CHEST

Global Physiology and Pathophysiology of Cough

Part 2. Demographic and Clinical Considerations: CHEST Expert Panel Report

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BACKGROUND: Cough characteristics vary between patients, and this can impact clinical diagnosis and care. The purpose of part two 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.

STUDY DESIGN AND METHODS: A review of the literature was conducted using PubMed and MEDLINE databases from 1951 to 2019 using prespecified search terms.

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

INTERPRETATION: 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. CHEST 2021; 160(4):1413-1423

KEY WORDS: airway clearance; cough; demographics; mucus; pathophysiology; physiology

ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; CF = cystic fibrosis; CHEST = American College of Chest Physicians; CPF = cough peak flow; EMST = expiratory muscle strength training; F-actin = filamentous actin; SHS = secondhand smoke; TBI = traumatic brain injury

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This is the second paper in a two-part update on global physiology and pathophysiology of cough in the 2006 American College of Chest Physicians (CHEST) cough guidelines.[1] Part one 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 two 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 sex 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 disease, and motor neuron disease on cough mechanics is presented. We carried out a review of the literature 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 the following: common etiologies of chronic cough,[4] assessment of outcomes, the maturational aspects of immunity (eg, innate, humoral, cellular),[5] and physiological aspects of the respiratory system (eg, airway size, respiratory muscle development) from childhood 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, because 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 subsequent section details available data.

Although the cough reflex first becomes evident at 1 to 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. 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 ear-cough reflex. The reflex is evoked by palpation of the posteroinferior wall, palpation of the anteroinferior wall of the external acoustic meatus (ear canal), or mechanical stimulation of the ear canal with insertion of cotton-tip applicator 3 to 5 mm for 2 to 3 s.[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 with 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

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		

MeSH = Medical Subject Headings.

but only in approximately 80% 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 boys and girls and therefore not influenced by sex. However, heightened cough sensitivity has been documented in postpubertal adolescents and adult women compared with men.[11]

Exactly when children's cough reflex becomes fully matured is unknown; however, it likely occurs in postpuberty. 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 prenatal and/or postnatal environmental conditions.[13,14] Elegant studies involving primates have shown differential effects of secondhand 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 of age) have a higher risk of both acute or chronic cough and impaired coughing compared with 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 people 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 worldwide study of 10,032 patients presenting with chronic cough, the most common age for presentation with chronic cough was 60 to 69 years of age.[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 comorbidities.[16] However, other comorbidities are also prevalent in older adults, including diabetes mellitus and constipation,[16] and significance of these in the etiology of chronic cough in older adults is not understood. In a 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 comorbid asthma.[19] In a study of Chinese patients with chronic cough attending a specialist clinic, older adults (> 50 years of age) had elevated cough sensitivity to inhaled capsaicin than younger patients. Whether this finding is directly associated with problems of chronic cough reported in older individuals is not certain.[20]

Impaired cough can occur in older adults and is strongly associated with pathologic states, such as neurologic 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-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 microaspiration leads to chronic airway inflammation, even in the absence of colonization by pathogens. This airway inflammation could enhance the risk of further dysphagia.[26]

Sex

Sex 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 sex effect is not evident in cough clinics in

China.[20] Population prevalence studies indicate that chronic cough is more prevalent among nonsmoking 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 sex effect reverses after 14 years of age, and adolescent girls report more cough than adolescent boys.[32] Cough as a side-effect of angiotensin converting enzyme inhibitor 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 Arnold nerve reflex, itself a form of allotussia, whereby cough is elicited by minimal mechanical stimulation, is also increased in adult women with chronic cough.[8,37] 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] Sex may also influence response to treatment for cough, with evidence that women with laryngopharyngeal reflux-associated cough, who respond to treatment with proton pump inhibitors, have delayed time to maximal treatment effect.[39] In contrast, sex is not observed to modify response to neuromodulator therapy (eg, amitriptyline, gabapentin) used to treat chronic cough.[40-42]

The reasons for these sex 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 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 provoke psychosocial issues such as embarrassment.[44] Similar sex 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 although 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 after 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 also well-studied indicators of cough intensity, with most data focusing on CPF of voluntary (rather than reflexive) cough. Decreased CPF is associated with increased risk of atelectasis and pneumonia. Because maximal expiratory pressure and gastric pressure during cough may overdiagnose 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 acute neurologic events (eg, stroke, traumatic brain injury [TBI], 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 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) because of the type or location of the stroke. Although cough reflex thresholds at 3 months poststroke may be similar to those of healthy control subjects,[49] patients in the acute phase with a middle cerebral artery infarct demonstrated lower functional residual capacity, lower cough inspired

volume, and lower voluntary CPF.[50] In a study of cough reflex testing with nebulized tartaric acid, conducted in 818 patients with acute stroke, 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 patients with stroke.[25] Inadequate cough after stroke may be caused by impaired afferent function or damage to the neural pathways contributing to reflexive coughing. Other factors including a physical disability accompanying a stroke (eg, paresis in an arm used for self-feeding or brushing teeth, 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 (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, 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 poststroke.[53] However, a second study evaluating EMST alone showed improvement of reflex CPF and cough volume acceleration after 4 weeks of training.[54] The study was limited by the absence of a sham-control group, but because participants were $>$ 6 months poststroke, the likelihood of improvement solely because of acute stroke recovery was low.

Individuals with TBI may have multiple comorbidities that increase risk resulting from disordered cough, including decreased cognitive and physical capacity. In a study comparing healthy control subjects with 25 patients with TBI, lower voluntary CPFs 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 patients with TBI 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 after 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 can have major changes in respiratory and cough function because of 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 spinal cord injury 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 because respiratory failure is the leading cause of death for those affected by the disease. Upper and lower motor neuron loss can provide a basis for deficits including decreased gas exchange,[63] reduced CPF, and reduced cough volume acceleration.[64-66] Because 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 $<$ $\sim$240 L/min is an indicator of unsafe swallowing in patients with ALS.[64,67] Other parameters of cough mechanics, such as cough volume acceleration and CPF rise time, showed better sensitivity and specificity, respectively, to detect aspiration vs safe swallowing.[67] Furthermore, EMST in patients with ALS has been shown to improve both cough efficacy and swallowing function.[68]

In Parkinson 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 disease, peak airflow of voluntary coughing is reduced compared with healthy control subjects.[24] As the disease progresses, sensory changes develop, evidenced 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 disease compared with reflexive coughs in the same patients.[73] Therefore, physicians 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 because of 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 CPFs.[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 CPFs in these patients.[77] Children with various neuromuscular diseases benefitted from the use of an intermittent positive pressure breathing device to increase CPFs.[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 and an inability to provide enough airway clearance.[62] Therefore, CPF $>$ 160 L/min is the minimum needed for successful extubation or tracheostomy tube decannulation. Patients with CPF $>$ 270 L/min are considered to have adequate cough, and those with CPF 160 to 270 L/min are candidates to use mechanical insufflation-exsufflation because they are at high risk of fatal pulmonary complications during respiratory tract infection.[79] However, the baseline CPF values suggested for starting assisted cough techniques in young children may have to be lower than the adult-specific values.[80]

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 $<$ $\sim$360 L/min were found to be at high risk of reintubation for both inadequate voluntary[82] and involuntary cough.[84] However, it has been reported that voluntary CPF is a better indicator to predict reintubation than involuntary CPF.[81] Measuring CPF in patients on ventilation has been problematic because it requires a dedicated flowmeter, a bacterial filter, and the patient's disconnection from the ventilator. Researchers have shown that measuring CPF by a built-in ventilator flowmeter 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 (eg, CoughAssist; Philips Respironics) that can augment CPF and clearance in patients with neuromuscular weakness.

Role of Airway Secretions in Cough Clearance

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 consisting 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 color 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 secretions 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 than 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.

Cough transportability also decreases during inflammation because of 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 (CF) 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, therefore degrading the mucin polymer. The archetype classic mucolytic is N-acetyl L-cysteine. There is no clinical evidence that N-acetyl L-cysteine or other classic mucolytics is effective in promoting cough clearance. The peptide mucolytics include dornase alfa (Pulmozyme; Genentech) 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 (eg, guaifenesin) and hyperosmolar solutions (eg, hypertonic saline, 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 (eg, 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 (eg, 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 improve both ciliary and cough clearance.

Gaps in Knowledge

Through the course of preparing this paper, 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 CNS is impacted by sex, aging, or acute and chronic neurologic disease. A preliminary assessment of cough processing in the brain using functional MRI scan demonstrated sex-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 neurologic similarities with cough) also differs with respect to sex and age, and changes in pain acuity are similarly seen with acute and chronic neurologic 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 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 shown in Table 1, cough testing approaches vary greatly in terms of the type of cough measured (reflex vs voluntary, single vs sequential), and reported measures, with most 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. Therefore, 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 controlled 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 women 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 physicians, scientists, and industry.

Conclusions

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 women for reasons that remain unclear. As a general rule, physicians should recognize that patients with troublesome cough may have comorbidities 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 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, whereas 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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