



Cough Hypersensitivity Syndrome: A Few More Steps Forward

Woo-Jung Song,¹ Alyn H. Morice^{2*}

¹Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

²Centre for Cardiovascular and Metabolic Research, University of Hull, Hull York Medical School, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom

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Cough reflex is a vital protective mechanism against aspiration, but when dysregulated, it can become hypersensitive. In fact, chronic cough is a significant medical problem with a high degree of morbidity. Recently, a unifying paradigm of cough hypersensitivity syndrome has been proposed. It represents a clinical entity in which chronic cough is a major presenting problem, regardless of the underlying condition. Although it remains a theoretical construct, emerging evidence suggests that aberrant neurophysiology is the common etiology of this syndrome. Recent success in randomized clinical trials using a P2X3 receptor antagonist is the first major advance in the therapeutics of cough in the past 30 years; it at last provides a strategy for treating intractable cough as well as an invaluable tool for dissecting the mechanism underpinning cough hypersensitivity. Additionally, several cough measurement tools have been validated for use and will help assess the clinical relevance of cough in various underlying conditions. Along with this paradigm shift, our understanding of cough mechanisms has improved during the past decades, allowing us to continue to take more steps forward in the future.

Key Words: Cough; hypersensitivity; pathophysiology

INTRODUCTION

“Three things cannot be hidden: coughing, poverty, and love.” This is originally Yiddish proverb, quoted in a popular Korean movie “Il Mare (2000),”¹ refers to the hypersensitive nature of cough. The cough reflex is an airway defence mechanism against aspiration, but dysregulated cough presents as irresistible bouts with hypersensitivity to even trivial environmental stimuli.²⁻⁵

Cough is a common medical problem. In a previous US survey, acute cough was the single most common symptom for seeking medical consultation.⁶ In a survey in Asian-Pacific countries, cough was the most frequent symptom and also was the main reason for medical visits among patients with respiratory diseases.^{7,8} Chronic cough is also a globally prevalent problem, affecting ~10% of adults in the general population.⁹ Positive correlations between older age and chronic cough prevalence suggest that the epidemiological burden is on the rise,¹⁰ following global trends in aging. Importantly, cough can seriously impair quality of life, as it includes psychological, social, and physical consequences.^{11,12} A survey among elderly individuals found that the impact of chronic persistent cough on mental health was comparable to that of stroke or Parkinson’s disease.¹³

Healthcare expenditures for the assessment and treatment of

cough are also substantial.^{14,15} Despite a meticulous diagnostic protocol for chronic cough, 12%-42% of patients remain unexplained or refractory.¹⁶ Additionally, anti-tussive medicines with proven efficacy and safety are nearly lacking.¹⁷ In a recent survey conducted in Europe, most subjects with chronic cough responded that their cough medication had limited or no effectiveness (57% and 36%, respectively).¹⁸ Substantial medical expenditures may currently be wasted on ineffective drugs, but this also underscores the need to verify the efficacy of current therapeutic tools and strategies using validated measurement tools.¹⁹ More importantly, precise pathophysiological mechanisms should be sought to identify novel targets to manage cough hypersensitivity.

In recent years, there have been major advances in the field of cough research. In this review, we will focus on the pathophysiology of cough hypersensitivity and also briefly discuss the research directions that should produce new breakthroughs for

Correspondence to: Alyn H. Morice, MD, FRCP, Head of Cardiovascular and Respiratory Studies, University of Hull, Hull York Medical School, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire, HU16 5JQ, United Kingdom
Tel: +44-0-1482-624066; Fax: +44-0-1482-624068;

E-mail: a.h.morice@hull.ac.uk

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use in clinical practice.

COUGH HYPERSENSITIVITY SYNDROME

Previously, chronic cough was thought to be primarily a consequence of chronic disease conditions, such as reactive airways (asthma and eosinophilic bronchitis), rhinosinusitis, or reflux disease, the “three Rs.”²⁰ However, a large proportion of patients with these conditions do *not* complain of chronic cough.^{21,22} Moreover, despite meticulous diagnostic and therapeutic trials, more than a few patients with chronic cough did not fit into any disease category, resulting in common diagnoses of idiopathic, refractory, or unexplained cough.¹⁶ Given this background, it could be reasonably suggested that cough is not always related to another disease condition but rather is a clinical entity with a distinct pathophysiology.^{23,24} Indeed, the cough reflex has its own neural pathways of regulation.²⁵ In turn, disease conditions, such as the 3Rs, could be associated with or act as triggers, rather than direct causes of cough.²⁶

Recently, a new paradigm, “cough hypersensitivity syndrome,” was proposed (Fig. 1).²⁷ This is defined as a clinical entity characterised by cough as a major component, which is often triggered by low levels of thermal, mechanical, or chemical exposure.²⁷ It is an umbrella term encompassing various cough-related conditions or unexplained cough.²⁷ Through this paradigm, we can interpret cough-related disease phenomena from the viewpoint of the cough itself.

EVIDENCE FOR NEUROPATHOLOGY IN COUGH HYPERSENSITIVITY SYNDROME

The main mechanism of cough hypersensitivity syndrome has been suggested to be dysregulated sensory neural pathways and central processing in cough reflex regulation.²⁸⁻³⁰ However, direct evidence for neural dysfunction is lacking because, except for peripheral lung tissues, human neural tissues are very difficult to obtain. Thus, at present, cough hypersensitivity syndrome is still a conceptual entity. However, accumulating evidence supports the notion that neuropathology is the key pathophysiology underlying this syndrome (Table 1).

Clinical profile

In clinical observations, chronic cough patients frequently report that their cough is triggered by innocuous stimuli, such as perfume, cold air, exercise, stress, singing, or talking (referred to as *allotussia*).²⁻⁵ Cough is frequently preceded by an *urge-to-cough*, a sensation of irritation or itching in the throat, which is also called *laryngeal paresthesia*.³¹ The frequency of *allotussia* or *urge-to-cough* varies according to population and methodology, but it is reported to occur in ~99% of these patients.^{2-5,31,32} Moreover, these characteristics of cough are similar to those of pain, such as *allodynia*, which is the pain caused by stimuli that do not normally provoke pain.²⁸ The left-shift of the *tussigen-cough* response curve (*hypertussia*: increased cough sensitivity to noxious stimuli) is another example of cough reflex hyper-

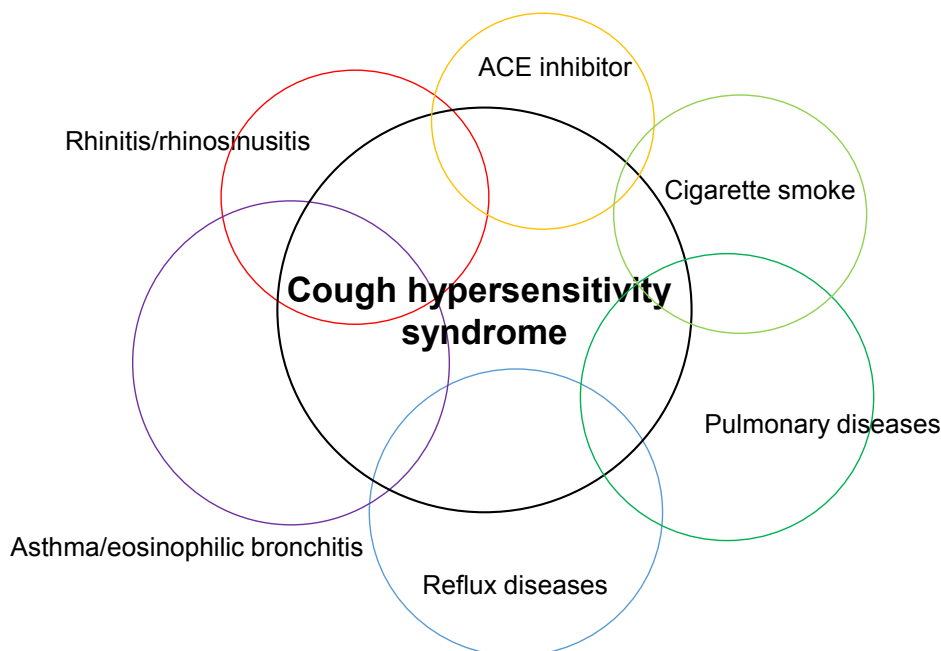


Fig. 1. Paradigm of cough hypersensitivity syndrome. This represents a clinical entity where chronic cough is a major presentation, irrespective of underlying conditions. Modified with permission from Asia Pac Allergy 2014;4:3-13.²⁶

Table 1. Evidences for neuropathology in cough hypersensitivity

Category	Characteristics
Clinical profile	Cough triggered by trivial stimuli such as cold air, perfume, stress, exercise, singing, or talking (allotussia) Urge-to-cough sensation More coughs evoked by tussigen inhalation (hypertussia)
Sensory neural activation in the airways	Phenotypic switch of sensory neurons by respiratory virus infection, allergen, or air pollutant Increased neuropeptides in bronchoalveolar lavage fluids TRPV1 up-regulation in bronchial epithelial nerves
Central neural alterations in cough processing	Increased activation of midbrain areas (presumably related to descending modulatory pathways) Decreased activation in brain areas implicated in cough suppression
Clinical trials	Proven efficacy of drugs with neuro-modulatory properties

TRPV1, transient receptor potential vanilloid-1.

sensitivity. The cough response to capsaicin inhalation can be enhanced by administration of angiotensin-converting enzyme (ACE) inhibitor.³³ Enhanced cough reflex sensitivity can commonly be observed in various conditions presenting as cough, such as cough variant asthma, reflux-associated cough, and idiopathic cough, but not observed in asthma without cough.^{34,35} Furthermore, control of these factors (*e.g.* ACE inhibition or associated disease conditions) usually normalizes the hypersensitivity in the cough reflex.³⁶

Sensory neural activation in the airways

Several peripheral inputs, such as viruses, allergens, and irritants, can induce phenotypic switches in sensory neurons and up-regulate host cough responses. Respiratory viruses infect and replicate in airway epithelial cells, leading to proinflammatory responses from the host to clear the invaders; airway epithelial cells can produce soluble neurotrophic factors in response to viral infections.^{37,38} However, they may also infect sensory neurons and rapidly induce a phenotypic switch, at least *in vitro*.³⁹ In a guinea pig experiment, intranasal parainfluenza-3 virus infection significantly increased transient receptor potential vanilloid-1 (TRPV1) expression in tracheal nodose A δ -neurons.⁴⁰ Nociceptive C-fibre neurons, but not A δ -neurons, typically express TRPV1 and produce neuropeptides, such as substance P or calcitonin gene-related peptide (CGRP); thus, the expression of TRPV1 has been used as a marker for a phenotypic switch in lung sensory neurons. These neuronal phenotypic switches are significantly correlated with cough responses to tussigens, such as capsaicin and citric acid, and have also been associated with increased expression of neurotrophic factor receptors in the neurons.⁴⁰ Similar phenotypic changes in

sensory neurons and heightened cough responses were observed in guinea pig models of allergic airway inflammation or particulate matter 2.5-induced airway inflammation.^{41,42} These phenotypic changes in peripheral sensory neurons may in turn provoke inflammatory responses from immune cells, so-called neurogenic inflammation. Released neuropeptides, such as substance P and CGRP, may induce local vascular dilatation,⁴³ chemotaxis,⁴⁴ immune cell activation, and promote type 2 helper T-cell polarisation.⁴⁵ Such neuro-immune interactions, particularly in cases of repeated sensory inputs (*e.g.* viruses or allergens), would lead to a vicious cycle of hypersensitive responses.⁴⁶

Functional up-regulation of airway sensory nerves is commonly found in chronic cough patients. In studies of bronchoalveolar lavage fluids, inflammatory mediators, such as histamine, CGRP, cysteinyl leukotrienes, and prostaglandins E2 and D2, were significantly increased in patients with chronic cough, regardless of the underlying conditions.⁴⁷⁻⁵⁰ O'Connell *et al.*⁵¹ demonstrated that the nerve staining density for CGRP, a common neuropeptide, was significantly increased in biopsied peripheral lung tissues from idiopathic cough patients compared with healthy controls. Expression of TRPV1 was also increased in the bronchial epithelial nerves of chronic cough patients compared with healthy controls,⁵² although other study has failed to find such changes.⁵³ Recently, West *et al.*⁵⁴ demonstrated dense and complex morphological characteristics of peripheral airway neural networks in unexplained cough patients using a whole-mount tissue immunofluorescence approach. This is considered a major technical advance, because previous studies using thin tissue sections had reported only sparse sub-epithelial innervation (1%–3%).^{51,52} Interestingly, protein gene product 9.5 (PGP9.5), a pan-neuronal marker-positive epithelial cells, referred to as pulmonary neuroendocrine cells, were observed throughout the epithelial layers,⁵⁴ suggesting their potential to mediate nerve-epithelial cross-talk. This methodological advance is expected to produce more insights into the neuropathological changes involved in cough hypersensitivity.

Central neural alterations in cough processing

The central neural processes of cough regulation are altered in chronic cough patients as demonstrated in functional brain imaging studies by Mazzone *et al.*³⁰ The sensation of laryngeal irritation (urge-to-cough) following tussigen inhalation normally accompanies activation in diverse areas of brain networks both in cough patients and healthy controls. However, the activation areas differed significantly in 3 areas of the mid-brain—the nucleus cuneiformis, periaqueductal grey, and dorsal raphe—where cough hypersensitive patients showed marked increases in activation signals, whereas controls showed no such increases.³⁵ These midbrain areas are known as components of the descending pain modulatory system;⁵⁵ thus, these changes in cough patients may indicate altered cen-

tral neural processing in cough control. Another notable finding was that cough hypersensitive patients showed significantly lower activation levels in brain areas (the dorsomedial prefrontal and anterior mid-cingulate cortices)³⁵ that have been implicated in cough suppression.⁵⁶ Loss of cough inhibitory control may be a distinct feature of chronic cough patients as suggested by a functional study measuring capsaicin inhalation-induced maximum cough responses.⁵⁷ It has been suggested that centrally acting anti-tussive agents, such as morphine⁵⁸ and first-generation antihistamines, such as chlorpheniramine and diphenhydramine,⁵⁹ act through agonist activity on these central inhibitory pathways. These effects are unrelated to sedation, which presumably occurs through different central pathways.⁶⁰

The origin of altered central cough processing is supposed to be peripheral sensory inputs and subsequent inflammation, but this needs further investigation. A few available pieces of evidence suggest that repeated peripheral stimulation induces changes in the central nervous system. In a rhesus monkey model of allergic asthma, repeated exposure to house dust mite allergen resulted in increased excitability of nucleus tractus solitarius (NTS) neurons.⁶¹ In a rat model of ovalbumin-allergic asthma, NTS cell firing activity in response to capsaicin exposure was increased compared with non-allergic controls.⁶² In a young guinea pig experiment, prolonged second-hand tobacco smoke exposure enhanced evoked synaptic transmission of lung sensory input in the NTS via substance P.⁶³

Clinical trials

Finally, evidence from clinical trials supports the new paradigm. Drugs with proven anti-tussive efficacy in unexplained

cough patients, such as opioids, gabapentin, pregabalin, and AF-219, do, indeed, have neuromodulatory properties,^{58,64-66} and they are also being used to alleviate neuropathic pain. Non-pharmacological speech pathology therapy has shown significant benefits in relieving cough outcomes, which is also considered to act on both peripheral and central parts of the cough reflex pathway.^{65,67}

WHAT IS THE KEY REGULATOR OF COUGH HYPERSENSITIVITY SYNDROME?

Capsaicin, the active ingredient of chilli pepper, has long been known to cause pain, burning sensation, and cough. It is one of the most potent tussigens used in inhalation cough challenge tests.⁶⁸ TRPV1, a sensory receptor for capsaicin, is expressed primarily in sensory nerve C-fibers, and its expression is increased in chronic cough patients.⁵² Thus, TRPV1 was considered to be a strong candidate target for the development of novel anti-tussive agents (Fig. 2).⁶⁹ However, contrary to expectations, a TRPV1 antagonist (SB-705498) failed to show any significant benefit in reducing cough frequency or improving cough-specific quality of life scores.⁷⁰

TRPA1, acting on vagal sensory neurons, has been considered as another candidate therapeutic target (Fig. 2). TRPA1 binds to a wide range of irritants, such as allyl isothiocyanate, cinnamaldehyde, and acrolein, which are abundant in pollutants and cigarette smoke, and was shown to mediate cough responses.⁷¹ TRPA1 also acts as a thermosensor for cold temperatures (<17°C). Indeed, as cough is frequently triggered by irritants and cold air exposure, the role of TRPA1 attracted scientific in-

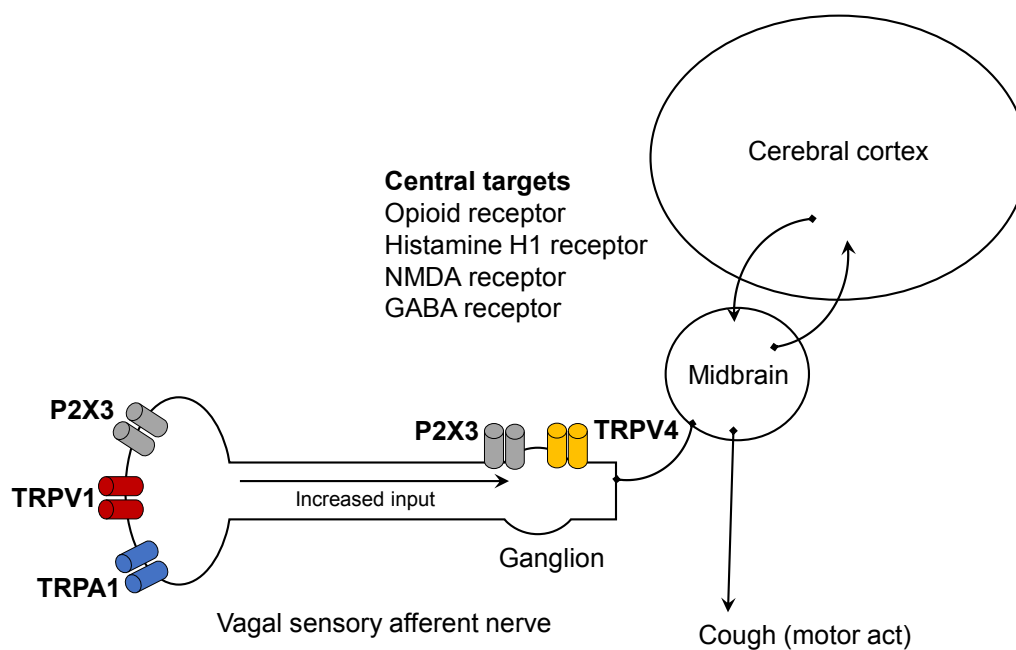


Fig. 2. Current potential therapeutic targets in cough hypersensitivity syndrome.

terest. However, a TRPA1 antagonist did not show significant anti-tussive effects in humans (unpublished data). These series of failures raised questions about whether targeting a single receptor at the peripheral nervous system level was a move in the right direction.

Adenosine triphosphate (ATP), a major damage-associated molecule released during cellular injury, is recognised by purinergic receptors. Two types of purinergic receptors have been described to date: the P2Y receptors respond mainly to adenosine and adenosine monophosphate, whereas the P2X receptors are relatively specific for ATP. These latter receptors are located primarily on small afferent neurons of the C-fiber class.⁷² It was hypothesised by Anthony Ford that they may play a role in the hypersensitivity of chronic cough. A randomized, controlled clinical study in patients with refractory chronic cough showed that AF-219, an antagonist of the P2X3 receptor, had a dramatic effect on cough counting.⁶⁶ Subsequent studies, as yet unpublished in full, have confirmed a high degree of efficacy in chronic cough patients, with the normalization of cough counts extending up to 12 weeks of therapy. Thus, the P2X3 receptor is clearly an important mediator of cough hypersensitivity (Fig. 2). Recently, we investigated the effects of ATP by inhalation in patients with chronic cough and in healthy volunteers.⁷³ Whilst there was a small leftward shift in the cough dose-response curve to ATP challenge in patients with chronic cough compared with healthy volunteers, it was similar to that seen with other commonly used cough challenge agents, such as capsaicin and citric acid.⁶⁸ This minor change was unlike that seen with methacholine or histamine challenge in asthmatics, where it could be argued that such a dramatic difference between normal and asthmatic subjects represents a fundamental mechanism in bronchial hyperresponsiveness. Thus, while the therapeutics of AF-219 suggest that the P2X3 receptor is an integral part of the cough hypersensitivity pathway, the findings that ATP administered to the bronchial tree does not cause a dramatic shift in cough sensitivity⁷³ suggest that it may be merely a link in the chain rather than the primary mediator of cough hypersensitivity.

Studies in isolated animal and human vagus nerves suggest that ATP itself causes a brief depolarisation. This is similar to the observed effect of ATP administration in humans in that there is a brief bout of coughing followed by rapid recovery. Belvisi *et al.*⁶⁸ have hypothesised upstream regulators of ATP-P2X3 pathways in cough hypersensitivity. ATP, a ubiquitous component of intracellular metabolism, is released into the extracellular space during cellular damage. This “distress signal” is then picked up by sensory neurons through the P2X3 receptor which is then responsible for the promotion of hypersensitivity. A potential trigger for ATP release has been elegantly described in studies using knockout mice where stimulation of TRPV4 produced a long-lasting depolarisation, and this was thought to act through pannexin channels that allow ATP to es-

cape into the extracellular milieu.⁷⁴ Mechanisms other than ATP release will almost certainly be described since even potent blockers of P2X3 receptors are not totally effective for treating chronic cough.⁶⁶ This development however is the first major advance in our understanding of cough in the past decades and at last suggests a therapeutic strategy for those with intractable cough as well as an invaluable tool in the dissection of the mechanism of cough hypersensitivity.

HOW TO MEASURE COUGH HYPERSENSITIVITY

There are few clinical measurement tools to define cough hypersensitivity.^{75,76} In a study using objective cough frequency monitoring, the geometric mean total cough counts per 24 hours were 16.8 (log-standard deviation 0.5) in healthy subjects, 33 (0.6) in smokers, 107 (0.3) in asthmatic patients, 321 (0.3) in cough variant asthmatic/eosinophilic bronchitis patients, and 477 (0.3) in unexplained chronic cough patients.⁷⁷ However, this measurement tool is still used for research purposes.

Conventional cough challenge tests using tussigen inhalation to measure the C5 endpoint (tussigen concentration to provoke 5 consecutive coughs following inhalation) has been limited to within-subject comparisons, because they do not sufficiently differentiate patients from controls.^{68,73} However, this finding is likely related to the limitations inherent in the conventional C5 endpoint. In a recent pharmacodynamic modelling study of capsaicin inhalation cough responses, maximal cough responses provoked by any concentration of capsaicin (Emax parameter) reflected clear differences between healthy controls and cough patients.⁵⁷ However whether this represents a difference in cough sensitivity or is simply an increase in response is unclear.

In our recent systematic review of epidemiological studies, the prevalence of chronic cough (usually defined by the presence of cough for longer than 3 months per year) in the community population showed an inconsistent pattern of gender association, but it frequently reflected a male predominance.⁷⁸ This finding was interesting, because an almost homogeneous female preponderance was observed in a multi-national survey of about 10,000 chronic cough patients recruited at referral clinics.⁷⁹ As the prevalence of chronic cough at the population level showed significant correlations with the smoking rate,⁷⁸ we hypothesize that a considerable proportion of chronic cough in the community is smoking-related. Cigarette smoke acts as an irritant for the cough reflex, and ending smoking causes a transient increase in cough reflex sensitivity but leads to a reduction in coughing.⁸⁰ Moreover, a female predominance in clinic population studies is feasible in that females show increased cough/urge-to-cough responses and also more activation in the somatosensory cortex after tussigen inhalation.^{4,79} Further work is needed to explain this gender discrepancy in

Table 2. Cough measurement tools and related outcomes

Category	Tools and outcomes
Subjective	
Cough-related quality of life	Leicester Cough Questionnaire, Cough-specific Quality-of-Life Questionnaire
Cough severity	Visual analog scale
Objective	
Cough frequency	Leicester Cough Monitor, Hull Automated Cough Counter, VitaloJAK
Cough reflex sensitivity	Tussigen inhalation challenge test (using capsaicin, citric acid, or ATP)/urge-to-cough, C2, C5, maximal cough responses evoked by any tussigen concentration (Emax)

ATP, adenosine triphosphate.

prevalence between community and clinical populations. Also, these findings suggest that a simple binary questionnaire asking about the presence of cough does not sufficiently capture cough hypersensitivity.

Although no objective measurement tool is available to define cough hypersensitivity in everyday clinical practice, several modalities have been validated for the purpose of assessing several domains of cough (Table 2).¹⁹ First, cough-related quality of life questionnaires, such as the Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality-of-Life Questionnaire, have been validated for use and translated into various language versions.^{12,81,82} These are valuable tools, because the major impact of cough is the deterioration in the quality of life, and the treatment goal is to resume a normal daily life but not to completely inhibit the cough reflex. A visual analog scale is a simple measure of cough severity, but this has not been rigorously validated.¹⁹ A second important tool is objective cough counting, such as with the Leicester Cough Monitor (Glenfield Hospital, Leicester, UK), Hull Automated Cough Counter (Castle Hill Hospital, Hull, UK), and VitaloJAK (Vitalograph Ltd, Buckingham, UK). A report on cough frequency in various conditions⁷⁷ suggested that cough frequency could be a useful index for distinguishing pathological cough from physiologic cough. However, the correlations between these subjective and objective indices are only moderate,⁸³ suggesting that each represents different facets of cough. Indeed, patients with cough-related incontinence or life-threatening cough syncope may have only occasional paroxysms of coughing.⁷⁶ Finally, a cough challenge test can be useful in phenotyping patients⁸⁴ and studying therapeutic agents in relation to specific channels.⁷⁰

CLINICAL IMPLICATION OF COUGH HYPERSENSITIVITY IN VARIOUS CONDITIONS

Cough hypersensitivity is not solely dependent on other underlying conditions, but its clinical implications remain largely

unclear. A good example is the relevance of cough in asthma. Type 2 airway inflammation contributes to cough hypersensitivity at peripheral levels and is frequent in asthma. Thus, the detection of type 2 airway inflammation using objective tools, such as induced sputum analyses or fractional exhaled nitric oxide tests,⁸⁵ may help relieve asthma-related cough in chronic cough patients.⁸⁶ However, cough in asthma appears to have more complex nature than expected, particularly among asthmatic patients already receiving asthma-specific treatment. In a recent study of 89 patients with physician-diagnosed asthma, objectively measured cough frequency showed a good correlation with asthma control, but not with airway obstruction or inflammation.⁸⁷ In another study of 262 adult patients with severe asthma, the LCQ score only showed moderate correlations with asthma control status, but not with sputum eosinophils (%).⁸⁸ Also, in a study using capsaicin cough challenge tests, the capsaicin-induced cough response was most pronounced in female non-atopic asthma patients, suggesting that sensory dysfunction is a potentially important trait in type 2-low asthma.⁸⁹ These findings suggest that cough is a major component contributing to asthma pathophysiology independently of conventional factors like lung function or inflammation. Thus, cough-specific assessment and treatment is required to further understand the clinical relevance of cough in asthma. However, currently existing measurement tools for asthma control, such as the Asthma Control Test⁹⁰ and Asthma Control Questionnaire,⁹¹ were not designed to capture the impact of cough on asthma. Meanwhile, clinical relevance of cough hypersensitivity in other conditions, such as bronchiectasis or idiopathic pulmonary fibrosis, is also being studied.^{92,93} Utilization of validated cough-specific measurement tools would be a key to the investigations.

CONCLUSIONS

The cough reflex is a vital protective mechanism against aspiration. It relies on a complex vagally mediated neuronal pathway which is still only partially understood. In some disease states, both acutely as in a viral respiratory tract infection and chronically, a state of hypersensitivity is created. This leads to excessive coughing, which is both distressing and disadvantageous. Our understanding of the mechanism of cough hypersensitivity and the realization that this represents a distinct clinical condition has advanced the field enormously over the past decades. More recently, advances in therapeutics offer the promise for new therapies targeting this “Cinderella” of the respiratory world.

REFERENCES

1. Wikipedia (US). Il Mare [Internet]. San Francisco (CA): Wikipedia; 2000 [Feb 1 2017]. Available from: <https://en.wikipedia.org/wiki/>

- Il_Mare.
2. Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. *J Voice* 2011;25:596-601.
 3. Matsumoto H, Tabuena RP, Niimi A, Inoue H, Ito I, Yamaguchi M, et al. Cough triggers and their pathophysiology in patients with prolonged or chronic cough. *Allergol Int* 2012;61:123-32.
 4. Song WJ, Kim JY, Jo EJ, Lee SE, Kim MH, Yang MS, et al. Capsaicin cough sensitivity is related to the older female predominant feature in chronic cough patients. *Allergy Asthma Immunol Res* 2014;6:401-8.
 5. Kanemitsu Y, Matsumoto H, Osman N, Oguma T, Nagasaki T, Izuhara Y, et al. "Cold air" and/or "talking" as cough triggers, a sign for the diagnosis of cough variant asthma. *Respir Investig* 2016;54:413-8.
 6. Schappert SM. National Ambulatory Medical Care Survey: 1991 summary. *Vital Health Stat* 13 1994:1-110.
 7. Cho SH, Lin HC, Ghoshal AG, Bin Abdul Muttalif AR, Thanaviratnanich S, Bagga S, et al. Respiratory disease in the Asia-Pacific region: cough as a key symptom. *Allergy Asthma Proc* 2016;37:131-40.
 8. Yoo KH, Ahn HR, Park JK, Kim JW, Nam GH, Hong SK, et al. Burden of respiratory disease in Korea: an observational study on allergic rhinitis, asthma, COPD, and rhinosinusitis. *Allergy Asthma Immunol Res* 2016;8:527-34.
 9. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015;45:1479-81.
 10. Kang MG, Song WJ, Kim HJ, Won HK, Sohn KH, Kang SY, et al. Point prevalence and epidemiological characteristics of chronic cough in the general adult population: the Korean National Health and Nutrition Examination Survey 2010-2012. *Medicine (Baltimore)*. 2017;96:e6486.
 11. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med* 1998;158:1657-61.
 12. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339-43.
 13. Song WJ, Morice AH, Kim MH, Lee SE, Jo EJ, Lee SM, et al. Cough in the elderly population: relationships with multiple comorbidity. *PLoS One* 2013;8:e78081.
 14. Morice AH. Epidemiology of cough. *Pulm Pharmacol Ther* 2002;15:253-9.
 15. Morice AH. Over-the-counter cough medicines: new approaches. *Pulm Pharmacol Ther* 2015;35:149-51.
 16. McGarvey LP. Idiopathic chronic cough: a real disease or a failure of diagnosis? *Cough* 2005;1:9.
 17. Dicipinigaitis PV. Cough: an unmet clinical need. *Br J Pharmacol* 2011;163:116-24.
 18. Chamberlain SA, Garrod R, Douiri A, Masefield S, Powell P, Bücher C, et al. The impact of chronic cough: a cross-sectional European survey. *Lung* 2015;193:401-8.
 19. Birring SS, Spinou A. How best to measure cough clinically. *Curr Opin Pharmacol* 2015;22:37-40.
 20. Gibson PG. Atopic cough. *Thorax* 2004;59:449.
 21. O'Hara J, Jones NS. "Post-nasal drip syndrome": most patients with purulent nasal secretions do not complain of chronic cough. *Rhinology* 2006;44:270-3.
 22. Hom C, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. *Gastroenterol Clin North Am* 2013;42:71-91.
 23. Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. *Lung* 2010;188 Suppl 1:S87-90.
 24. Chung KF. Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough. *Pulm Pharmacol Ther* 2011;24:267-71.
 25. Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest* 2014;146:1633-48.
 26. Song WJ, Chang YS, Morice AH. Changing the paradigm for cough: does 'cough hypersensitivity' aid our understanding? *Asia Pac Allergy* 2014;4:3-13.
 27. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014;44:1132-48.
 28. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. *Lancet Respir Med* 2013;1:414-22.
 29. Niimi A, Chung KF. Evidence for neuropathic processes in chronic cough. *Pulm Pharmacol Ther* 2015;35:100-4.
 30. Driessen AK, McGovern AE, Narula M, Yang SK, Keller JA, Farrell MJ, et al. Central mechanisms of airway sensation and cough hypersensitivity. *Pulm Pharmacol Ther*. Forthcoming 2017.
 31. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. *Respir Med* 2015;109:701-7.
 32. Sinha A, Lee KK, Rafferty GF, Yousaf N, Pavord ID, Galloway J, et al. Predictors of objective cough frequency in pulmonary sarcoidosis. *Eur Respir J* 2016;47:1461-71.
 33. Morice AH, Lowry R, Brown MJ, Higenbottam T. Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987;2:1116-8.
 34. Prudon B, Birring SS, Vara DD, Hall AP, Thompson JP, Pavord ID. Cough and glottic-stop reflex sensitivity in health and disease. *Chest* 2005;127:550-7.
 35. Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ. Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax* 2016;71:323-9.
 36. O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. *Am J Respir Crit Care Med* 1994;150:374-80.
 37. Othumpangat S, Gibson LF, Samsell L, Piedimonte G. NGF is an essential survival factor for bronchial epithelial cells during respiratory syncytial virus infection. *PLoS One* 2009;4:e6444.
 38. Omar S, Clarke R, Abdullah H, Brady C, Corry J, Winter H, et al. Respiratory virus infection up-regulates TRPV1, TRPA1 and ASIC3 receptors on airway cells. *PLoS One* 2017;12:e0171681.
 39. Abdullah H, Heaney LG, Cosby SL, McGarvey LP. Rhinovirus up-regulates transient receptor potential channels in a human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. *Thorax* 2014;69:46-54.
 40. Zaccone EJ, Lieu T, Muroi Y, Potenzieri C, Udem BE, Gao P, et al. Parainfluenza 3-induced cough hypersensitivity in the guinea pig airways. *PLoS One* 2016;11:e0155526.
 41. Udem BJ, Taylor-Clark T. Mechanisms underlying the neuronal-based symptoms of allergy. *J Allergy Clin Immunol* 2014;133:1521-34.
 42. Lv H, Yue J, Chen Z, Chai S, Cao X, Zhan J, et al. Effect of transient receptor potential vanilloid-1 on cough hypersensitivity induced by particulate matter 2.5. *Life Sci* 2016;151:157-66.
 43. McCormack DG, Mak JC, Coupe MO, Barnes PJ. Calcitonin gene-

- related peptide vasodilation of human pulmonary vessels. *J Appl Physiol* (1985) 1989;67:1265-70.
44. Numao T, Agrawal DK. Neuropeptides modulate human eosinophil chemotaxis. *J Immunol* 1992;149:3309-15.
 45. Mikami N, Matsushita H, Kato T, Kawasaki R, Sawazaki T, Kishimoto T, et al. Calcitonin gene-related peptide is an important regulator of cutaneous immunity: effect on dendritic cell and T cell functions. *J Immunol* 2011;186:6886-93.
 46. Song WJ, Chang YS. Cough hypersensitivity as a neuro-immune interaction. *Clin Transl Allergy* 2015;5:24.
 47. McGarvey LP, Forsythe P, Heaney LG, MacMahon J, Ennis M. Bronchoalveolar lavage findings in patients with chronic nonproductive cough. *Eur Respir J* 1999;13:59-65.
 48. Forsythe P, McGarvey LP, Heaney LG, MacMahon J, Ennis M. Sensory neuropeptides induce histamine release from bronchoalveolar lavage cells in both nonasthmatic coughers and cough variant asthmatics. *Clin Exp Allergy* 2000;30:225-32.
 49. Chaudhuri R, McMahon AD, Thomson LJ, MacLeod KJ, McSharry CP, Livingston E, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *J Allergy Clin Immunol* 2004;113:1063-70.
 50. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. *Am J Respir Crit Care Med* 2004;169:15-9.
 51. O'Connell F, Springall DR, Moradoghli-Haftvani A, Krausz T, Price D, Fuller RW, et al. Abnormal intraepithelial airway nerves in persistent unexplained cough? *Am J Respir Crit Care Med* 1995;152:2068-75.
 52. Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A, et al. Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. *Am J Respir Crit Care Med* 2004;170:1276-80.
 53. Mitchell JE, Campbell AP, New NE, Sadofsky LR, Kastelik JA, Mulrennan SA, et al. Expression and characterization of the intracellular vanilloid receptor (TRPV1) in bronchi from patients with chronic cough. *Exp Lung Res* 2005;31:295-306.
 54. West PW, Canning BJ, Merlo-Pich E, Woodcock AA, Smith JA. Morphologic characterization of nerves in whole-mount airway biopsies. *Am J Respir Crit Care Med* 2015;192:30-9.
 55. Lau BK, Vaughan CW. Descending modulation of pain: the GABA disinhibition hypothesis of analgesia. *Curr Opin Neurobiol* 2014;29:159-64.
 56. Mazzone SB, Cole LJ, Ando A, Egan GF, Farrell MJ. Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci* 2011;31:2948-58.
 57. Hilton EC, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. *J Allergy Clin Immunol* 2013;132:847-855.e1-5.
 58. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007;175:312-5.
 59. Birring SS, Brew J, Kilbourn A, Edwards V, Wilson R, Morice AH. Rococo study: a real-world evaluation of an over-the-counter medicine in acute cough (a multicentre, randomised, controlled study). *BMJ Open* 2017;7:e014112.
 60. Dickinson RS, Morjaria JB, Wright CE, Morice AH. Is opiate action in cough due to sedation? *Ther Adv Chronic Dis* 2014;5:200-5.
 61. Chen CY, Bonham AC, Schelegle ES, Gershwin LJ, Plopper CG, Joad JP. Extended allergen exposure in asthmatic monkeys induces neuroplasticity in nucleus tractus solitarius. *J Allergy Clin Immunol* 2001;108:557-62.
 62. Spaziano G, Luongo L, Guida F, Petrosino S, Matteis M, Palazzo E, et al. Exposure to allergen causes changes in nts neural activities after intratracheal capsaicin application, in endocannabinoid levels and in the glia morphology of NTS. *Biomed Res Int* 2015;2015:980983.
 63. Sekizawa S, Chen CY, Bechtold AG, Tabor JM, Bric JM, Pinkerton KE, et al. Extended secondhand tobacco smoke exposure induces plasticity in nucleus tractus solitarius second-order lung afferent neurons in young guinea pigs. *Eur J Neurosci* 2008;28:771-81.
 64. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583-9.
 65. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. *Chest* 2016;149:639-48.
 66. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015;385:1198-205.
 67. Chamberlain Mitchell SA, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017;72:129-36.
 68. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dipinigitis PV, et al. ERS guidelines on the assessment of cough. *Eur Respir J* 2007;29:1256-76.
 69. Morice AH, Geppetti P. Cough. 5: the type 1 vanilloid receptor: a sensory receptor for cough. *Thorax* 2004;59:257-8.
 70. 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.
 71. Birrell MA, Belvisi MG, Grace M, Sadofsky L, Faruqi S, Hele DJ, et al. TRPA1 agonists evoke coughing in guinea pig and human volunteers. *Am J Respir Crit Care Med* 2009;180:1042-7.
 72. Burnstock G, Brouns I, Adriaensen D, Timmermans JP. Purinergic signaling in the airways. *Pharmacol Rev* 2012;64:834-68.
 73. Fowles HE, Rowland T, Wright C, Morice A. Tussive challenge with ATP and AMP: does it reveal cough hypersensitivity? *Eur Respir J* 2017;49:1601452.
 74. Bonvini SJ, Birrell MA, Grace MS, Maher SA, Adcock JJ, Wortley MA, et al. Transient receptor potential cation channel, subfamily V, member 4 and airway sensory afferent activation: role of adenosine triphosphate. *J Allergy Clin Immunol* 2016;138:249-261.e12.
 75. Turner RD, Bothamley GH. Cough hypersensitivity syndrome: clinical measurement is the key to progress. *Eur Respir J* 2015;45:1507-8.
 76. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Cough hypersensitivity syndrome: clinical measurement is the key to progress. *Eur Respir J* 2015;45:1509-10.
 77. Yousaf N, Monteiro W, Matos S, Birring SS, Pavord ID. Cough frequency in health and disease. *Eur Respir J* 2013;41:241-3.
 78. Song WJ, Chang YS, Faruqi S, Kang MK, Kim JY, Kang MG, et al. Defining chronic cough: a systematic review of the epidemiological literature. *Allergy Asthma Immunol Res* 2016;8:146-55.
 79. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B,

- et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014;44:1149-55.
80. Pisinger C, Godtfredsen NS, Jørgensen T. Smoking reduction and cessation reduce chronic cough in a general population: the Inter99 study. *Clin Respir J* 2008;2:41-6.
 81. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality-of-life questionnaire. *Chest* 2002;121:1123-31.
 82. Kwon JW, Moon JY, Kim SH, Song WJ, Kim MH, Kang MG, et al. Reliability and validity of a Korean version of the leicester cough questionnaire. *Allergy Asthma Immunol Res* 2015;7:230-3.
 83. Faruqi S, Thompson R, Wright C, Sheedy W, Morice AH. Quantifying chronic cough: objective versus subjective measurements. *Respirology* 2011;16:314-20.
 84. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410-9.
 85. Song WJ, Kwon JW, Kim EJ, Lee SM, Kim SH, Lee SY, et al. Clinical application of exhaled nitric oxide measurements in a Korean population. *Allergy Asthma Immunol Res* 2015;7:3-13.
 86. Song WJ, Kim HJ, Shim JS, Won HK, Kang SY, Sohn KH, et al. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: a systematic review and meta-analysis. *J Allergy Clin Immunol*. Forthcoming 2017.
 87. 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;149:1460-6.
 88. Natarajan S, Free RC, Bradding P, McGarvey L, Siddiqui S. The relationship between the Leicester cough questionnaire, eosinophilic airway inflammation and asthma patient related outcomes in severe adult asthma. *Respir Res* 2017;18:44.
 89. 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.
 90. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
 91. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
 92. Guan WJ, Gao YH, Xu G, Lin ZY, Tang Y, Li HM, et al. Capsaicin cough sensitivity and the association with clinical parameters in bronchiectasis. *PLoS One* 2014;9:e113057.
 93. van Manen MJ, Birring SS, Vancheri C, Cottin V, Renzoni EA, Russell AM, et al. Cough in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2016;25:278-86.