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Global physiology and pathophysiology of cough: Part 2. Demographic and clinical considerations: CHEST Expert Panel report

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ABSTRACT

Background: Cough characteristics vary between patients and this can impact clinical diagnosis and care. The purpose of Part 2 of this state-of-the-art review is to update the American College of Chest Physicians (CHEST) 2006 guideline on global physiology and pathophysiology of cough.

Methods: A review of the literature was conducted using PubMed and Medline databases from 1951 to 2019 using pre-specified search terms.

Results: We describe the demographics of typical cough patients in the clinical setting, including how cough characteristics changes across age. We summarize the effect of common clinical conditions impacting cough mechanics and the physical properties of mucus on airway clearance.

Conclusions: This is the second of a two-part update to the 2006 CHEST Cough Guideline; it complements part one on basic phenomenology of cough by providing an extended clinical picture of cough along with the factors that alter cough mechanics and efficiency in patients. A greater understanding of the physiology and pathophysiology of cough will improve clinical management.

Abbreviations:

ALS, amyotrophic lateral sclerosis
CF, Cystic fibrosis
COPD, Chronic obstructive pulmonary disease
CVA, Cough volume acceleration
EMST, Expiratory muscle strength training
IMST, Inspiratory muscle strength training

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PCFRT, Peak cough flow rise time
PPI, Proton pump inhibitors
SCI, Spinal cord injury
SHS, Second-hand smoke
TBI, Traumatic brain injury

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Introduction

This is the second manuscript in a two-part update on global physiology and pathophysiology of cough in the 2006 CHEST Cough Guidelines [1]. Part 1 of this update summarized the motor and sensory traits of cough, common presenting descriptive characteristics, physiology of mechanics of cough, how cough is assessed and, where available, how cough characteristics can differ between health and disease. Part 2 of the update comprises the following applied topics; cough demographics, clinical conditions impacting cough mechanics and the relationship between cough and airway secretions in airway clearance. In this update we provide perspective on the physiological and pathophysiological consequences of age on the cough reflex which were not previously addressed in the 2006 guideline. Likewise, the influence of gender on cough in the clinical setting with specific reference to cough hypersensitivity is addressed. As a further extension to the 2006 guideline, the clinical impact of stroke, Parkinson's disease and motor neuron disease on cough mechanics is presented. A review of the literature was carried out by the authors using PubMed and Medline from 1951 to 2019 using the search terms shown in Table 1.

Cough Demographics

Children

The previous [2] and current [3] CHEST guidelines recommended using pediatric-specific cough pathways when managing children with chronic cough. Reasons for this are many and include key differences between children and adults with respect to: common etiologies of chronic cough [4], assessment of outcomes and; the maturational aspects of immunity (e.g. innate, humoral and cellular) [5] and physiological aspects of the respiratory system (e.g. airway size, respiratory muscle development) from child to adulthood. Specific to the cough reflex, there are however little data in children, despite the increased knowledge regarding cough physiology over the last decade. Nevertheless, as the physiology of the cough pathway is intrinsically linked with the respiratory system (including the expiratory reflex, respiratory control and the pump mechanism), these maturation aspects of the cough pathway are important. The section below details available data.

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While the cough reflex first becomes evident at 1-2 months of age and develops with increasing maturity, it is weak in premature infants [6]. Stimulation of the laryngeal chemoreflex in young infants results in swallowing, apnea and laryngeal closure [6]. With maturation, cough becomes an increasingly prominent component of the laryngeal chemoreflex response. Recent animal work suggests that feeding behavior also influences its maturation where expiration reflex dominates in younger pups while cough was more readily triggered in weaning animals [7].

In some people, stimulation of the auricular branch of the vagus nerve can elicit Arnold's ear-cough reflex. The reflex is evoked by palpation of the postero-inferior wall, palpation of the antero-inferior wall of the external acoustic meatus (ear canal) or mechanical stimulation of the ear canal with insertion of cotton-tip applicator 3-5mm for 2-3 seconds [8, 9]. Data suggest differences between children and adults with a similar prevalence of the reflex in children with chronic cough and healthy individuals, contrasting the 11-fold higher prevalence in adults with chronic cough compared to healthy adults and those with respiratory disease without cough [8].

Exercise modulates the cough reflex. One study examined the capsaicin cough sensitivity and found that exercise reduced cough sensitivity in all healthy adults but only in approximately 80 per cent of healthy children [10]. Although the reason for this difference is not known, a higher incidence of personal and familial atopy may be present in children who did not show a reduction in cough during exercise compared with children who did. [10].

Another aspect in cough-specific physiological maturation influence is the age and sex-related differences in cough sensitivity. In prepubertal children, cough sensitivity is similar in males and females and therefore not influenced by sex. However, heightened cough sensitivity has been documented in post pubertal adolescents and adult females compared to males [11].

Exactly when children's cough reflex becomes fully matured is unknown, although likely in post-puberty. The critical windows of exposure in utero and early childhood for health, disease and even social determinants have long been appreciated [12]. Like other parts of neural development, developmental plasticity for the cough reflex is also likely important with the interplay between the young child with pre-natal and/or post-natal environmental conditions [13, 14]. Elegant studies involving primates have shown differential effects of second hand smoke (SHS) exposure to intrinsic and synaptic excitabilities of the nervous system [14]. The authors postulated that the “influence of SHS exposure on age-related (in utero, neonatal, infant) and neurophenotype specific changes may be associated with age-specific respiratory problems (e.g. bronchiolitis in infants and asthma in children), for which SHS exposure can increase the risk” [14].

Older Adults

Older adults (≥65 years) have a higher risk of both acute or chronic cough as well as impaired coughing compared to younger adult cohorts [15]. The incidence of chronic cough in older adults is relatively high, approaching 10% [16]. The largest analyses that have focused specifically on cough demographics have included mainly persons of Asian descent [15, 16]. In a meta-analysis, Song et al [17] presented evidence that chronic cough was more frequent in western countries than in Asia or Africa, but they did not specifically identify older adults in their analyses. In a world-wide study of 10,032 patients presenting with chronic cough, the most common age for presentation with chronic cough was 60-69 years [18].

Causes of enhanced coughing in this group mirror well known underlying conditions that cause chronic cough in the general population, with smoking, asthma, and rhinitis being the most common co-morbidities [16]. However, other co-morbidities are also prevalent in the elderly, including diabetes mellitus and constipation [16], and significance of these in the etiology of chronic cough in older adults is not understood. In a recent report of 1,000 older adult participants in the Korean Longitudinal Study of Health and Aging, the prevalence of depression was approximately 5% and associated with the presence of chronic cough rather than co-morbid asthma [19]. In a study of Chinese chronic cough patients attending a specialist clinic, older adults (> 50 years) had elevated cough sensitivity to inhaled capsaicin compared to younger patients. Whether this finding is directly associated with problem of chronic cough reported in older individuals is not certain [20].

Impaired cough can occur in older adults and is strongly associated with pathological states, such as neurological diseases [21-24]. In these conditions, there is a strong association of impaired cough mechanics and cough sensitivity with dysphagia [23, 25]. The presence of both dysphagia and impaired coughing has been linked to an increased risk of aspiration pneumonia [21, 22, 26, 27]. Co-

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occurrence of these impairments is thought to lead to increased vocal cord penetration and aspiration of pathogen-laden saliva and food materials [21, 26, 28-30]. Impaired coughing reduces the ability of the subject to expectorate this pathogen-laden material, thereby increasing exposure of the airway mucosa to colonization [27].

Ebihara et al [26] have proposed a model in which age-related cognitive decline is associated with the emergence of dysphagia and later dystussia. Further declines lead to loss of ambulation and/or impaired consciousness, silent aspiration, and community-acquired pneumonia. Silent aspiration is the lack of coughing in response to intrusion of material into the larynx and/or lower airways. These investigators have proposed that repeated micro-aspiration leads to chronic airway inflammation, even in the absence of colonization by pathogens. This airway inflammation could enhance the risk of further dysphagia [26].

Gender

Gender modifies many aspects of cough. Both cough prevalence and cough reflex sensitivity are increased in adult women and studies from many countries consistently report a preponderance of female patients (approximately two-thirds) presenting to clinics [18]. However, this gender effect is not evident in cough clinics in China [20]. Population prevalence studies indicate that chronic cough is more prevalent among non-smoking adult women than men [31]. Among ex-smokers, there is a similar prevalence of cough in men and women. In children, boys experience more cough than girls during the first decade of life, whereas this gender effect reverses after the age of 14, and adolescent girls report more cough than adolescent boys [32]. Cough as a side-effect of angiotensin converting enzyme inhibitor (ACE-I) therapy is more common in women than men [33].

Cough hypersensitivity is more prevalent in adult women and can be demonstrated experimentally with an increased cough response to inhaled capsaicin not only among adult women with chronic cough [18, 20] but also in healthy adult women [34, 35]. The clinical features that characterize cough hypersensitivity are more prevalent in adult women with chronic cough. These include allotussia (cough triggered by nontussive stimuli) and laryngeal paresthesia (somatic sensations experienced without direct stimulation and localized to the laryngeal area) [36]. The

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Arnold's nerve reflex, itself a form of allotussia, whereby cough is elicited by minimal mechanical stimulation, is also increased in adult women with chronic cough [37] [8]. Patients with chronic cough report somatic sensations in the throat, often associated with an urge-to-cough. These sensations include 'irritation' and 'tickle' and represent laryngeal paresthesia [38] and are more prevalent among women with chronic cough [36]. Gender may also influence response to treatment for cough with evidence that women with laryngopharygeal reflux associated cough, who respond to treatment with proton pump inhibitors (PPI), have delayed time to maximal treatment effect [39]. In contrast, gender is not observed to modify response to neuromodulator therapy (e.g. amitriptyline, gabapentin) used to treat chronic cough [40-42].

The reasons for these gender effects are not known. Several proposed cough mechanisms are known to be modified by female sex hormones. This includes capsaicin hypersensitivity that is mediated by the increased activity of transient receptor potential (TRP) channels expressed on vagal C-fibers mediating cough, and mast cells that are known to express receptors for female sexual hormones [43]. Another explanation as to why women more frequently than men complain of chronic cough relates to the observations that the health-related quality of life of women is more adversely affected than men because women are more likely to seek medical attention because they are more apt to experience physical complaints associated with coughing such as urinary stress incontinence that then provokes psychosocial issues such as embarrassment [44]. Similar gender differences in health-related quality of life have not been seen during acute cough [45].

Clinical conditions impacting on cough mechanics

Various clinical conditions can affect cough efficacy and while glottic closure enhances the compressive phase of coughing, it is not essential for an effective cough [46-48]. For example, individuals with a tracheostomy or endotracheal tube can produce an effective cough by performing a huffing maneuver performed with an open glottis. Therefore, in patients with endotracheal tubes in place, a tracheostomy need not be performed to just improve cough effectiveness [1]. Cough efficacy is determined by several factors, including the lung volume at cough initiation, compression phase duration and development of tracheal pressure, cough peak flow (CPF) rate, acceleration to CPF, and sustained airflow following the peak. This requires tight coordination of inspiratory, expiratory, laryngeal, pharyngeal and oral musculature. Of these, CPF is thought to be one of the most crucial and has been well studied as an indicator of cough intensity, with the majority of data focusing on CPF of voluntary (rather than reflexive) cough (appendix 1 provides a summary table of CPF and other cough airflow measures where available, in clinical populations). Decreased CPF is associated with increased risk of atelectasis and pneumonia. Because maximal expiratory pressure and gastric pressure during cough may over-diagnose an ineffective cough, CPF has now become a global measure of voluntary cough [49]. In this section, we will focus on clinical conditions affecting CPF, and other mechanical components of cough. We will summarize the impact of the following acute neurological events; stroke, traumatic brain injury and spinal cord injury, on cough mechanics and discuss implications for management of these cases. We will follow this with comment on the neurodegenerative consequences of amyotrophic lateral sclerosis (ALS) and Parkinson's disease and conclude the section with a perspective on chronic neuromuscular disorders

Neurologic disorders - Sudden Onset

Some patients with stroke may be at particular risk of disordered cough (dystussia) due to the type or location of the stroke. While cough reflex thresholds at 3 months post stroke may be similar to those of healthy controls [49], patients in the acute phase with a middle cerebral artery infarct demonstrated lower functional residual capacity, lower cough inspired volume, and lower voluntary peak cough flow [50]. In a study of cough reflex testing with nebulized tartaric acid, conducted in 818 acute stroke patients, 82 had weak or absent cough responses. Of these, 11% developed pneumonia compared with 3.5% of those who had a normal response to the cough challenge [51]. Brainstem and cerebral strokes were associated with disordered response to reflex cough testing and development of pneumonia [51]. It is also reported that the capacity to generate higher CPF is associated with a lower risk of aspiration in stroke patients [25]. Inadequate cough following stroke may be due to impaired afferent function or damage to the neural pathways contributing to reflexive coughing. Other factors including a physical disability accompanying a stroke such as paresis in an arm used for self-feeding or brushing teeth, or weakness in legs resulting in reduced mobility could additionally contribute to the risk for developing pneumonia [52]. A few studies have examined the effect of respiratory

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(inspiratory and expiratory) strength training, with mixed results as to the effect on cough. In one study, expiratory muscle strength training (EMST), inspiratory muscle strength training (IMST) and a sham training group showed equivalent improvement in CPF after 28 days of training, suggesting that the active training groups did not receive additional benefit beyond natural recovery post-stroke [53]. However, a second study evaluating EMST alone showed improvement of reflex CPF and cough volume acceleration (CVA) after 4 weeks of training [54]. The study was limited by the absence of a sham-control group, but since participants were more than 6-months post stroke, the likelihood of improvement due solely to acute stroke recovery was low.

Individuals with traumatic brain injury (TBI) may have multiple comorbidities that increase risk resulting from disordered cough, including decreased cognitive and physical capacity. In a study comparing healthy controls to 25 patients with TBI, lower voluntary peak cough flows and laryngeal cough reflex airflows to citric acid were evident in the patient group [55]. The authors reported a strong correlation between the two cough measures and proposed that in TBI patients who are unable to follow directions for voluntary cough testing, cough reflex with citric acid provides a reasonable estimate of voluntary cough flow [55]. Intubation rates are high in the acute-phase following TBI [56], and cough can be a powerful predictor of extubation success [57]. The consequences of TBI on cough may be long lasting and there is evidence of a blunting in the urge to cough years after tracheostomy in patients who required tracheostomy [58].

People who experience spinal cord injury (SCI) can have major changes in respiratory and cough function due to loss of nerves and connectivity at multiple levels. This is most evident in high cervical cord injuries and can result in low lung volumes, weak or absent coughs [59], and increased production of secretions that need to be cleared from the airway. Mechanically assisted coughing can be beneficial to these patients to increase peak airflows to clear secretions from the lower airways [60, 61]. Additionally, electrical stimulation of the abdominal muscles may improve cough in people with SCI by enhancing the dynamic compression of the airways when stimulation is delivered as the patients begin coughing [62].

Neurodegenerative Disorders

Cough impairment in patients with ALS is particularly concerning as respiratory failure is the leading cause of death for those affected by this disease. Upper and lower motor neuron loss can provide a basis for deficits including decreased gas exchange [63], reduced peak cough flow, and reduced cough volume acceleration [64-66]. As laryngopharyngeal muscles play a crucial role on both cough intensity and swallowing physiology, the co-occurrence of dysphagia and dystussia is common in patients with ALS and other neurodegenerative diseases. It is reported that CPF < ~240 L/min is an indicator of unsafe swallowing in patients with ALS [64, 67]. Other parameters of cough mechanics such as CVA, and peak cough flow rise time (PCFRT) showed better sensitivity and specificity, respectively, to detect aspiration versus safe swallowing [67]. Further, EMST in patients with ALS has been shown to improve both cough efficacy and swallowing function [68].

In Parkinson's disease, underlying causes of cough dysfunction include slowed and stiff movement of respiratory muscles or obstruction of the upper airway [69]. Symptoms related to declines in motor function are likely to precede declines in sensory integrity that can compound the impact of disordered cough. For instance, in the early stages of Parkinson's Disease, peak airflow of voluntary coughing is reduced compared to healthy controls [24]. As the disease progresses, sensory changes develop, evinced in this case by higher thresholds of irritants required to evoke a cough [24, 70], and reduced perception of urge-to-cough [71]. The changes in sensory thresholds are potentially explained by impaired afferents or disordered integration of sensory and motor signals [72]. It has also been demonstrated that voluntary coughs are more forceful in patients with Parkinson's disease compared to reflexive coughs in the same patients [73]. Thus, clinicians should bear in mind that values obtained in voluntary cough tasks likely overestimate the strength of a patient's cough that occurs in response to lower airway invasion, and that the frequency of reflexive coughing is likely depressed due to reduced sensory feedback.

Neuromuscular Diseases

A multitude of chronic disorders affect muscular systems that support respiration and lay the foundation for functional coughing. Patients with Duchenne Muscular Dystrophy, who experience weakness in respiratory musculature, benefit from mechanically assisted cough to significantly increase peak cough flows [60, 74, 75]. Maximum expiratory pressures may be a useful indicator of cough strength in patients with muscular dystrophy [75, 76]. However, inspiratory capacity is critically related to ability to generate "effective" peak cough flows in these patients [77]. Children with various neuromuscular diseases benefitted from the use of an intermittent positive pressure breathing device to increase peak cough flows [78].

For patients with neuromuscular diseases, CPF is used to predict the risk of respiratory complications. The presence of CPF <160 L/min is associated with inefficient cough, unable to provide enough airway clearance [62]. Therefore, CPF>160 L/min is minimum needed to successful extubation or tracheostomy tube decannulation. Patients with CPF >270 L/min are considered to have adequate cough, and those with CPF 160-270 L/min are candidates to use Mechanical Insufflation-Exsufflation (MI-E) because they are high risk of fatal pulmonary complications during respiratory tract infection [79]. However, the baseline peak cough flow values suggested for starting assisted cough techniques in young children may have to be lower than the adult-specific values [80].

The role of CPF measurements in the intensive care setting

In adults, CPF has been measured before extubation as a predictor of reintubation [81-83]. Patients with CPF < ~360 L/min were found to be high risk of reintubation for both inadequate voluntary [82] and involuntary coughs [84]. However, it has been reported that voluntary CPF is a better indicator to predict reintubation than involuntary CPF [81]. Measuring CPF in ventilated patients has been problematic because it requires a dedicated flow meter, bacterial filter and patient's disconnection from the ventilator. Recently, researchers showed that measuring CPF by a built-in ventilator flow meter did not differ from CPF measured by a spirometer [81, 85]. Therefore, a CPF value of 360 L/min has been suggested as an indicator for safe extubation. There are a variety of maneuvers such as abdominal thrusts and breath stacking, and devices such as rapid insufflation/exsufflation using devices such as the CoughAssist that can augment CPF and clearance in patients with neuromuscular weakness.

The Role of Airway Secretions in Cough Clearance

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Physical properties of secretions

Cough is an important mechanism for expectorating sputum and CPF is a critical determinant of clearance efficacy. The most effective secretion transport occurs in the area of airway constriction referred to as the equal pressure point, which propagates cephalad during a cough [86]. However, secretion properties also influence the effectiveness of cough. These include the bulk rheologic (viscoelastic) properties and surface properties that influence the interaction between the airway secretion and the epithelium. A distinction should be made between mucus, phlegm, and sputum [87]. *Mucus* is the normal protective layer of secretions comprised of water and polymeric secreted proteins, called mucins. Normal mucus protects the epithelium from dehydration and the invasion from particulates, which are constantly swept upward into the trachea and oropharynx and then swallowed. Rarely is excessive normal mucus a problem leading to airflow limitation and obstruction [88]. *Phlegm*, from the Greek word for inflammation, is the result of a host response with recruitment of macrophages and neutrophils, airway damage and debris, and release of DNA and filamentous actin (F-actin) polymers. Activated inflammatory cells and their products colors secretions yellow to green, and when this phlegm is expectorated, it is then called *sputum*.

Mucus and sputum are complex polymers and behave as gels that initially store energy elastically and then begin to deform with increasing stress, exhibiting viscosity. The appropriate balance between viscosity and elasticity is important for mucus to spread onto the epithelium and still be transported by beating cilia. The ability for cough to clear secretions *in vitro* is relatively independent of viscosity [89]. When viscosity is very low and secretion flow like water, this impedes air-mucus interaction and cough transport. Under an increasing applied stress, some gels will exhibit a sudden collapse of viscoelasticity with transformation from a relatively solid state to a liquid state and resultant flow; this is called the *yield stress*. A gel that resists collapse can be better cleared by cough then secretions that do not. Furthermore, a mucus gel simulant is more easily cleared in a simulated cough machine when the artificial tracheal column is upright or at an angle that presents a larger droplet profile to the airflow column [90]. This may be why patients prefer to cough and expectorate in a sitting or standing position rather than lying supine.

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Cough transportability also decreases during inflammation due to the presence of polymeric DNA and F-actin which increases the surface adhesion of secretions [91]. Cohesion is the energy needed to break the strings or strands that form with gel distraction. The combination of adhesion and cohesion is tenacity and this is one of the most important mechanisms reducing the effectiveness of cough in patients who have cystic fibrosis or COPD.

Modifying the physical properties of secretions

There are diverse medications that have been developed to modify the properties of secretions so that they can be more easily cleared by cough. These include classic mucolytics that contain free thiol or sulfhydryl groups that sever disulfide bonds on the cysteine residues that linearly link mucin monomers to form polymers; thus degrading the mucin polymer. The archetype classic mucolytic is N-acetyl L-cysteine. There is no clinical evidence that N-acetyl cysteine or other classic mucolytics are effective in promoting cough clearance. The peptide mucolytics include dornase alfa (Pulmozyme, Genentech, South San Francisco, CA) with newer forms of dornase undergoing clinical trials. These peptide mucolytics are designed to degrade the DNA and F-actin copolymers particularly prominent in the CF airway. Although dornase alfa has been tried as therapy for non-CF bronchiectasis and in COPD, there is no evidence that it is effective in treating these diseases and it is reported to increase mortality when used in diseases other than CF [92].

Expectorants such as guaifenesin, and hyperosmolar solutions such as hypertonic saline or hyperosmolar mannitol are meant to increase the hydration of the surface liquid and mucus to aid cough detachment from the airway expectoration. Guaifenesin or glycerol guaiacolate is ineffective as an expectorant and of no benefit in treating patients with sputum retention [93]. However, hypertonic saline and inhaled dry powder mannitol may improve pulmonary function and/or quality of life in CF and in non-CF bronchiectasis [94, 95]. These medications are sometimes referred to as “hydrators”.

Patients with secretions that are exceptionally thin and watery, such as those with bronchorrhea, also have poor cough clearance. It has been proposed that mucus thickening drugs or mucospissics may improve the effectiveness of cough [96, 97]. Although tetracycline has mucospissic activity, as does airway acidification**,** neither of these have been shown to be effective in treating patients with bronchorrhea.

Because failure of sputum and mucus clearance can lead to significant morbidity in patients with CF, COPD, severe asthma, bronchiectasis, diffuse panbronchiolitis, and other diseases, there is renewed interest in developing medications to improve mucus cough clearance by increasing airflow, decreasing tenacity, or optimizing viscoelasticity. Although some medications, such as beta agonists, can increase ciliary beat frequency, this seems to have only a negligible effect on mucus clearance. However, decreasing mucus adherence to the epithelial surface would likely to improve both ciliary and cough clearance.

Gaps in knowledge

Through the course of preparing this manuscript, we identified several knowledge gaps which if filled could help improve clinical management of patients. An improved understanding of cough reflex maturation from infancy to adulthood, particularly to help protect children from silent and recurrent small volume aspiration, was considered important. Linked to this is a need to understand how the complex integration between the peripheral and central nervous system is impacted by gender, aging or by acute and chronic neurological disease. A preliminary assessment of cough processing in the brain using fMRI demonstrated gender-related differences in the activity of the somatosensory cortex during inhaled challenges with capsaicin [18]. Similar imaging strategies could be used to distinguish between central sensory and motor neural changes that accompany altered coughing seen clinically. In this regard, it is interesting that the perception of pain (which shares many neurological similarities with cough) also differs with respect to gender and age, and a change pain acuity are similarly seen with acute and chronic neurological disease. In this field, brain imaging has offered many new insights into putative mechanisms contributing to this pain plasticity. Improving our knowledge in this area could help to minimize complications associated with aspiration. There is a need to accurately identify and intervene in individuals with ineffective cough most at risk of aspiration. Creating normative values based on demographic and clinical variables and a standardized methodology for the measurement of CPF and other clinically meaningful cough metrics represent important knowledge gaps in this field. As can be appreciated in Table 1 included in the appendix, cough testing approaches vary greatly in terms of the type of cough measured (reflex versus voluntary; single versus sequential), and reported measures, with the vast majority of studies reporting CPF only. As well, in these populations there is *reduced* cough output, as opposed to the hypersensitive, increased output, seen with chronic cough. Thus, the focus with these populations is evaluating the ability to effectively clear the airways and there is critical need to develop therapeutic techniques with this goal in mind. Currently, although there are a large number of airway clearance devices and medications used to promote airway hygiene, there are few well-controlled randomized clinical trials evaluating the safety and effectiveness of these interventions. The design and delivery of such trials remain a priority. As with clinical scenarios associated with ineffective cough, the cause and treatment of cough hypersensitivity remain unresolved. In particular, the observation of a heightened cough reflex sensitivity in females is widely reported but poorly understood. Identifying clinical and biological factors responsible for this finding will help contribute to a more complete understanding of cough hypersensitivity syndrome and provide direction to the development of new treatments. This will require the coordinated work of clinicians, scientists and industry.

Conclusion

Part two of the update to the 2006 CHEST Cough Guideline reviews the advances in knowledge of cough physiology and pathophysiology, specifically exploring the demographics of patients presenting with chronic cough and the clinical factors impacting cough efficiency. The cough reflex changes during early development and throughout life, for reasons that are not well understood. Although cough can be troublesome at any time in an individual's life, chronic cough is more often encountered as a clinical problem in older females for reasons that remain unclear. As a general rule, clinicians should recognize that patients with troublesome cough may have co-morbidities that are important to consider when managing their condition. Conditions associated with impairment in the nervous or muscular systems may contribute to deficits in cough mechanics, the consequences of which can in

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some cases be predicted by assessing CPF and other measures. Airway secretions are cleared by coughing when mucociliary clearance is inadequate or overwhelmed, but the physical properties of secretions may impact cough efficiency. Respiratory maneuvers and devices can augment CPF, while medications can modify the physical properties of secretions. These approaches may be of particular help with cough efficiency in some patients, especially with neuromuscular weakness or with difficulty in sputum expectoration.

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Table 1. Search terms used for reviewing the literature.

MeSH search terms		
Cough AND Aging OR Aged OR Elderly	Cough AND Effort	Cough AND Mucus
Cough AND Gender OR Sex OR Sex factors	Cough AND Pathophysiology OR Mechanics	Cough AND Mucins
Cough AND Neuromuscular	Cough AND Airway compression	Cough AND Mucociliary OR Mucociliary clearance
Cough AND Emphysema OR Decreased airflow OR Flow rates	Cough AND Airway collapse	Cough AND children AND physiology OR reflex OR mechanism
Cough AND Chronic disease OR Obstructive disease		

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