



Mechanisms of cough

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Purpose of review

To review recent developments in the mechanisms of chronic cough.

Recent findings

Although cough prevalence is similar across the world, there are significant regional differences in the diseases associated with cough. This may represent regional differences in diet, environmental exposure, and diagnostic assessment and labelling. Cough can be reliably measured using several validated questionnaires and objective tools that monitor cough frequency and cough reflex sensitivity. Cough with eosinophilic bronchitis responds to anti-inflammatory therapy with corticosteroids and montelukast. The absence of airway hyperresponsiveness may be because of the release of a bronchoprotective mediator, prostaglandin E₂. Cough with neutrophilic bronchitis is associated with rhinitis and gastroesophageal reflux disease. Laryngeal hypersensitivity (LHS) is an important new concept that explains cough mechanisms, identifies potentially new pharmacotherapies that target neural pathways and also transient receptor channels, and demonstrates how behavioural therapies can be effective in refractory cough. The concept also explains symptoms in a variety of related syndromes such as vocal cord dysfunction.

Summary

New insights into cough mechanisms that focus on LHS help explain cough symptoms and the place of effective therapies including speech pathology intervention and neuromodulators.

Keywords

cough, eosinophilic bronchitis, laryngeal hypersensitivity, speech pathology

INTRODUCTION

Cough is one of the most common complaints leading patients to seek medical assistance in the ambulatory care setting. Cough is initially classified based upon its duration, and the classifications of cough are: acute cough (<3 weeks), subacute cough (3–8 weeks), and chronic cough (>8 weeks) [1]. Recent studies have explored the prevalence and diseases associated with cough from a global perspective, and have evaluated the role of inflammation in cough. A novel concept of laryngeal hypersensitivity (LHS) has emerged that has allowed characterization and understanding of a range of diverse cough-related syndromes, as well as offering treatment pathways using behavioural therapies and novel pharmacotherapies.

EPIDEMIOLOGY

Epidemiological studies from the United Kingdom identify that 12% of people are bothered by their cough on a daily or weekly basis [2]. Studies have now extended these observations to Asian countries, where a survey of 1087 college students in the

Guangzhou region of southern China found that the overall prevalence of cough was 10.9%, and that this comprised 7.6% with acute cough, and 3.3% with chronic cough [3]. In people from the Caucasian countries, chronic cough is more common among adult women, whereas in China, the prevalence was equal between males and females [4].

CAUSE

The clinical conditions that are associated with chronic cough can be identified using a systematic approach called the ‘anatomic–diagnostic protocol’

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KEY POINTS

- A systematic approach to chronic cough is effective.
- Eosinophilic bronchitis without asthma occurs because of the preservation of deep inspiration bronchoprotection and release of PGE₂.
- LHS is a new and important concept in cough and a range of other disorders with LHS as vocal cord dysfunction and globus.
- The LHS that is present in patients with chronic refractory cough responds to speech pathology intervention, behavioural management of cough.
- There are parallels in the mechanisms of chronic cough and neuropathic pain, that explain the success of neuromodulators such as gabapentin on chronic cough

[1]. The most common diseases linked to chronic cough are upper airway cough syndrome (UACS, previously called postnasal drip syndrome), cough variant asthma (CVA), gastroesophageal reflux disease (GERD), and eosinophilic bronchitis [1,3,5]. It has been proposed that these diseases are linked with cough due to the cough hypersensitivity syndrome. There are significant regional differences in the cause of cough. In China, a study [4] of 704 patients with chronic cough found that the most common causes were CVA, followed by UACS, eosinophilic bronchitis and atopic cough. Two recent studies from Japan [6,7] found that asthma was the most common cause of cough, followed by atopic cough, and then sinobronchial syndrome.

These studies show that while the overall prevalence of cough is similar around the world, there are important regional differences in some aspects of cough, such as the sex ratio, the frequency of associated etiological diagnoses, and the diagnostic labels assigned as the cause of chronic cough. It is possible that these differences could be due to lifestyle and environmental factors. For example, there are differences in air pollution exposure in some countries that could account for increased UACS, whereas difference in diet and obesity could account for a higher prevalence of GERD and cough.

There is an opportunity to standardize diagnostic assessment, perhaps via global cough guidelines. Key areas that require standardization are the recognition and use of terms to describe rhinitis and UACs, and standardized terminology for the eosinophilic airway disorders associated with chronic cough (Table 1). It is likely that there is overlap in the diagnostic labels applied to diseases considered to cause chronic cough. For example, there may be significant overlap between UACS, sinobronchial

Table 1. Regional variation in diagnostic labelling for cough syndromes

Cough with eosinophilia	Cough with upper airway disorders
Eosinophilic asthma	UACS
CVA	Postnasal drip syndrome
Nonasthmatic eosinophilic bronchitis	Rhinitis
Atopic cough	Chronic rhinosinusitis
Allergic rhinitis	Sinobronchial syndrome

CVA, cough variant asthma; UACS, upper airway cough syndrome.

syndrome, LHS, and forms of rhinitis. A randomized trial has now established that the management of children with chronic cough in accordance with a standardized algorithm leads to improved clinical outcomes, and that this effect can be demonstrated irrespective of when the standardized algorithm is applied [8[¶]]. This should provide the impetus to replicate these findings in adults and different regions. This work will require standardization of diagnostic assessments in chronic cough.

Nonasthmatic eosinophilic bronchitis, atopic cough, CVA, and allergic rhinitis can all lead to chronic cough with airway eosinophilia, yet it is unclear to what extent these conditions overlap or respond to a similar therapeutic approach, such as inhaled corticosteroids (ICS). This issue could be resolved by randomized trials in patients with chronic cough who are assessed using each of the available diagnostic criteria for chronic cough and eosinophilia.

Similarly, nasal disease is frequently associated with chronic cough and can be labelled as rhinitis, chronic rhinosinusitis, sinobronchial syndrome, or UACS. There may also be overlap between these disorders and the emerging concept of the 'irritable larynx' or cough hypersensitivity syndrome. It is unclear to what extent these conditions represent similar conditions or respond to a similar therapeutic approach.

MEASUREMENT OF COUGH

Valid cough measurement tools are essential to objectively assess cough and monitor response to treatment. A systematic review of 78 studies [9[¶]] evaluated measurement instruments in patients with unexplained or refractory chronic cough. The Leicester Cough Questionnaire and Cough-specific Quality of Life Questionnaire were found to be the most widely studied instruments in adults with moderate strength of evidence supporting their

validity in assessing severity/quality of life in cough. Among children, the Parent Cough-specific Quality of Life Questionnaire and Paediatric Cough Questionnaire were found to be valid and reliable. Electronic recording devices such as the Leicester Cough Monitor were found to be reliable and accurate for assessing cough frequency, but showed variable correlation with other cough measurement tools. Although visual analogue scales are easy to administer and have face validity, this review did not identify any studies to formally validate their accuracy in assessing cough.

Capsaicin cough reflex sensitivity (CRS) testing has been used in clinical research for nearly 30 years and has consistently been shown to be well tolerated and reproducible. A review [10] of 56 studies found that capsaicin cough challenge was able to assess the effect of a pharmacological intervention on CRS, thereby supporting the role of cough challenge as a useful tool in the evaluation of potential antitussives. Interestingly, those studies with a predominance of healthy volunteers as participants did not show inhibition of CRS by therapy. As healthy volunteers do not have a hyperresponsive cough reflex, this may limit the usefulness of this group in the evaluation of potential antitussives.

Cough provocation tests with hypertonic aerosols such as hypertonic saline and mannitol powder are novel types of cough provocation tests. Cough sensitivity to hypertonic aerosols is associated with asthma and treatment with ICS attenuates the cough sensitivity [11,12]. The isotonic saline challenge test was found to be useful for monitoring the effect of ICS in chronic cough but could not predict responsiveness to this treatment.

Urge to cough (UTC) is the sensation of irritation prior to the motor act of coughing. It can be measured with a modified Borg scale (where 1 equates to no sensation; 10 is maximal UTC) and is usually performed in conjunction with a cough provocation test such as the capsaicin cough challenge. The UTC threshold (C_u) was found to be reproducibly measured using a modification of standard cough challenge methodology, and may represent an additional relevant end point for studies investigating treatments for cough and CRS [13].

COUGH AND EOSINOPHILIC BRONCHITIS

Lower airway inflammation (bronchitis) commonly accompanies cough, and can be heterogeneous in pattern. In asthma there is evidence that the different inflammatory phenotypes exhibit differential treatment responses. This concept has been applied to chronic cough with eosinophilic bronchitis. Since its description in 1989, eosinophilic bronchitis has

consistently been identified as a cause of chronic cough around the world. In people from the Caucasian countries, eosinophilic bronchitis represents between 7 and 20% of chronic cough in referral clinics [14], whereas it is more common in Asian countries, being present in up to 35% of cases of chronic cough [3,4]. It has previously been unclear if eosinophilic bronchitis is a cause of cough in children; however, this issue was resolved by a study [15] from Korea identifying 109 children with cough and eosinophilic bronchitis, and comparing them to similar numbers with asthma and healthy children. The children with eosinophilic bronchitis had a similar elevation of exhaled nitric oxide to the children with asthma.

It is important to recognize eosinophilic bronchitis as a cause of chronic cough because it responds well to corticosteroid. A recent systematic review of corticosteroid for undifferentiated cough, or cough based on symptom duration showed mixed results [16]. Eight randomized trials involving 570 patients with cough were assessed. Although there was a significant overall effect, the results were highly varied. This means that treating with ICS based on the assessment of cough duration is of limited benefit, whereas treatment based on the assessment of inflammatory phenotype leads to a good cough response in cough with eosinophilic bronchitis [17]. In addition to ICS, the leukotriene antagonist montelukast may also benefit patients with chronic cough and eosinophilic bronchitis [18–20]; however, this requires confirmation in larger trials before its use can be recommended.

It is puzzling that although asthma and eosinophilic bronchitis can share a similar pattern of eosinophilic inflammation, unlike asthma, the airways are not hyperresponsive in eosinophilic bronchitis. The response to deep inspiration may explain this anomaly [21[■]]. A deep inspiration in normal individuals has a bronchoprotective effect, whereas this can be lost in asthma, resulting in paradoxical bronchoconstriction after a deep inspiration. It is considered an effect of the increased airway smooth muscle mass in asthma. Preservation of deep inspiration bronchoprotection is proposed as a fundamental pathophysiologic difference between eosinophilic bronchitis and asthma [21[■]]. Increased release of prostaglandin E₂ (PGE₂), an endogenous bronchodilator, may explain the preservation of deep inspiration bronchoprotection in eosinophilic bronchitis. Bronchial biopsies from patients with eosinophilic bronchitis showed upregulation of both the PGE₂ enzymatic pathway and prostaglandin receptor expression compared with the samples from patients with asthma [22,23[■]]. Furthermore, sputum supernatants from patients with eosinophilic bronchitis

contained PGE2 that had an enhanced antiproliferative effect on bronchial smooth muscle when compared with sputum supernatants from patients with asthma and healthy controls. Overall these results indicate that while patients with eosinophilic bronchitis have the airway inflammatory response seen in asthma, they may be protected from developing significant variable airflow obstruction (asthma) by endogenous PGE2 release.

COUGH AND NONEOSINOPHILIC ASTHMA

Although there is a consensus that asthma is an inflammatory disorder of the airways with a several different inflammatory subtypes [24,25], little is known about the triggers of symptoms and airways hyperresponsiveness in patients noneosinophilic asthma or neutrophilic asthma. Clinical observations suggest that both cough and rhinitis are prominent features of the noneosinophilic asthma phenotype. Part of unlocking the ongoing mystery of managing noneosinophilic and neutrophilic asthma may be discovered in the detailed exploration of the patients with these inflammatory subtypes and new research to investigate management and treatment strategies aimed to reduce symptoms and minimize exacerbations. Of particular importance is the complex relationship between asthma, cough, and rhinitis. A recent analysis of the symptoms reported from patients with asthma identified that most patients with neutrophilic asthma reported a significant cough, with 75% reporting a cough of moderate severity. There was also increased comorbidity from GERD and rhinosinusitis in neutrophilic asthma compared with eosinophilic and paucigranulocytic asthma [26].

Neutrophilic inflammation can also be a feature of chronic cough in both children and adults. In steroid naïve CVA (where cough is present as an exclusive symptom), neutrophilic CVA occurs in more than 40% of participants studied [19]. The significance and effective treatment of neutrophilic bronchitis in chronic cough require further study.

COUGH AS A SENSORY NEUROPATHY

Sensory hyperresponsiveness is a key feature of chronic cough. Peripheral sensitization has been demonstrated with enhanced capsaicin reflex hypersensitivity and increased neural expression of transient receptor potential channels (TRP). There is also evidence of central reflex sensitization, and there are important similarities between refractory cough and other conditions with central sensitization, such as neuropathic pain [27]. The clinical features which indicate central sensitization in

neuropathic pain such as paraesthesia (abnormal sensation), hyperalgesia (pain triggered by a lower level exposure to a known painful stimulus), and allodynia (pain triggered by a nonpainful stimulus) show parallels with the often described clinical features of refractory cough such as an abnormal throat sensation or 'tickle' representing laryngeal paraesthesia, increased cough sensitivity in response to known tussigens (hypertussia), and cough triggered in response to nontussive stimuli such as talking or cold air (allotussia). These symptoms indicate central sensitization of the cough reflex and a neuropathic response [28,29]. This new concept in chronic cough is supported by studies showing successful treatment with neuromodulators such as gabapentin in refractory chronic cough [30[■]], and an enhanced treatment effect seen in those patients with cough and LHS. This has important implications for both cough mechanisms and for new therapeutic developments, such as speech pathology intervention, behavioural therapy, and pharmacological; therapy using TRP blockers (TRPV1, TRPA1). The similarities between the pain and cough pathways have been closely reviewed together with the new treatment directions this brings identified [27].

SPEECH PATHOLOGY TREATMENT OF LARYNGEAL HYPERSENSITIVITY

The LHS that is present in patients with chronic refractory cough can be termed cough hypersensitivity syndrome [31] and responds to speech pathology intervention [32], and behavioural management of cough [33]. Both approaches involve voice therapy techniques and breathing retraining in patients with cough persisting despite optimal treatment. The effectiveness of this approach has not been studied in chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and bronchiectasis, and the approach is not thought to be effective for patients with significant sputum production [33]. This means that careful patient selection is needed before implementing the intervention.

The specific components of speech pathology intervention for cough were reviewed ([32], Table 2) and include education, cough suppression strategies, vocal hygiene training, and psychoeducational counselling. The education component is seen as critical as patients need a strong rationale to change their behaviour. Vocal hygiene includes increasing hydration, behavioural management of reflux, reduction of phonotraumatic vocal behaviours, and reducing inhaled or ingested irritating substances [32].

The benefits of this approach include reduced symptoms, reduced CRS [34], improved voice

Table 2. Mechanism of speech pathology treatment

Component	Examples	Mechanism
Education	No physiological benefit to cough, negative side-effects of cough, capacity for voluntary control of cough	Improve adherence
		Increase acceptance of a behavioural approach
Cough suppression strategies	Cough can be suppressed despite irritating sensation	Reduce deliberate coughing
	Identify UTC and substitute competing response	Improve awareness and voluntary control over cough
	Cough suppression swallow	Vocal fold adduction replaces cough but without causing laryngeal irritation
	Cough control breathing	Mimics fast airflow through larynx but moves point of constriction from larynx to the lips. Creates positive pressure in oral cavity to prevent vocal folds closing
	Release of laryngeal constriction	Retracts false vocal folds and improves voluntary control of laryngeal posture during breathing and phonation
Vocal hygiene training	Relaxed throat breathing	Treats underlying vocal cord dysfunction
	Behavioural management of reflux	Reduce reflux events
	Increased systemic and surface hydration	Reduced phonation threshold pressure, improve wound healing, reduce risk of injury
	Reduce exposure to irritating substances	Reduce exposure to triggers
Psychoeducational counselling	Reduce phonotraumatic behaviours, e.g. hard glottal attack, laryngeal constriction, hyperadduction	Reduced vocal fold impact stress; Reduced laryngeal constriction; reduced laryngeal inflammation (Verdolini)
	Supportive counselling, motivational interviewing, validate concerns	Increase acceptance of a behavioural approach
		Increase motivation
		Reduce anxiety
	Manage emotion as a trigger for cough	

UTC, urge to cough.

quality, and improved laryngeal sensation [35]. The mechanisms of these effects were examined [36] in a study that tested the effect of a range of clearing behaviours on laryngeal sensation. Coughing can cause laryngeal dysfunction because of the significant mechanical force that occurs when the vocal folds and arytenoids close during the compressive phase of cough, and because of the amplitude and high velocity of forces imparted to the vocal fold mucosa that leads to mechanical stress and shear. It is also possible that the velocity of airflow during cough could have a drying effect on the vocal folds. There was no change in laryngeal sensation after the hard cough and silent cough manouvers; however, there was more improvement in laryngeal sensation following swallowing with water.

LARYNGEAL HYPERSENSITIVITY AND VOCAL CORD DYSFUNCTION

The LHS concept can also be usefully applied to a range of other disorders wherein LHS can be demonstrated (Table 3) such as vocal cord dysfunction

[37], globus, muscle tension dysphonia [37], severe asthma [38,39], work-related laryngeal symptoms [40], cough in elite athletes [41], and respiratory symptoms after disasters such as the World Trade Centre attacks [42].

This extension of the LHS concept has important implications for the assessment and management of these syndromes, and indicates a need to develop measurement tools to assess LHS and then study the treatment efficacy of speech pathology treatment and other approaches [43].

CONCLUSION

Cough is a common symptom; its underlying mechanisms can now be understood as linked to different patterns of lower airway inflammation and to LHS (Table 3). This involves both peripheral hypersensitivity and central mechanisms. This new understanding of cough mechanisms has direct treatment implications. It has led to the successful application of existing therapies to cough, such as speech pathology intervention and gabapentin,

Table 3. Cause, mechanisms, and management of chronic cough

Cause	Mechanism	Diagnostic tests	Treatment	LHS
Eosinophilic asthma	Bronchial hyperresponsiveness	Exhaled nitric oxide (FENO)	Corticosteroid	Yes
Neutrophilic asthma	Bronchial hyperresponsiveness	Induced sputum	?	Yes
Paucigranulocytic asthma	Bronchial hyperresponsiveness	Induced sputum	?	Yes
Eosinophilic bronchitis	Increased CRS	Exhaled nitric oxide (FENO), induced sputum	Corticosteroid	?
Atopic cough	Triggers asthma and rhinosinusitis	Specific IgE	Antihistamine, corticosteroid	Yes
GERD	Laryngopharyngeal inflammation	Symptoms, pH study, gastroscopy	Proton pump inhibitors, lifestyle modification	Yes
Rhinosinusitis	Increased CRS	History, rhinoscopy	Nasal corticosteroid, antihistamine	Yes
ACE-I inhibitor	Increased CRS	History	Withdraw ACE-I inhibitor	Yes
Obstructive sleep apnoea	?	Polysomnography	Continuous positive airways pressure	?
Vocal cord dysfunction	Extrathoracic airway hyperresponsiveness	Laryngoscopy	Speech pathology	Yes

ACE-I, angiotensin converting enzyme inhibitor; CRS, cough reflex sensitivity; GERD, gastroesophageal reflux disease; LHS, laryngeal hypersensitivity. ?, unknown.

and provides direction in the search for new antitussives.

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Conflicts of interest

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