reflects may reflect larger/smaller airways pathophysiology represented by IOS and nitric-oxide levels. We concluded that asthmatic cough may possibly arise predominantly from larger airways inflammation [38], where evidence from animal studies suggests most of the airway nerves are located [39]. This might be consistent with the efficacy of BT, an ablation predominantly of larger airways, on cough of asthma [35].

6. Emerging evidence possibly linking the two mechanisms of cough in asthma

After the presentation of above issues at the 2018 London Cough Symposium, two important papers regarding eosinophilic airway

inflammation, nerves and cough in asthma have been published. In asthma, airway nerve dysfunction leads to excessive bronchoconstriction and cough. It is well established that eosinophils alter nerve function and that airway eosinophilia is present in 50–60% of asthmatics. In airways of fatal asthmatics, more eosinophils are found clustered around airway nerves than in other airway compartment, such as around blood vessels or within the airway parenchyma [40]. However, the effects of eosinophils on airway nerve structure have not been established. Drake and colleagues tested whether eosinophils alter airway nerve structure, and measured the physiological consequences of those changes, by using human airway tissues and a mice model. Airway innervation and substance P expression were increased in moderate asthmatics compared to mild intermittent asthmatics and healthy subjects. The increased innervation was associated with: 1) increased eosinophilic inflammation of blood and airways, 2) a lack of bronchodilator responsiveness, and 3) increased irritant sensitivity as examined by “exposure to environmental stimuli” domain of Asthma Quality of Life Questionnaire, that may be associated with cough. In a mouse model of eosinophilic airway inflammation, the increase in nerve density and AHR were mediated by eosinophils. These results indicate that airway nerve remodeling is induced by eosinophilic inflammation, and may be a key mechanism for increased irritant sensitivity, presumably leading to cough, and exaggerated AHR in eosinophilic asthma [41]. Satia and colleagues sought to investigate the effects of allergen exposure on CRS in patients with mild atopic asthma [42]. They performed a 9-visit, randomized, single-blind, placebo-controlled, 2-way crossover study comparing CRS to inhaled capsaicin in patients after allergen challenge compared with diluent control. Full-dose capsaicin challenge was performed at screening to determine the capsaicin dose inducing a half-maximal response, which was subsequently administered at 30 min and 24 h after inhaled allergen/diluent challenge. Spontaneous coughing was measured for 24 h after allergen/diluent.

Table 5
Comparison of the larger- and smaller-airway-eosinophil predominant asthma subgroups [38].

	Larger airway-eosinophil-predominant (n = 22)	Smaller airway- eosinophil-predominant (n = 13)	p
Age (years)	51.6 (12.7)	47.5 (14.0)	0.37
Sex (Male/Female)	10/12	6/7	1.0
Smoking status (never/ex)	11/11	7/6	0.83
Classic asthma/cough variant asthma	12/10	12/1	0.02
Disease duration (years)	15.4 (13.9)	14.1 (14.0)	0.45
BMI (body mass index), kg/m ²	22.7 (3.3)	24.0 (4.9)	0.37
ACT (asthma control test; score)	18.6 (4.9)	18.7 (6.0)	0.94
ICS treatment (yes/no)	8/14	6/7	0.72
ICS dose (equivalent of fluticasone), µg	757.5 (443.4)	593.3 (72.3)	0.55
LABA (yes/no)	5/17	6/7	0.26
LTRA (yes/no)	3/19	5/8	0.12
GINA severity (2/3/4/5) †	3/6/13/0	3/1/8/1	0.30
Asthma exacerbations requiring OCS for > 3 days/yr	0.46 (1.40)	0.30 (0.50)	0.90
Peripheral blood eosinophils, %	3.51 (2.48)	5.25 (5.49)	0.84
Total IgE, IU/L median [range]	405 [26–2510]	232 [5.4–1210]	0.44
Early-phase sputum eosinophils, %	2.88 0.25–70.0]	0.75 [0–51.25]	0.06
Late-phase sputum eosinophils, %	0.54 [0–18.0]	1.25 [0.25–55.5]	0.08
FVC (% pred)	103.4 (18.0)	94.8 (11.3)	0.12
FEV ₁ (% pred)	95.4 (19.6)	87.3 (19.4)	0.31
FEF _{25–75} (% pred)	64.6 (25.0)	59.3 (26.4)	0.49
R5 (kPa/L/s)	0.31 (0.08)	0.33 (0.10)	0.67
R20 (kPa/L/s)	0.28 (0.07)	0.29 (0.07)	0.65
R5-R20 (kPa/L/s)	0.03 (0.03)	0.04 (0.04)	0.32
× 5 (kPa/L/s)	−0.10 (0.03)	−0.12 (0.03)	0.10
Fres (L/s)	10.4 (2.8)	12.6 (3.7)	0.032
AX (kPa/L)	0.25 (0.22)	0.39 (0.34)	0.015
FeNO50 (ppb)	48.2 (48.9)	39.4 (33.9)	0.68
CANO [TMAD] (ppb; median [range])	3.59 [3.5–13.3]	11.0 [8.1–31.5]	0.047
Dmin (units)	16.7 (21.7)	16.3 (23.3)	0.75

*Data are presented as mean (± SD) unless otherwise indicated.

Methacholine challenge and sputum induction were performed before and after allergen/diluent challenge. Twelve steroid-naïve subjects completed the study. Allergen inhalation caused both an early and late decrease in FEV₁ and an increase in sputum eosinophil counts 24 h later (after diluent: 1.9% by median; after allergen: 14.9%; $p = 0.005$). There was also an increase in capsaicin-evoked coughs after allergen exposure compared with diluent at both 30 min (geometric mean coughs, 21.9 vs 9.8; $p = 0.001$). Allergen exposure was also associated with an increase in spontaneous coughs over 24 h. The authors concluded that allergen-induced bronchoconstriction and airway eosinophilia result in increased CRS to capsaicin associated with an increase in 24-h spontaneous coughing [42].

Eosinophils has been considered to play important roles in the pathogenesis of cough of asthma [43], but ICSs, the most potent suppressor of eosinophilic inflammation, insufficiently attenuate cough and CRS of asthmatic subjects. These facts were the basis of the two hypothesized mechanisms of cough in asthma (Fig. 1). These mechanisms, however, may not be distinct from, but may be linked to, each other, as has been suggested by the novel evidence described above [41,42].

7. Conclusions

Cough is a troublesome and often refractory symptom of asthma, which is associated with poor control of disease. The pathogenesis of asthmatic cough has mainly been attributed to classical asthmatic response or bronchoconstriction [44], but recent evidence indicate that cough reflex hypersensitivity or neuronal dysfunction is a feature of asthma, even in those with mild stable disease. Cough response based on such mechanisms is likely resistant to the mainstay treatment ICS/LABA which successfully inhibits classical asthmatic response. Such refractory cough might manifest more predominantly in the day-time rather than night-time.

Treatment options of such refractory cough (or cough reflex hypersensitivity) in asthma include LTRAs, tiotropium, and potentially

BT. It may be of therapeutic implication if we could clarify which of the two mechanisms of asthmatic cough is more prominent in each patient, although these mechanisms may be linked to each other.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pupt.2019.101854>.

R/X, respiratory resistance/reactance; Fres, resonant frequency; AX, low-frequency reactance area of impulse oscillometry. FeNO50, fraction of exhaled NO at 50 ml/s. CANO, alveolar/small airway fraction of FeNO. Dmin, cumulative dose of inhaled methacholine at inflection point where respiratory resistance begins to increase (marker of AHR) [21].

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